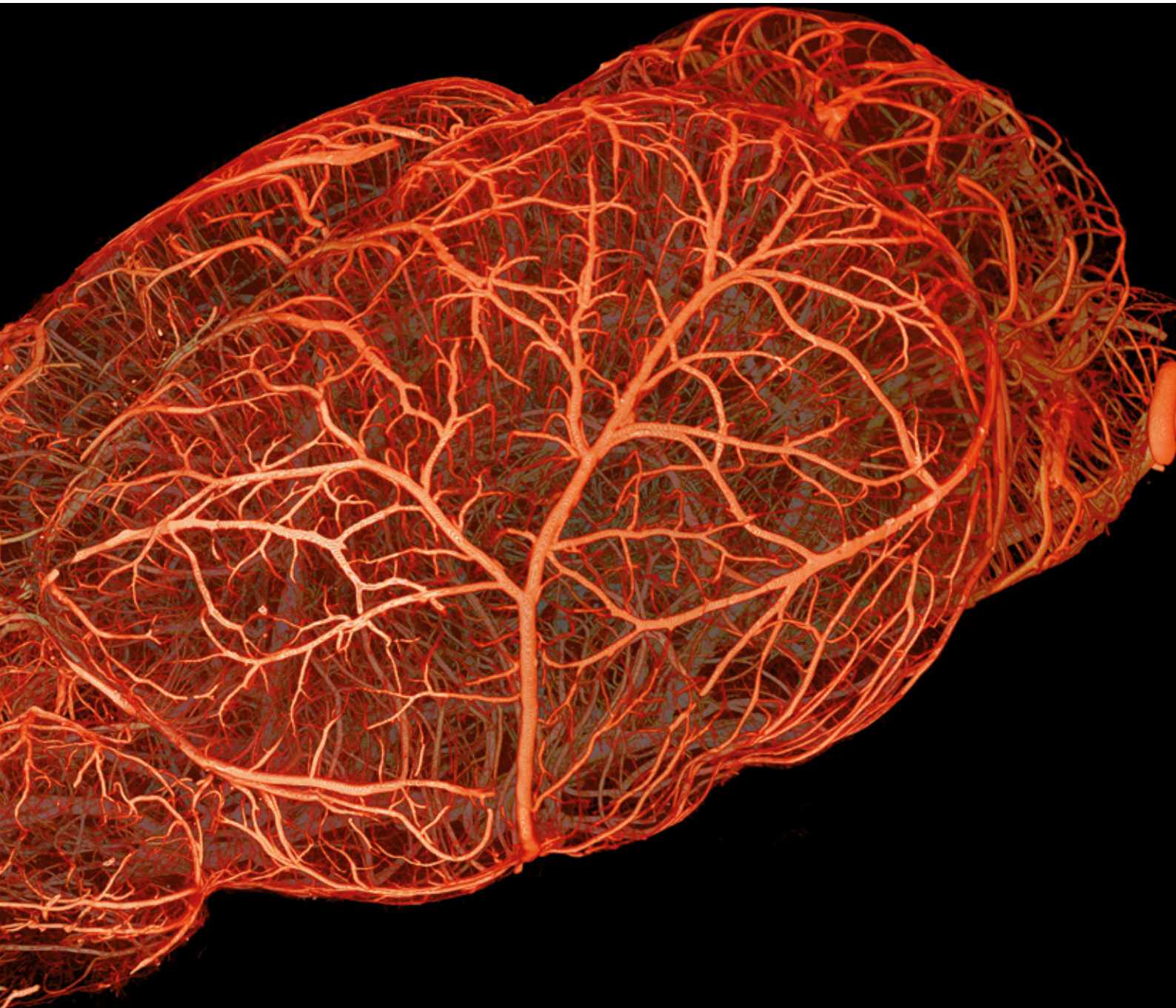


Medical Faculty  
[www.medizin.unibe.ch](http://www.medizin.unibe.ch)

# Annual Report 2018



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## FOREWORD

The University of Bern was founded in 1834 and has from the beginning included a Faculty of Medicine. In the last 184 years, many personalities formed and developed our Faculty, including Theodor Kocher, who was awarded the Nobel Prize in 1909 for his work on the thyroid gland. Theodor Kocher was the first surgeon and the first Swiss medical doctor to have received the Prize. Today the Faculty of Medicine is one of the five complete medical faculties in Switzerland offering a full program of study in Medicine and Dental Medicine. In addition, Master studies in Biomedicine and Biomedical Engineering have been established. Our faculty is ranked among the top 100 medical institutions world-wide.

High-quality **undergraduate teaching** and close student - faculty contact remain central to our philosophy. The popularity of our teaching is reflected by the number of medical students enrolled which has increased continuously in the last decade and is the highest in Switzerland. Beginning in September 2018, we have accommodated an additional 100 students in the first year of study; the total first year medical class now numbers approximately 340. In the last years, we have worked hard to optimally plan the **new content of our teaching programs**, as well as resources and logistics, which needed to be adapted to the increased numbers of students. We are happy to say that we continue to offer a **problem-oriented study** program, which demands a high proportion of well-trained teaching staff. In addition, the Faculty of Medicine, together with its University Hospitals (Inselspital and UPD) offer medical **resident programs** in each medical field. The resident programs are being continuously updated and require close collaboration between the different clinics.

The Faculty of Medicine of Bern provides excellent opportunities for high quality research. Together with the Board of Directors of the Inselspital, our **research strategy (p. 10)** was updated in 2017. **Basic research** is carried out in the pre-clinical institutions (Anatomy, Physiology, Biochemistry and Molecular Medicine, Pharmacology, Pathology and Infectious Diseases). Additional basic research is facilitated by the Department of Biomedical Research (DBMR), which offers all clinics of the Inselspital and UPD excellent opportunities, infrastructure and technical support for their work. **Clinical research**, including participation in large international trials, is performed with the

support of the Clinical Trial Unit (CTU). In 2018, we planned the structure of a **new Department of Clinical Research** (DCR), which will accommodate the CTU as a service unit. The DCR will also develop its own research and teaching programs. It will be located in the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel, p. 42), in close proximity to the clinical departments of the Inselspital. We are currently seeking a qualified individual in the rank of a full professor to lead the DCR. To promote patient-oriented clinical research, an innovative **MD-PhD program in Clinical Sciences (p. 30)** was started in 2017. Our Faculty gives strong support to the promotion of young researchers and to gender equality. We offer intramural grant opportunities for clinical (e.g. CTU grants) and basic researchers.

**Translational research** programs in the fields of biomedical engineering were greatly energized by the creation of the unique Center for Artificial Organs (ARTORG, p. 36) in 2008. Accordingly, research in biomedical engineering enjoys excellent conditions. Furthermore, it is planned that some research groups in this field will be re-located in the sitem-insel this year. Another strategic step to strengthen Translational Medicine was the decision to build up the **Bern Center for Precision Medicine (BCPM)** which has begun its work on January 1, 2019. Together with other local platforms (e.g. the unique **Bern Liquid Biobank**, which was inaugurated in 2017), this Center will give Bern a strong position within the Swiss Personalized Health Network (SPHN) initiative. It is planned that Precision Medicine be integrated in the daily medical practice of our clinical departments. The aim is to make the Inselspital one of the leading University Hospitals in the world in consequence of this important translational focus.

We hope that you will enjoy reading this report, which was prepared to promote familiarity with the breadth of knowledge and collaborations represented within and outside our University. We take this opportunity to thank all our employees and partners for their outstanding commitment which has made 2018 a very successful year for the Faculty of Medicine of Bern.

Hans-Uwe Simon  
Dean  
(on behalf of the Board of the Faculty of Medicine)



## A BRIEF HISTORY OF THE FACULTY

### Precursors

A medical faculty, called *facultas medica* or *collegium medicum*, existed already in the 16<sup>th</sup> century, long before the foundation of the University. This was, however, not a research or teaching institution but an appointed body of physicians and surgeons providing medical care and expertise for the city and State of Bern. A first proper but still very humble educational institution, the Medical Institute (*Medizinisches Institut*), was established in 1797 as a private initiative of local physicians, surgeons and apothecaries. In 1805, it was transformed into the Medical Faculty of the newly established Academy which in its turn was the precursor of the University, founded in 1834.

### German brains

In the early 19<sup>th</sup> century, Switzerland was academically still a developing country. Thanks to the reigning liberal attitude the State and the University of Bern were willing to attract the best scholars from

Germany, the leading nation in research at that time. The whole first group of full medical professors and 65% of all those appointed in the 19<sup>th</sup> century were Germans. Gabriel Gustav Valentin (1810–1883) is a good example. Originating from Breslau, he was a very promising young scholar who had just detected together with his teacher Jan Evangelista Purkyně the mechanisms of the ciliated epithelium.

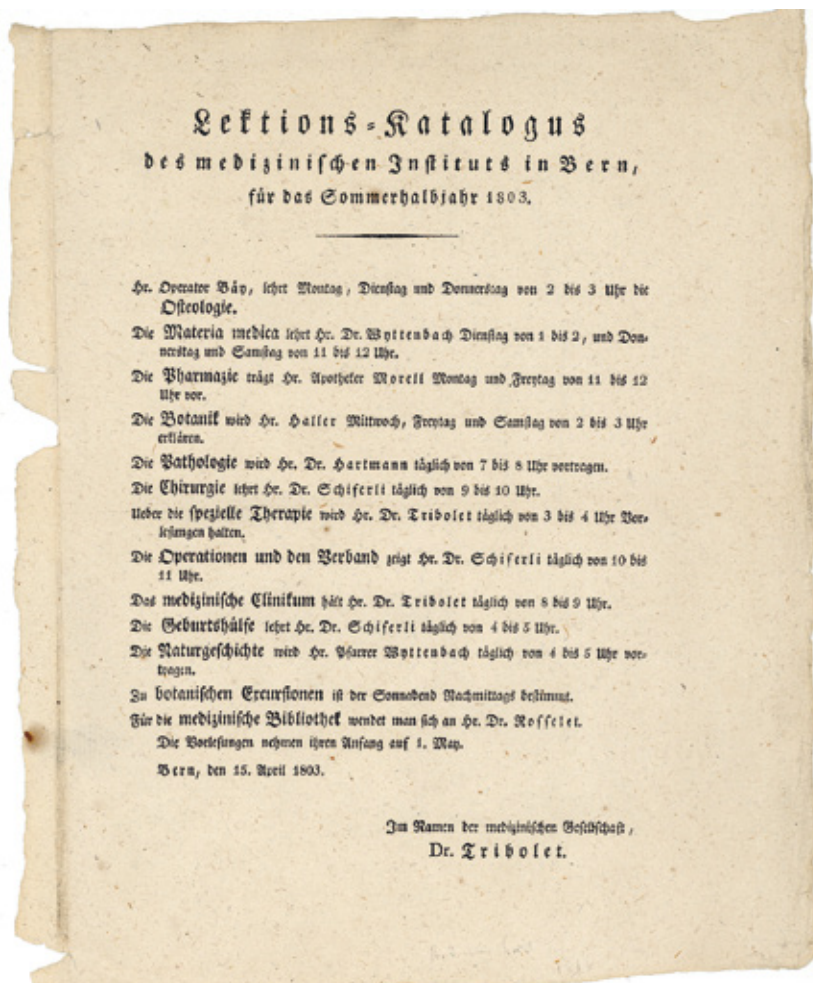
At the early age of 26, he was appointed as full professor of physiology and comparative anatomy, becoming thus the first Jewish professor at a German-language university. During his many years in Bern, he published extensively and established himself as a leading authority in cytology.

Some of Valentins German colleagues staid in Bern only for a few years, e.g. Theodor Langhans (1839–1915), discoverer of the Langhans giant cells or Ludwig Lichtheim (1845–1928), one of the founders of modern neurology. They helped, however, to

strengthen Bern's reputation and to attract further eminent and internationally acclaimed scientists. Among those we may mention Hugo Kronecker (1839–1914), a master of physiological methods with an extensive professional network and pupils all over the world. Another important figure was Alexander Tschirch (1856–1939), the undisputed authority on pharmacognosy, recipient of six honorary doctoral degrees and honorary memberships of 40 academic societies. And finally, there was Josef Jadassohn (1863–1936), whose name is connected with a series of dermatoses and anomalies and who transformed Bern into an international center of dermatology.

### Theodor Kocher, Nobel laureate

The most prominent figure of the early period was, however, Theodor Kocher (1841–1917), a Swiss. As professor and head of the surgical clinic he shaped the Medical Faculty and was the figurehead of the University for



Program of lectures at the Medical Institute, 1803.

45 years. He performed detailed clinical-pathological observations and physiological experiments in order to establish a more solid basis of surgery. In his highly influential surgical handbook – translated into several languages – he presented a ‘system of safe surgery’ based on slow operating techniques and painstaking haemostasis (using ‘Kocher clamps’). He had a particular impact on the emerging American medicine, especially through the dozens of surgeons who visited him each year. According to his manifold innovations and his high standing, he was elected first president of the International Society of Surgery in 1903 and was awarded the 1909 Nobel Prize in Medicine for his contributions to the physiology, pathology, and surgery of the thyroid.



Theodor Kocher, famous surgeon of the thyroid. Drawing by Rudolf von Fellenberg, medical student in the 1890s.

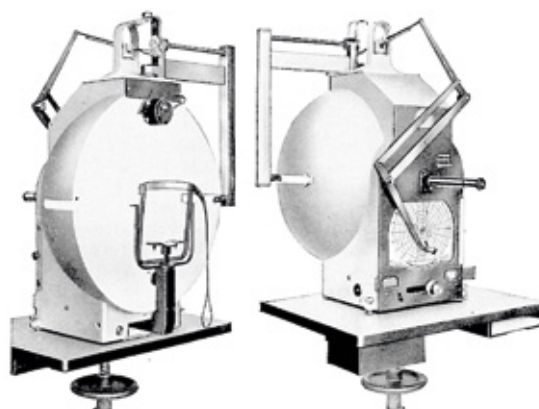
### Medical technology

Kocher was not only the key figure to establish the Medical Faculty as an internationally renowned institution, he started also Bern’s tradition of excellence in medical technology. He designed a whole series of surgical instruments, produced by Schaerer Inc., which served as models for generations. His successor, Fritz de Quervain (1868–1940) continued the collaboration with Schaerer and constructed together with the industrial company the world’s first fully adjustable operation table in 1912. Hermann Sahli (1856–1933), head of the medical clinic, developed a series of analytical devices to measure pulse, blood pressure etc. which allowed general practitioners to keep up with the increasing demands of modern medicine. His hemometer, a simple instrument used for colorimetric measurement of hemoglobin, was copied and used for decades in medical practices all over the world. Since the 1880s,

there was also close collaboration between University and industry in the area of ophthalmology. It gained a new level of importance with Prof. Hans Goldmann (1899–1991) and Haag-Streit Inc. who developed split lamps, perimeters and tonometers which set new international standards.

Of even greater consequence was the work of Maurice E. Müller (1918–2009). Together with a group of young surgical colleagues and engineers he developed new materials and techniques for internal plate fixation of fractures (osteosynthesis) and hip prosthesis. Establishing new standards in a globalized medical world meant not only a medical but also an economic success. Müller’s inventions led to the establishment of several foundations and the creation of various companies (Mathys, Synthes, Straumann; Protek, later Sulzer, then Zimmer). In recognition of his international impact, Müller was named “Orthopaedic Surgeon of the 20<sup>th</sup> Century” by the International Society of Orthopaedic Surgery and Traumatology.

Müller generously founded the University’s Institute for Biomechanics, today’s Institute for Surgical Technology and Biomechanics. The ISTB, the ARTORG Center for Biomedical Engineering Research and other institutions continue our tradition of developing internationally acclaimed new medical technologies.



Hans Goldmann’s new perimeter, 1944.

### Increasing demands

The history of the Medical Faculty is, of course, deeply intertwined with the history of the local hospital, the Inselspital, a charitable foundation dating back to 1354. Some clinical teaching at the hospital was already offered in the premodern period and



required little regulations. With the foundation of the University in 1834, however, the hospital had to assume new duties. Besides the traditional care of poor people, it now had to provide beds and patients for teaching and research and increasingly serve as a medical center for the whole region – obligations the foundation could carry out only with the support of the Canton of Bern. From 1834 to today, a series of contracts lays down the financial and organizational details of this cooperation.

The history of the Medical Faculty is deeply intertwined with the history of the local hospital, the Inselspital.

In reaction to the growing demands, in 1884 – not least thanks to the efforts of Kocher – a new hospital was built on a site outside the city walls.

Increasing specialization and need of infrastructure led soon to new institutes, clinics and thus new buildings on the hospital site as well as in the nearby city district. Around 1900, the still modest student numbers rose considerably. This was not, however, due to local interest but to women who were not allowed to study at most universities but accepted by the liberal universities of Bern, Zurich, Lausanne and Geneva. Between 1864 and 1914, more than 7,000 women from foreign countries, mainly Russia, pursued a medical course in Switzerland (1,600 in Bern), more than in the rest of Europe combined. It took several decades until another sharp increase in student numbers occurred in the 1960s thanks to the generation of the baby boomers. This increase was coupled with large investments in infrastructure, medical research and technology. After some 20 years of consolidation a new sharp rise of student numbers started around 2000 which is mainly due to an increased demand for locally trained medical doctors and new master programs in biomedicine.



Aerial view of the University Hospital (1970) showing the radical transformation of the campus. The new main building towers over the old structures from the earlier century.

## Deans of the Medical Faculty

1834–1835	Hugo Mohl	1938–1940	Jakob Klaesi
1835–1838	Hermann Askan Demme	1940–1941	Hans Bluntschli
1838–1843	Wilhelm Philipp Friedrich Vogt	1941–1943	Alexander von Muralt
1843–1847	Gabriel Gustav Valentin	1943–1945	Eduard Glanzmann
1847–1849	Friedrich Miescher	1945–1947	Hans Goldmann
1849–1852	Friedrich Wilhelm Theile	1947–1949	Joseph Dettling
1852–1857	Wilhelm Rau	1949–1951	Curt Hallauer
1857–1860	Wilhelm Philipp Friedrich Vogt	1951–1953	Karl Lenggenhager
1860–1861	Wilhelm Rau	1953–1955	Bernhard Walthard
1861–1865	Gabriel Gustav Valentin	1955–1957	Walther Wilbrandt
1865–1867	Daniel Jonquière	1957–1959	Erich Hintzsche
1867–1869	Christoph Theodor Aeby	1959–1961	Walter Neuweiler
1869–1871	Karl Emmert	1961–1963	Hugo Aebi
1871–1874	Georg Albert Lücke / Henri Dor	1963–1965	Adolf Zuppinger
1874–1876	August Breisky / Th. Kocher	1965–1967	Franz Escher
1876–1878	Heinrich Irenäus. Quincke	1967–1969	Johann Kuske
1878–1880	Theodor Langhans	1969–1971	Eugen Läuppi
1880–1882	Ernst Pflüger	1971–1973	André Schroeder
1882–1884	Ludwig Lichtheim	1973–1978	Jürg Hodler
1884–1886	Marcellus Wilhelm von Nencki	1978–1981	Beat Roos
1886–1888	Hugo Kronecker	1981–1983	Herbert A. Fleisch
1888–1890	Rudolf Demme	1983–1985	Harald Reuter
1890–1892	Ernst Pflüger	1985–1987	Rudolf Berchtold
1892–1894	Hans Strasser	1987–1989	Max Hess
1894–1896	Hermann Sahli	1989–1991	Georg Eisner
1896–1898	Alexander Tschirch	1991–1993	Alfred H. Geering
1898–1900	Theodor Kocher	1993–1995	Hans-Rudolf Lüscher
1900–1902	Arthur Carl Wilhelm Heffter	1995–1997	Bernhard H. Lauterburg
1902–1904	Theodor Langhans	1997–1999	Kurt Schopfer / H.-R. Lüscher
1904–1906	Josef Jadassohn	1999–2004	Emilio Bossi
1906–1908	August Siegrist	2004–2008	Martin Täuber
1908–1910	Wilhelm Kolle	2008–2016	Peter Eggli
1910–1911	Emil Bürgi	2016–	Hans-Uwe Simon
1911–1912	Leon Asher		
1912–1914	Hans Strasser		
1914–1916	Hans Guggisberg		
1916–1918	Leon Asher		
1918–1920	Carl Wegelin		
1920–1921	Fritz de Quervain		
1921–1923	Georg Sobernheim		
1923–1924	Fritz de Quervain		
1924–1926	Friedrich Lüscher		
1926–1928	Emil Bürgi		
1928–1930	Hans Guggisberg		
1930–1932	Carl Wegelin		
1932–1934	Walther Frey		
1934–1936	Emil Bürgi		
1936–1938	Paul Casparis		



# RESEARCH STRATEGY

## Research strategy

The Medical Faculty of the University of Bern has developed a joint research strategy for the period 2017–2021 together with the University Hospital (Inselspital) and Psychiatric Services of the University of Bern (UPD). This strategy includes the vision of strengthening Bern as a city with a strong medical school and intensive research activities, and of encouraging interactions with companies developing medical products. A network of strong basic and clinical research projects is to be developed, with the goal of transferring knowledge and technology for medical use. For instance, it has been decided that our Faculty will actively support the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel), the site for which is currently under construction on the Inselspital Campus in close proximity to all University Hospital clinics. In the following, we will briefly describe the content of our research strategy.

A network of strong basic and clinical research projects is to be developed, with the goal of transferring knowledge and technology for medical use.

## Financial support

Our academic institutions can obtain financial support in three ways:

- All institutions receive basic support for their development
- Additional support is provided according to institutional performance based on an annual evaluation of all institutions
- Excellent individual researchers performing highly competitive research can expect additional support

## Support of young researchers

The support of young academics has the highest priority and takes place at each level of support. We have programs aiming to prepare our undergraduate students for an academic career. The development of more and higher qualified clinician-scientists represents our central goal. To achieve this, we have

established a new graduate program, our Graduate School for Health Sciences, in which doctoral degrees in Clinical Sciences can be earned. Importantly, this program grants young researchers who are engaged in clinical service 50% protected research time over a period of 4 years. Among other important issues, we promote gender-equal opportunity. In particular, our goal is to encourage the training of more female scientists. Other important goals are the early scientific independence of our young academics and their competitive acquisition of research grants from external resources.

## Research foci

The Medical Faculty of the University of Bern promotes synergies and translational medicine, in consequence supporting the creation and consolidation of centers sharing common research topics and technologies. The use of common methodological platforms is vital to encourage exchange of knowledge between different teams and to be able to finance the changing infrastructures needed for competitive research. The following functional research units of the Medical Faculty represent open platforms providing infrastructure and technical competence which can be used by all researchers against payment of fees:

- Clinical trial unit (CTU)
- Department for Biomedical Research (DBMR)
- ARTORG Center for Biomedical Engineering Research
- Experimental Animal Center (EAC), including a Clean Mouse Facility (CMF)
- Microscopy Imaging Center (MIC)
- Bern Center for Precision Medicine (BCPN), starting 2019

Thematic foci have been defined according to scientific performance. Here, we intend to use synergistic activities in accordance with the following strategic foci of the University Hospital and the UPD:

- University Center for Heart and Vascular Diseases
- University Neurocenter
- University Cancer Center Inselspital

This research strategy was confirmed by majority vote of all Faculty members in May 2017.

## THE MEDICAL FACULTY IN NUMBERS

**1'865** students in **2** Bachelorprograms and **4** Masterprograms,  
**210** students in **22** CAS / DAS / MAS programs

**341** Final Master Degrees, thereof **229** in Medicine, **34** in Dental Medicine,  
**21** MSc in Biomedical Sciences, **47** MSc in Biomedical Engineering

**268** Doctorate Degrees, thereof **230** Dr. med., **38** Dr. med. dent.,  
**55** from the Graduate School for Cellular and Biomedical Sciences and  
**14** from the Graduate School of Health Sciences

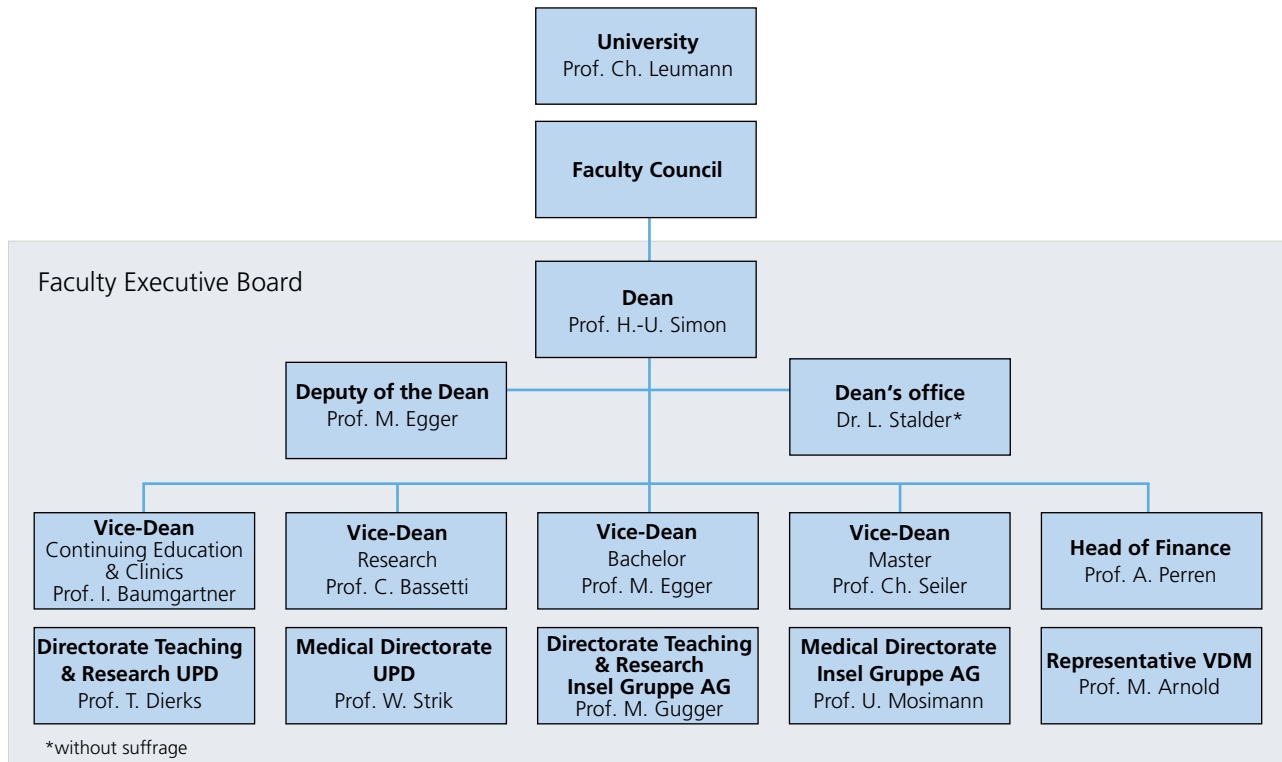
**102** Full Professors, **19** Assistant Professors,  
**136** Associate Professors and **371** Lecturers

**1** Faculty, **3** Organisations,  
**38** Clinics, **18** Institutes

**183'621'500** Mio Budget,  
additionally **29'860'030** Mio from the Swiss National Science Foundation and  
**37'048'595** Mio third party funds for research

**1'992** Original Articles published,  
**129'647** hours of teaching

# ORGANIGRAM



University  
Prof. Ch. Leumann



Dean  
Prof. H.-U. Simon



Deputy of the Dean  
Prof. M. Egger



Dean's office  
Dr. L. Stalder



Vice-Dean  
Continuing  
Education & Clinics  
Prof. I. Baumgartner



Vice-Dean  
Research  
Prof. C. Bassetti



Vice-Dean  
Bachelor Study  
Prof. M. Egger



Vice-Dean  
Master Study  
Prof. Ch. Seiler



Head of Finance  
Prof. A. Perren



Directorate Teaching  
& Research UPD  
Prof. T. Dierks



Medical  
Directorate UPD  
Prof. W. Strik



Directorate Teaching  
& Research  
Insel Gruppe AG  
Prof. M. Gugger



Medical Directorate  
Insel Gruppe AG  
Prof. U. Mosimann



Representative VDM  
Prof. M. Arnold

## KEY PEOPLE

### RESEARCH BOARD (AUSSCHUSS FÜR FORSCHUNG)

#### **President**

- Prof. Claudio Bassetti

#### **Members**

- Prof. Christoph Aebi
- Prof. Marcel Arnold
- Prof. Iris Baumgartner
- Prof. Thomas Dierks
- Prof. Matthias Egger
- Prof. Britta Engelhardt
- Prof. Jürg Gertsch
- Prof. Matthias Gugger
- Prof. Andrew Macpherson
- Prof. Christoph Müller
- Prof. Thomas Nevian
- Prof. Adrian Ochsenbein
- Prof. Robert Rieben
- Prof. Nicolas Rodondi
- Prof. Mark Andrew Rubin
- Prof. Martin Schimmel
- Prof. Hans-Uwe Simon
- Dr. Katharina Stegmayer
- Prof. Daniel Surbek
- Prof. George Thalmann
- Prof. Stefan Weber

#### **Consultative member**

- Dr. Lukas Stalder

#### **Administration**

- Daniela Hügli

### TEACHING BOARD (AUSSCHUSS FÜR LEHRE)

#### **President**

- Prof. Christian Seiler

#### **Members**

- Prof. Drahomir Aujesky
- Prof. Urs Brägger
- Prof. Andrew Chan
- Prof. Marcel Egger
- Dr. Peter Frey
- Prof. Robert Greif
- Prof. Matthias Gugger
- Prof. Sissel Guttormsen
- Dr. Dario Häberli
- Prof. Thomas Müller
- Prof. Nicolas Rodondi
- Prof. Stephan Rohr
- Prof. Ralph Schmid
- Prof. Hans-Uwe Simon
- Prof. Maja Steinlin
- PD Dr. Stefan A. Tschanz
- PD Dr. Matthias Widmer
- Prof. Ursula Wolf
- Prof. Philippe Zysset

#### **Students's representative**

- Noemi Fischer
- Anne Cloé Schaub

#### **Consultative member**

- Dr. Lukas Stalder

#### **Administration**

- Therese Sifeddine



## INSTITUTIONAL OVERVIEW



ARTORG Center for Biomedical Engineering Research  
Murtenstrasse 50  
3010 Bern



Department for BioMedical Research (DBMR)  
Murtenstrasse 35  
3008 Bern



Microscopy Imaging Center (MIC)  
Freiestrasse 1  
3012 Bern



Swiss Institute for Translational and Entrepreneurial Medicine  
Freiburgstrasse 18  
3010 Bern



University Neurocenter  
Freiburgstrasse 16  
3010 Bern



University Cancer Center  
Freiburgstrasse 10  
3010 Bern



Clinical Trial Unit Bern  
Mittelstrasse 43  
3012 Bern



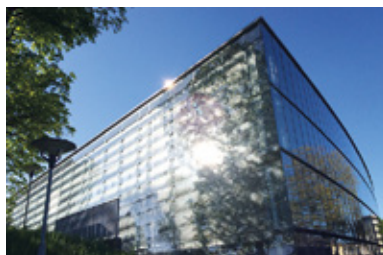
Institute of Anatomy  
Baltzerstrasse 2  
3012 Bern



Institute of Biochemistry and Molecular Medicine  
Bühlstrasse 28  
3012 Bern



Institute for the History of Medicine  
Bühlstrasse 26  
3012 Bern



Institute of Pharmacology  
Inselspital, INO-F  
3010 Bern



Institute of Physiology  
Bühlplatz 5  
3012 Bern



Institute of Social and Preventive Medicine (ISPM)  
Mittelstrasse 43  
3012 Bern



Institute for Surgical Technologies and Biomechanics (ISTB)  
Stauffacherstrasse 78  
3014 Bern



Theodor Kocher Institute (TKI)  
Freiestrasse 1  
3012 Bern



Institute for Infectious Diseases  
Friedbühlstrasse 51  
3001 Bern



Institute of Pathology  
Murtenstrasse 31  
3008 Bern



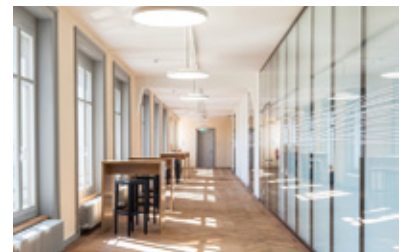
Institute of Forensic Medicine  
Bühlstrasse 20  
3012 Bern



Institute of Primary Health Care (BIHAM)  
Mittelstrasse 43  
3012 Bern



Institute of Complementary and Integrative Medicine (IKIM)  
Freiburgstrasse 46, 3010 Bern  
Fabrikstrasse 8, 3012 Bern



Institute for Medical Education (IML)  
Mittelstrasse 43  
3012 Bern



School of Dental Medicine  
Freiburgstrasse 7  
3010 Bern



University Psychiatric Services  
Bolligenstrasse 111  
3000 Bern 60



Inselspital, Bern University Hospital  
Freiburgstrasse  
3010 Bern



## STRUCTURAL DEVELOPMENT

### **New building for Research on the area of the University Hospital**

The Preclinical Institutes will move to the campus of the University Hospital (panel 07). This move is partly being driven by the planned extension of the Central Railway Station of Bern. This relocation will create synergies between, e.g. Anatomy, Physiology, ARTORG and ISTB. The first phase of planning has been finished successfully; the order, which formulates the specific requirements for research of the Preclinical Institutes has been submitted to the canton of Bern by the end of December 2018. In 2019 the architecture competition will take place, the completion of the building is planned to be in 2027.



Next to panel 7: View from the Friedbühlstrasse to the "Bettenhochhaus" of the Inselspital.

### **New building for Teaching on the area of the University Hospital**

As mentioned in the foreword, an additional 100 students started their first year of study in human medicine in September 2018. This increase of +100 students raises the need for teaching rooms. At the UniZiegler (former Renferhaus) additional rooms for seminars, examination, small group tutorials and an additional learning center have been temporarily made available in September 2018 for a couple of years. In the long term, however, a new education and training area must be created for the students of the Medical Faculty.

In April 2018, the canton of Bern has granted the set-up of a new building for teaching (panel 03). After a brief but intensive phase of planning, the order has been submitted to the canton of Bern by the end of December 2018.

### **New building for the Institute of Dental Medicine**

The Institute of dental medicine has grown continuously over the last years, and there is no end in sight yet. Furthermore, due to the digitization, the existing building at Freiburgstrasse 7 is limiting the technological change. The planning for a new building as replacement of the existing building has been finished successfully and the order has been submitted to the canton of Bern by the end of December 2018.

An additional 100 students started their first year of study in human medicine in September 2018. This increase of +100 students raises the need for teaching rooms.

### **Installation of laboratories in the building Murtenstrasse 40/42**

The Department of Biomedical Research (DBMR) has been obliged to give up a substantial part of its laboratory space due to the demolition of the Haller/Ludwig House, Pavilion 52 and the conversion of the 6<sup>th</sup> floor of the Institute of Pathology. In the first basement of the Murtenstrasse 40/42 building, the University Hospital has, therefore, installed new, modern laboratories that are used by the DBMR since February 2016.

### **New laboratory building Murtenstrasse 24 for the Department of Biomedical Research (DBMR) and the Institute of Legal Medicine (IRM)**

After the clear "Yes" of the Bernese voters in February 2016 to the financing of a new building at the



The construction site of the Murtenstrasse 24.

Murtenstrasse 24, construction work began in the summer of 2016. The building being constructed will have five upper, one attic and five basement floors. The flexibly usable upper floors will provide modern research and training space for the DBMR and the IRM. In the 1<sup>st</sup> to 3<sup>rd</sup> basements, additional usable space will be created for the institutes. The car-parking garage in the 4<sup>th</sup> and 5<sup>th</sup> basement will be accessed via the existing entrance to the University Hospital parking. Because of the heavy groundwater inflow encountered during excavation, a construction delay of up to one year will result. DBMR and IRM are now expected to move into the new building in May 2021.

### sitem-insel

The building for the Swiss School for Translation and Entrepreneurship in Medicine is under construction and should be ready to move in in May 2019. Several platforms from the University and from the University Hospital are planned. Furthermore, a new center for diabetes research (Diabetes Center Bern) will be built. This new center at the interface of research, development and industry further strengthens the medical focus of the Canton of Bern.



View from the top of the Bettenhochhaus towards the Railway Station. At the front right the school of dental medicine, in the center the new building of sitem-insel.

### University Hospital: Theodor-Kocher-Haus

The new building located at the Friedbühlstrasse is the first building as part of the "Masterplan Inselspital". Currently, this building is used as a temporary location for the Clinic for Obstetrics and Gynecology during their re-construction period. Afterward, following slight modifications and expansion, it will house the Organ and Tumor Center. The expansion for this

definitive use will include five additional floors. The laying of the cornerstone took place on December 6, 2016, in a festive setting.



View from the Theodor-Kocher-Haus (left) and the Institute for Infectious Diseases (right) to the INO-building of the Inselspital.

### University Hospital: New building for the Heart and Vascular Center

The new building on panel 12 provides space for the Swiss Cardiovascular Center and other specialist clinics. With the new building, clinics will be brought closer together promising an optimization of interdisciplinary treatment concepts. For example, in the new Building 12, cardiologists and cardiac surgeons will treat heart attacks on one floor together.



Construction place panel 12.



# SCHOOL OF HUMAN MEDICINE

## FACTS 2018

### Bachelor of Medicine

Study places: human medicine	320
Dental medicine	35
Students (including repeaters) human medicine	352
Students (including repeaters) dental medicine	54
Beginners, bachelor program human medicine 2015	220
Ending with bachelor degree human medicine 2018	181
Dropouts human medicine in the bachelor program	17.7%

Mobility	Incoming bachelor students	1
	Outgoing bachelor students	16

### Master of Medicine

Study places: human medicine 2018	250
Beginners master program human medicine 2018	240
Beginners master program human medicine 2015	234
Ending with master degree human medicine 2018	228
Dropouts in the master program during 2015-2018	2.5%

Mobility	Incoming students	
	masterprogram (electives)	150
	Outgoing students	
	masterprogram (electives)	70

### Federal Examinations

Multiple choice exam, candidates 2018	228
Multiple choice exam, passed 2018: 100%	228
Clinical skills exam, candidates 2018	228
Clinical skills exam, passing 2018 (99.6%)	227

For more than 200 years, physicians and medical doctors have been trained at the Faculty of Medicine Bern. The in Bern Faculty is currently the second largest institution for the education of medical professionals in Switzerland. In 2007, the curriculum was changed to the Bologna system, which subdivided the program into Bachelor's and Master's-degree programs. The curriculum for human medicine in Bern is characterised by a comprehensive and balanced training concept and is one of the best educational programs in Switzerland. A unique feature is the high practical relevance and the patient-orientated training.

Based on the national strategy to increase the number of study places in Switzerland from 900 to 1300 students, the University of Bern increased the number from 220 to 320 students beginning the first year of Medicine in September, 2018. Including the dental students and repeaters there are now 406 students in the first year!

Another unique feature of medical education in Bern is that the Bachelor's program in human medicine is based on the educational approach of problem-based learning (PBL). The curriculum comprises distinct, but complementary training methods, which includes tutorial training sessions, lectures, practical courses and training in clinical skills, internships in primary care, electronic learning media, as well as continuous evaluation of student progress in formative and summative assessments.

In order to increase the number of study places in 2018, the curriculum of the years 1 and 2 was reorganized, the schedule was changed, and the number of PBL cases had to be reduced by half. On the other hand the number of students in each PBL group could be limited to 7 students. To equalise the knowledge level of students in the basic sciences, the first 11 weeks of problem-based group-sessions were replaced by assignment-based learning groups.

The modern didactic concepts used in the Bachelor's and Master's programs allow students to successfully complete the human medicine degree program at the Faculty of Medicine Bern and pass the Federal examination.

The Master's program in Bern offers a subject-specific and practice-oriented study model with a high emphasis on bedside teaching in the Teaching Hospitals. Special emphasis is placed on communication training. The Inselspital Bern, a University hospital focussing primarily on treatment, offers comprehensive training in more than 50 disciplines. Integrated also within the Master's curriculum is a scientific Master thesis and a mandatory internship in General Practice. The „Bern Family Doctor internship“ is groundbreaking in Switzerland and German-speaking countries.

In 2018, the learning objectives for clinical training were adapted to the new PROFILES (Principal Relevant Objectives and Framework for Integrative Learning and Education in Switzerland), which forms the basis of the Federal examinations. The principle of research-led teaching, which is supported in the Medical

Faculty, ensures a close relationship and incorporation of current research findings in teaching.

The modern didactic concepts used in the Bachelor's and Master's programs allow students to successfully complete the human medicine degree program at the Faculty of Medicine Bern and pass the Federal examination (based on the MedBG Art. 6).

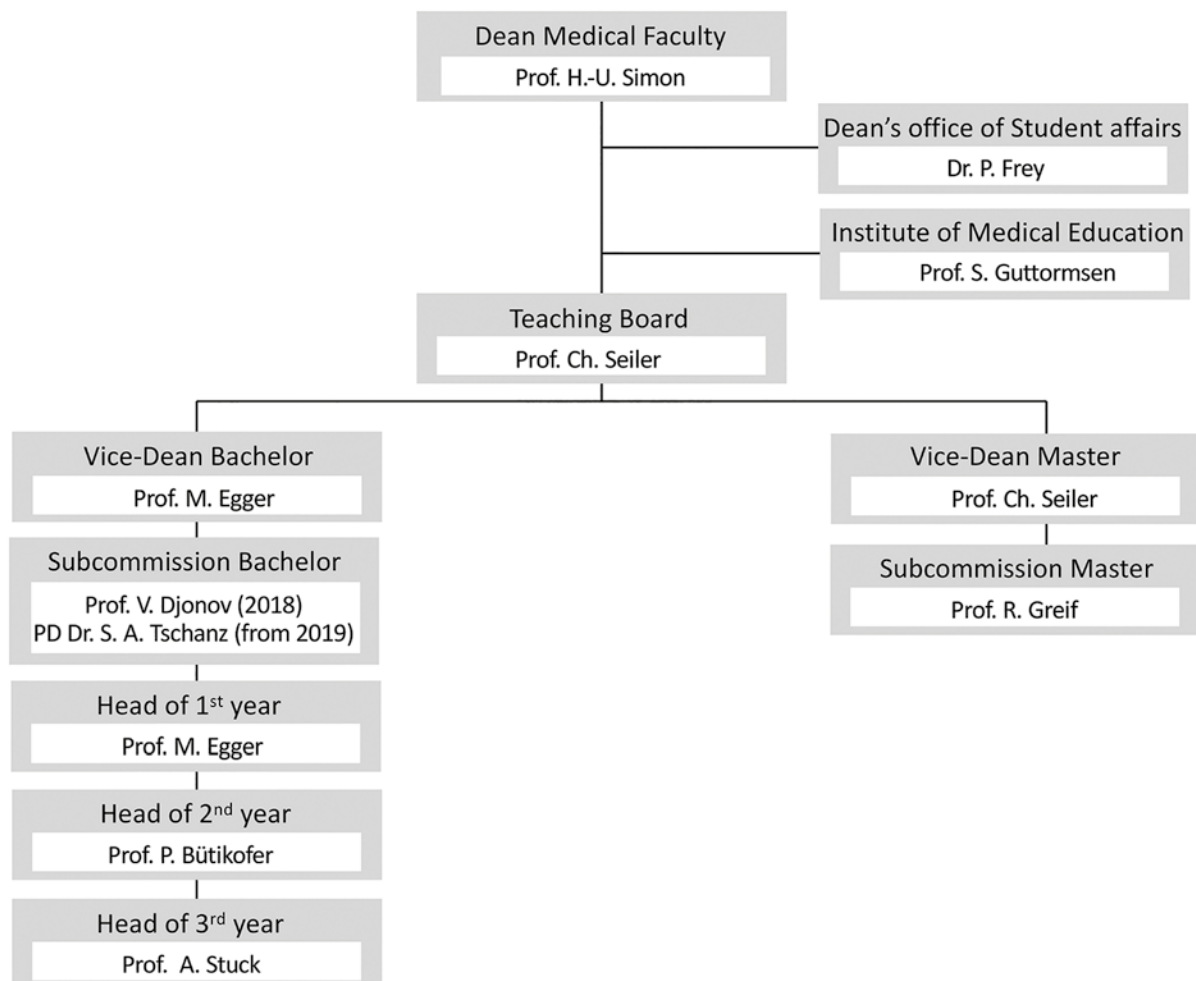
Bern graduates taking the Swiss Federal Licensing Examinations achieve very good results compared to the national average, and these graduates enter further training as „ready to practice“ and well organised.

In terms of infrastructure, there are deficits. The lecture room/auditory space is likely to remain unsatisfactory. The lectures of year 1 were transmitted

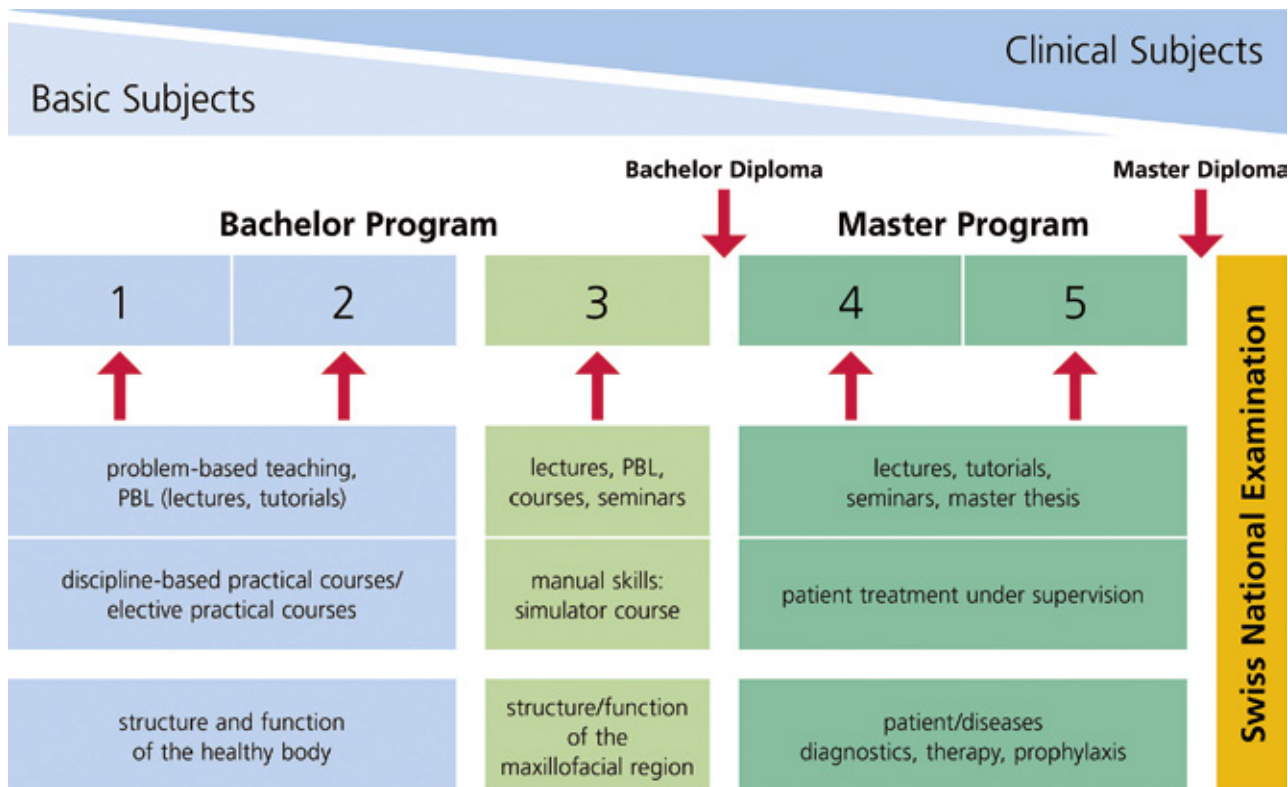
by video from the main lecture hall to another auditory ‚Aula‘. Initiated since autumn 2018 for small group activities like clinical skills training, there are additional and sufficient seminar and examination rooms available in the ‚UniZiegler‘, as well as an additional learning centre for students.

We conclude that the Human Medicine curriculum of Bern is successful and well established. Challenges to a continuously developing curriculum within the national frameworks and structures, and within our university that aims to adapt to new requirements flexibly, are being approached in a constructive way. Both within the faculty and the University, there is a will to maintain professional expertise and there are the means to keep up the quality of this curriculum with its longstanding tradition.

### Committees for undergraduate medical education



# SCHOOL OF DENTAL MEDICINE



The **zmk bern (ZMK Bern)** is one of the few schools of dental medicine in the world offering a fully integrated interdisciplinary synoptic program.

- a report of academic research (e.g. clinical trial protocol), or
- a fully elaborated e-learning case.

The course of studies in dental medicine is based on the detailed national curriculum for dental medicine. Evidence-based treatment concepts ensure the high quality of dental care in Switzerland. The Bachelor and the Master programs in Dental Medicine at the University of Bern were accredited in December 2018 by the Rectors' Conference of the Swiss Universities based on the recommendation of the Swiss Center of Accreditation and Quality Assurance in Higher Education.

After completing the master program, candidates are tested on their ability to correctly and independently perform interdisciplinary treatment on patients as well as on their theoretical and analytical competence. Furthermore, they have to present a Master thesis that can consist of either

- an academic discussion of a topic relevant to dentistry
- an extended case study involving at least one case and relevant literature (evidence-based)



**Swiss national examination in dental medicine**

Upon completion of the Master degree, candidates have to take the Swiss National Examination in dental medicine. Since 2011, the examination has been based on a multiple-choice test that is conducted simultaneously nationwide. The qualifications required by the national syllabus ensure a national standard of high quality.

The numbers of students and the male/female ratios are listed in the table below.

After the Master degree is awarded and the Swiss National Examination in dental medicine has been passed, the young dentists are qualified to treat patients independently in private practice.

After the Master degree is awarded and the Swiss National Examination in dental medicine has been passed, the young dentists are qualified to treat patients independently in private practice.

In 2018, 34 of 35 candidates successfully passed the Master exam as well as the Swiss National Examination in dental medicine.

**Number of students 2018 (year 3-5)**

	female	male	total
<b>Spring 2018</b>	56 (54.37%)	47 (45.63%)	<b>103</b>
<b>Fall 2018</b>	65 (59.63%)	44 (40.37%)	<b>109</b>





## BACHELOR AND MASTER PROGRAM IN PHARMACY

Substantial progress was made in 2018 on the detailed planning of the new 3<sup>rd</sup> year of the Bachelor program in Pharmaceutical Sciences (at the Faculty of Sciences) and on the definition of the structure and focus of the Master program in Pharmacy (at the Medical Faculty). The ambitious time schedule for the start of the 3<sup>rd</sup> year Bachelor in the autumn semester 2019 and of the Master program in the autumn semester 2020, will be met.

The 3<sup>rd</sup> year of the Bachelor course covers basic pharmaceutical subjects, including Pharmaceutical Chemistry, Pharmaceutical Technology, Pharmaceutical Biology, and Pharmacology. In addition, subjects such as Clinical Chemistry, Epidemiology, and Nutrition will be included. The subject of Pharmaceutical Technology (Galenics) presented a special challenge. A newly created Full Professorship in Pharmaceutical Technology as well as the necessary laboratory infrastructure both for the professor's own research group and for students' practical courses were needed. The Full Professor position for Pharmaceutical Technology and a second professorship for Pharmaceutical Chemistry, could both be filled. Planning of construction work to install the required laboratory infrastructure at the Department of Chemistry and Biochemistry is well underway. Furthermore, lecturers for all subjects were recruited, and the regulatory documents for the Bachelor program were completed.

The Full Professor position for Pharmaceutical Technology and a second professorship for Pharmaceutical Chemistry could both be filled.

The 2-year Master program in Pharmacy, which is going to be set up in the Medical Faculty, will lead to the Federal Exam in Pharmacy, hence all requirements specified in the Federal Law on Medical Personnel (MedBG) and in the Swiss learning catalogue for Pharmacy must be covered. The main focus of the Master course in Pharmacy will be on patient-oriented education, on the role of the pharmacist in primary

healthcare, and on inter-professional collaboration with other healthcare professionals. In order to realize the latter focus, the University has agreed to create a new Professorship in Primary Healthcare in Pharmacy and Medicine. This professorship will be shared by a pharmacist and a physician whose task is the development of a teaching and research program in interprofessional collaboration for primary healthcare. This shared professorship will be unique in Switzerland and is also welcomed by the pharmacists' and medical associations of the Canton of Bern.



In the first year of the Master course, subjects taught in the Autumn semester will include common diseases and their pharmacotherapy, health promotion and disease prevention, and the Swiss health system as well as health and pharmacoconomics. In the Spring semester, students carry out their 6-month master's thesis. In the second and final year of the Master course, students will be placed in public pharmacies (in cooperating pharmacies) for a period of 30 weeks of practical training. Before and during the practical training, the subjects taught will include clinical pharmacy and pharmaceutical care, diagnosis and treatment of common diseases, and clinical skills including vaccination. The detailed content of the modules and lectures is now being developed in close collaboration with institutes of the Medical Faculty (BIHAM, IML, ISPM), clinics of the Inselspital, and pharmacists. This close collaboration should ensure a high-quality, patient-oriented education for our future generations of pharmacists.

## MASTER PROGRAM IN BIOMEDICAL SCIENCES

Since many years, Swiss academic institutions and companies doing research have faced a considerable shortage of biomedical scientists. This problem has been generally compensated by employing researchers from abroad. Having the goal to ease this situation, universities have multiplied the educational opportunities in life sciences and biomedicine in recent years. Among these efforts, the Biomedical Science studies of the Universities of Fribourg (Bachelor) and Bern (the consecutive Master) have played a pioneering role. Established 2006, the joint curriculum of the two universities remains unique in Switzerland as it is focused on exposing the students to a translational teaching environment involving both basic and medical sciences. To achieve this goal, the first study year is dedicated to forming a firm foundation in natural science while, in the second year, students share the curriculum of medical students, thereby acquiring important knowledge of human anatomy, physiology and biochemistry. During the third and the fourth years, students participate in a systematic introduction into the pathophysiology of all organ systems with lecturers who are associated with basic science research institutions, the university hospital and pharmaceutical companies. Going beyond imparting translational knowledge, students are presented with state-of-the-art research methodologies using different formats (lectures, practical courses and 3-week

visits to research laboratories of their choice). The Master Thesis at the end of the students' studies is conducted in a laboratory of their choice and also includes collaborative projects with industry. Based on the specific design of the curriculum, graduates in biomedical sciences have an exquisite and broad portfolio of both knowledge and skills at the interface between basic sciences and clinical research that endorses their qualification to participate successfully in basic, translational and clinical research. It is, therefore, not surprising that Masters in Biomedical Sciences are in high demand for doctoral positions in academia and for research positions in the industry. When looking to the future, we feel that the broad education offered by the Biomedical Science curriculum will also form a solid basis for participating in presently emerging new research fields such as artificial intelligence and personalized medicine. Since awarding the first diplomas in 2011, 156 students have graduated in Biomedical Sciences in the Medical Faculty of the University of Bern with the best 3 Master's degrees of each year being honored by a generous prize from CSL Behring. A further prize for the best Master thesis is provided by the Biomedical Science Alumni organization that exists since 2013 and is highly active in providing educational events and career counseling to students (<http://biomedicalsciences.ch/>).



# MASTER PROGRAM IN BIOMEDICAL ENGINEERING

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Master Thesis  
Coordinator

## Introduction

In the academic year 2018/19, 57 regular and 2 exchange students were admitted to our master's program in Biomedical Engineering. 43 biomedical engineers graduated from the program in 2018. Hallmarks of our program remain the proximity to the local hospital network, a focus on research oriented towards clinical applications, the "internationality" with all mandatory courses in English, compatibility of the study calendar with a part-time job, and accessibility to bachelor students from universities as well as universities of applied sciences.

## Curriculum

The full-time study program offered in cooperation with the Bern University of Applied Sciences takes 4 semesters, but can be extended to a maximum of 6 semesters. To support regular part-time work, mandatory courses take place on only 3 days per week.

## Preparation Courses

Our program's interdisciplinary nature mirrors our students' diverse backgrounds. Especially students with a non-engineering background, e.g. in medicine, biosciences or related fields, may not fulfil all course prerequisites. Therefore, preparation courses in MATLAB, Programming, Electrical Engineering, Engineering Mechanics, and Mathematics were introduced to bridge knowledge gaps.

## Basic Modules

The basic modules Human Medicine, Applied Mathematics, and Biomedical Engineering provide students with the basic knowledge and tools to master the more complex subject matter in the specialized courses.

## Major Modules as Specialization

While all basic modules are mandatory, the choice between the major modules Biomechanical Systems, Electronic Implants, or Image-Guided Therapy constitutes the first opportunity for specialization. The overall concept gives rise to a high degree of diversity and flexibility. It allows for numerous course combinations, thus making choices with regard to personal preferences and professional prospects possible.



Marc Stadelmann concentrating on an experiment.  
Picture: Adrian Moser, 2017.



### **Module Complementary Skills**

Apart from the rapid development of technology itself, today's biomedical engineers are increasingly challenged by complementary issues such as ethical aspects, project planning, quality assurance and product safety, legal regulations and intellectual property rights, as well as marketing aspects. Language competence in English is of paramount importance both in industrial and academic environments. In the module, Complementary Skills, students select courses like Innovation Management, Regulatory Affairs and Patents, Ethics in Biomedical Engineering, Scientific Writing in Biomedical Engineering, Introduction to Epidemiology and Health Technology Assessment.

### **Master's Thesis**

The final semester is dedicated to a master's thesis project on an individually suited topic in an academic research group at the University of Bern or the Bern University of Applied Sciences or, also for particular cases, in an industrial R & D department.



Iwan Paolucci, RMS award winner 2018, is networking at the Biomedical Engineering Day. The 2018 event attracted almost 300 students, researchers, alumni, and company representatives. Picture: Adrian Moser, 2018.

# CAS, DAS AND MAS DEGREE PROGRAMS

## HUMAN MEDICINE

The Medical Faculty of the University of Bern presents several CAS, DAS and MAS titles in various areas of Human Medicine: [http://www.medizin.unibe.ch/dienstleistungen/rechtssammlung/weiterbildung/index\\_ger.html](http://www.medizin.unibe.ch/dienstleistungen/rechtssammlung/weiterbildung/index_ger.html)  
[www.zuw.unibe.ch](http://www.zuw.unibe.ch)

### **Public Health (CAS / DAS / MAS)**

This program is hosted by the medical faculties of the universities of Basel, Zürich and Bern. The main goal is to provide key skills to future Public-Health-Professionals. The program consists of the "CAS in Epidemiology and Biostatistics", "CAS in Health Promotion and Prevention", "CAS in Health Systems" and "CAS in Health Economy and Health Economic Evaluation". These 4 CAS lead to the MAS in Public Health.

<https://www.public-health-edu.ch/mas>

### **Hepatology (CAS / DAS)**

Liver diseases are frequent and complex. If the patients fail to receive the correct therapy, they are at risk to develop severe complications. In this CAS/DAS, one learns by working in an excellent liver unit embedded in a multidisciplinary clinic about diagnosis, management and treatment of patients affected by liver disease.

[http://www.unibe.ch/unibe/portal/content/e152701/e332574/e344598/e623092/wb\\_rgl\\_hepatologie\\_ger.pdf](http://www.unibe.ch/unibe/portal/content/e152701/e332574/e344598/e623092/wb_rgl_hepatologie_ger.pdf)

### **Experimental and Translational Nephrology (CAS / DAS)**

The continuous education program Translational Nephrology provides extensive insights into the basics of nephrology by studying the physiological and pathophysiological of kidney function in health and disease. The program is intended for national and international graduates with a natural- and medical science background who are interested in basic- and clinical- renal research.

<http://www.nephrologie.unibe.ch/>

### **Sleep, Consciousness and Related Disorders (CAS)**

The CAS in Sleep, Consciousness and related disorders program provides medical and scientific insight into sleep medicine. An international team of specialist lecturers ensure that course subject matter is on the latest scientific knowledge. The course offers a variety of efficient learning methods, such as classroom lectures, seminars and remote online learning. The CAS is intended for professionals with a degree in health related disciplines, natural science or engineering who wish to gain an in-depth knowledge of sleep medicine.

<http://www.asc.unibe.ch/>

### **Clinical Nutrition (CAS)**

The Certificate of Advanced Studies in Clinical Nutrition is a cooperation between the « Gesellschaft für Klinische Ernährung der Schweiz » (GESKES) and the Medical Faculty. The main goal is the promotion of evidence-based knowledge and training in Clinical Nutrition for physicians, nutritionists, nurses, pharmacists and nutritional scientists. The teaching program is given in the form of lectures, practical sessions, case studies, self-directed learning, seminars and workshops.

<http://www.geskes.ch/>

The Medical Faculty's Department of Continuing Education conveys practice-oriented knowledge based on state-of-the-art scientific research, and is designed for people with a University degree and professional experience.

### **Spiritual Care**

The Certificate of Advanced Studies in Spiritual Care is a cooperation between the Theological Faculty, the Faculty of Human Sciences and the Medical Faculty. The main goal is a reflected and professional handling of spiritual topics.

[http://www.theol.unibe.ch/weiterbildung/cas\\_spiritual\\_care/index\\_ger.html](http://www.theol.unibe.ch/weiterbildung/cas_spiritual_care/index_ger.html)



### **Interprofessional Specialized Palliative Care (CAS)**

The main goal of this advanced training course is to present palliative care knowledge to physicians, nurses and other health professionals. Students receive further education as specialists allowing them to play a leading or supporting role in specialized palliative care teams.

<http://www.palliativzentrum.insel.ch/de/palliivakademie/cas-interprofessionelle-spezialisierte-palliative-care/>

### **Continuing education programs in exercise therapy in sports and medicine (CAS/DAS)**

The continuing education programs in exercise and sports therapy provides extra-occupational, practice-oriented and theory-supported further education for movement and sports therapy of disease, including cardiovascular disease, diabetes, and cancer.

The programs are aimed at graduates with a bachelor's and / or master's / licentiate's degree in sports and physical education, a bachelor's degree in health sciences and technology, as well as dipl. Gymnastic and sports teachers I / II, dipl. Physiotherapist, dipl. Physical education teacher FH. Offered are the Diploma or Certificate of Advanced Studies Swiss Exercise Therapy in Sports and Medicine (DAS / CAS SwissETSM Unibe) and the specific Certificate of Advanced Studies Swiss Cardiovascular and Diabetes Therapy (CAS SwissCDT Unibe). [www.sportmedizin.insel.ch/uni-bern-module](http://www.sportmedizin.insel.ch/uni-bern-module)

### **Exercise and sports therapy in orthopedics, rheumatology and traumatology (CAS ORT)**

The further education in movement and sports therapy for orthopedics, traumatology and rheumatology provides theoretical and practical basis for movement therapy interventions in patients with orthopedic, rheumatological and traumatological disorders for inpatient and outpatient rehabilitation as well as for secondary prophylaxis.

[https://svgs.ch/wp-content/uploads/2018/12/broschuere-cas-ort\\_2019-2020.pdf](https://svgs.ch/wp-content/uploads/2018/12/broschuere-cas-ort_2019-2020.pdf)

### **Exercise and sports therapy for mental illness (CAS PSY)**

The CAS movement and sports therapy for the treatment of mental illness provides a theoretical and practical basis for movement and sport therapy interventions in patients with mental illness for inpatient and outpatient rehabilitation as well as for secondary prophylaxis.

[https://svgs.ch/wp-content/uploads/2018/10/broschuere-cas-psy\\_2019.pdf](https://svgs.ch/wp-content/uploads/2018/10/broschuere-cas-psy_2019.pdf)

### **Master of Medical Education (MAS)**

The Master of Medical Education program in Bern is based on a systematic and evidence-based approach. The main goal is to acquire the required skills in order to meet future challenges in medical teaching.

<https://www.iml.unibe.ch/angebote/lehre/master-of-medical-education-mme>

### **Clinical Research in Health Care Organisations (CAS)**

The Certificate of Advanced Studies in Clinical Research is coordinated by the Institute of Social and Preventive Medicine. The main goal is to learn how to plan and conduct clinical research projects and how to communicate their results.

[www.cas-clinicalresearch.ch](http://www.cas-clinicalresearch.ch)

### **Leadership in Healthcare Organisations (CAS)**

This Certificate of Advanced Studies is coordinated by the Institute of Social and Preventive Medicine. It conveys leadership competence-oriented towards health care organizations and focuses on appropriate forms of the integration of medicine and management.

<https://www.cas-leadership.ch/>

### **Managing Medicine in Health Care Organisations (CAS)**

This Certificate of Advanced Studies is coordinated by the Institute of Social and Preventive Medicine. The CAS provides management competence for health care organizations and an understanding of organized health care against the background of the rapid changes in medicine.

[http://www.ispm.unibe.ch/continuing\\_education/cas\\_managing\\_medicine/index\\_eng.html](http://www.ispm.unibe.ch/continuing_education/cas_managing_medicine/index_eng.html)

## CAS, DAS AND MAS DEGREE PROGRAMS

### **Leading Learning Medical Organisations (MAS)**

The three „CAS Leadership in Health Care Organisations, „CAS Managing in Health Care Organisations“ and the „CAS Clinical Research“ leads to the „Master of Advanced Studies in Leading Learning Medical Organisations, Universität Bern“. [http://www.ispm.unibe.ch/continuing\\_education](http://www.ispm.unibe.ch/continuing_education)

### **Translation and Entrepreneurship in Medicine (CAS / DAS / MAS)**

These continuous education programs are coordinated by the Swiss Institute for Translational and Entrepreneurial Medicine in Bern (sitem-insel). The sitem-insel School aims to promote researchers and train executives in the fields of translational medicine and biomedical entrepreneurship. Participants are expected to acquire the necessary skills to initiate and implement the translation process from the stage of development in industry or basic science institutions into clinical applications with the ultimate purpose of commercialization. Participants should have a MS or higher degree in life sciences, medicine, biomedical engineering or equivalent. For the MAS they should in addition submit a proposal for a translational medicine project on which they will work during the MAS. <https://sitem-insel.ch/en/school/program>

## DENTISTRY

The Medical Faculty of the University of Bern presents six MAS-titles in various areas of Dentistry: [http://www.zmk.unibe.ch/weiterbildung/weiterbildung/master\\_of\\_advanced\\_studies/index\\_ger.html](http://www.zmk.unibe.ch/weiterbildung/weiterbildung/master_of_advanced_studies/index_ger.html)

### **Master of Advanced Studies in Implant Dentistry (MAS IMP)**

A 3-year, full-time program (180 ECTS), which combines all surgical and prosthodontic aspects of implant dentistry. The postgraduate students usually spend one year in the Department of Oral Surgery and two years in the Department of Reconstructive Dentistry and Gerodontology.

### **Master of Advanced Studies in Orthodontics and Dentofacial Orthopedics (MAS ORTHO)**

A 4-year, full-time program (240 ECTS), which aims to provide dentists with a solid evidence-based academic education and broad, high-level clinical training in order to become specialists in Orthodontics and Dentofacial Orthopedics.

### **Master of Advanced Studies in Cariology, Endodontology and Pediatric Dentistry (MAS REST)**

A 3-year, full-time program (180 ECTS), which teaches postgraduate students theoretically and clinically in evidence-based cariology and restorative dentistry, endodontology as well as pediatric dentistry. The structured curriculum consists of weekly lectures and seminars as well as daily clinical training supervised by experienced instructors.

### **Master of Advanced Studies in Oral and Implant Surgery (MAS ORALSURG and IMPSURG)**

A 3-year, full-time program (180 ECTS), which provides a thorough and comprehensive clinical and theoretical training in all aspects of oral surgery as well as the surgical aspects of implant dentistry. The postgraduate students follow a strict curriculum with a gradually increasing level of difficulty and challenge according to SAC-classifications.

### **Master of Advanced Studies in Periodontology and Implant Dentistry (MAS PER and IMP)**

A 3-year, full-time program (180 ECTS) aiming to provide dentists with a broad high-level clinical training in periodontology and implant dentistry as well as a solid evidence-based academic education in order to become specialists in Periodontology.

### **Master of Advanced Studies in Reconstructive and Implant Dentistry (MAS REC and IMP)**

A 3-year, full-time program (180 ECTS), which integrates advanced clinical and theoretical training in reconstructive dentistry/ dental implant therapy and its associated disciplines within a strict and structured curriculum. The MAS REC and IMP Unibe provides the basis with which a dentist can become a Swiss federal specialist in Reconstructive Dentistry SSO.







## PHD EDUCATION

The Medical Faculty is associated with two graduate schools offering structured doctoral programs:

- the Graduate School for Cellular and Biomedical Sciences (GCB); <http://www.gcb.unibe.ch/>
- the Graduate School for Health Sciences (GHS); <http://www.ghs.unibe.ch/>

In addition to the Faculty of Medicine, the GCB is also supported by the Faculty of Science and the Vetsuisse Faculty, while the Faculty of Human Sciences is supporting the GHS.

Both graduate schools offer research-oriented curricula with a wide choice of courses and special workshops tailored to the individual interests and

needs of PhD candidates. The focus is on the individual thesis projects where the candidates get the best possible support from an expert supervisory committee in their respective research area. In addition, emphasis is put on high-quality training in research methods and study design, which is ensured by the provision of appropriate courses.

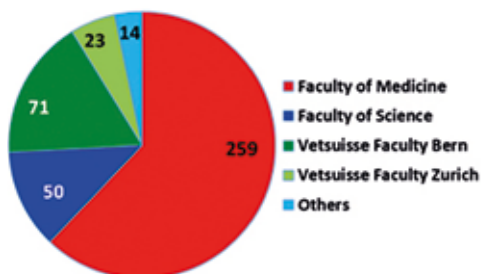
The PhD programs direct the candidates towards independent scientific work and enable them to assume scientific responsibility.

### MD-PhD fellowships

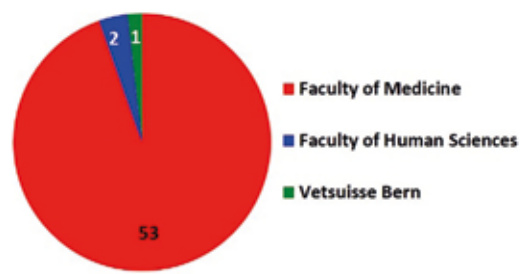
The MD-PhD-studies are supported by competing scholarships of the SNSF and SAMW.



### Number of participants on 31.12.2018



417 within the GCB  
Others: 6 from IRB Bellinzona; 5 from Biotechnology Institute Thurgau; Kreuzlingen; 1 AO Research Davos; 1 RMS Foundation Bettlach



56 within the GHS

### Number of PhD degrees in 2018

Type of Degree	F	M	Total
MD,PhD	2	4	6
DVM,PhD	8	1	9
PhD in Biomedical Engineering	4	8	12
PhD in Biomedical Sciences	12	11	23
PhD in Immunology	6	3	9
PhD in Neuroscience	0	3	3
PhD of Science in Biochem. & Mol.Biol.	15	8	23
PhD of Science in Cell Biology	6	3	9
<b>Total</b>	<b>53</b>	<b>41</b>	<b>94</b>

94; 56 of them were from the Faculty of Medicine  
Prize for best PhD degree: Anina Bauer, Vetsuisse Bern.

Speciality area; PhD in Health Sciences	F	M	Total
Clinical Epidemiology and Biostatistics	1		1
Epidemiology	1		1
Sports & Medicine		1	1
Cardiology		1	1
Medical Education	2	1	3
Neurosciences	5	2	7
<b>Total</b>	<b>9</b>	<b>5</b>	<b>14</b>

14; all of them were from the Faculty of Medicine



## GRADUATE SCHOOL FOR CELLULAR AND BIOMEDICAL SCIENCES

### Focus

Training in experimental research with state of the art methods in molecular life sciences, biomedical sciences and biomedical engineering. Research areas include cell biology, biochemistry, molecular biology, immunology, genetics, biomedical sciences, epidemiology as well as tissue engineering and computer-assisted surgery. GCB also offers two areas of specialization: „Cutting edge microscopy“ & „Stem Cell Research in Regenerative Medicine“.

### Requirements

Master's degree in molecular life sciences, biomedicine, medicine, biomedical engineering or a related field depending on the project.

### Program structure

*Five expert committees*

- Biological Systems
- Biomedical Sciences
- Cell Biology
- Molecular Biology/Biochemistry
- Biomedical Engineering

*Thesis committee*

Each candidate is supported by a thesis committee consisting of supervisor, co-advisor and a member of an expert committee as mentor.

*Intermediate assessment*

During the mid-term evaluation, the doctoral candidates present their research data in the form of a seminar where the requirements for a successful completion is determined.

### Awarded PhD titles

- PhD of Science in Cell Biology
- PhD of Science in Biochemistry & Molecular Biology
- PhD in Biomedical Sciences
- PhD in Immunology
- PhD in Neuroscience
- PhD in Biomedical Engineering

### Curricula for medical doctors

*MD-PhD program*

The focus is on basic sciences, but the PhD candidates can spend 20% of their time in the clinic. Graduates receive one of the following titles:

- MD,PhD (Doctor of Medicine and Philosophy)
- DDS,PhD (Doctor of Dentistry and Philosophy)
- DVM,PhD (Doctor of Veterinary Medicine & Philosophy)

## GRADUATE SCHOOL FOR HEALTH SCIENCES

### Focus

Studies of social, psychological, physiological and environmental factors that determine the health of individuals and populations, as well as the effects of these factors on physical and mental health. Both basic and applied research deals with topics from the fields of epidemiology, social medicine, psychology, neurosciences and clinical sciences. Within the GHS, participation in the PhD program of the Swiss School of Public Health (SSPH+) is possible.

### Requirements

Master's degree in psychology, medicine, biomedicine, epidemiology, geography, sport science or other fields depending on the respective research project.

### Program structure

*Three expert committees*

- Medical Education, Preventive and Social Medicine, Public Health, Psychology and Rehabilitation
- Neurosciences
- Clinical Sciences

*Thesis committee*

Each candidate is supported by a supervisor and a co-referee.

*Intermediate assessment*

Two intermediate evaluations after the 1 and 2 year are required, offering an opportunity to document and discuss the candidate's progress and assessing what is still necessary for the successful completion of their doctoral studies.

### Awarded PhD titles

- PhD in Health Sciences (specialist area)

### Curricula for medical doctors

*PhD in Clinical Sciences; 50:50 model*

Patient-oriented research and clinical career. The PhD candidates work 50% in research and 50% in the clinic. Graduates receive the title:

- PhD in Health Sciences (Clinical Sciences)

# GRANTS

## **Graduate School in Health Science (GHS)**

Health Sciences, Cognitive Neurosciences, Clinical Sciences

Career stage: young MD's (open to other health professionals, psychologist, biologists, engineers)

Duration: 3–5 years

Number of calls/year: for Clinical Sciences: 1x per year, otherwise continuously

Funding source: Medical Faculty

## **Graduate School for Cellular and Biomedical Sciences (GCB)**

Career stage: biologists, engineers, MedVet, MD's

Duration: 3–4 years

Number of calls/year: continuously

Funding source: Medical Faculty

## **CTU Grants**

Career stage: MD's before Habilitation

Duration: 1.5 years

Number of calls/year: 2x per year

Funding source: University Hospital

## **Uni Bern Initiator Grant**

Career stage: postdocs and young PI

Number of calls/year: 2x per year

Funding source: University

Additional Information: open to all disciplines; support for proposals for third-party funded career schemes (SNF mobility fellowships, Ambizione, SNSF-professorship; EU Marie-Curie-S. fellowships, ERC grants, etc.)

## **Numerous Foundations**

Career stage: during BSc or MSc

Duration: 1–5 years

Number of calls/year: 1x per year

Funding source: Foundations

Additional Information: open for students registered at University of Bern in academic years 2–6

## **Travel Grants**

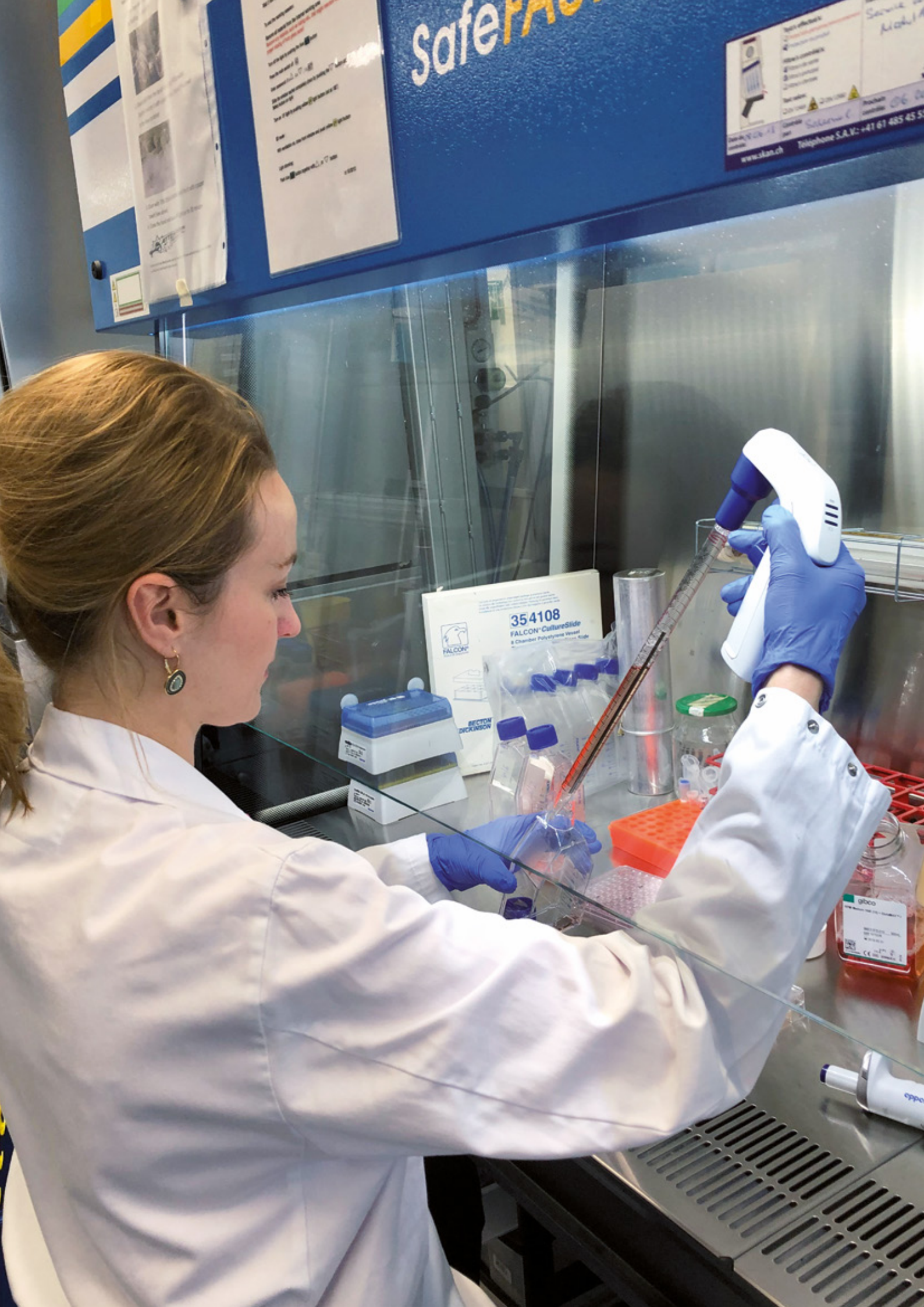
Career stage: during BSc or MSc

Duration: 1–6 years

Number of calls/year: continuously

Funding source: Dean's office

Additional Information: open for students registered at University of Bern in academic years 1–6





# GENDER EQUALITY IN THE MEDICAL FACULTY

Murtenstrasse 11  
3008 Bern



Prof. Britta Engelhardt  
President and Representative of the Pre-Clinic



Prof. Gabriela M. Baerlocher  
Representative of the Association of Lecturers of the University of Bern



PD Dr. Lukas Brügger  
Representative of the Clinic



PD Dr. Nadia Corazza  
Representative of the Service Institutions



Prof. Martin Schimmel  
Representative of the School of Dental Medicine



Dr. Kristina Tänzler  
Representative of the Association of Swiss Assistant and Senior physicians (VSAO)



Delia Kläger  
Representative Students SUB



Lilian Fankhauser  
Co-Head Office for Gender University of Bern



Svea Lehmann  
Coordinator Office for Gender Equality Medical Faculty



Prof. Christine Peinelt  
Representative NCCR TransCure

## Research Partners

- Office for Gender Equality (AfG), University of Bern, Bern, Switzerland
- NCCR Transcure Bern, Bern, Switzerland
- Vice Rectorate for Gender Equality of the University of Bern, Bern, Switzerland
- Coordinators of the Office for Gender Equality, Bern University Hospital, Bern, Switzerland
- Coordinators of the Office for Gender Equality of all Faculties of the University of Bern, Bern, Switzerland
- Coordinator of the Office for Gender Equality of the University of Zürich, Zürich, Switzerland
- Coordinator of the Office for Gender Equality of the University Hospital of Basel, Basel, Switzerland

## Profile

The Medical Faculty Commission for Equality (Innerfakultäre Kommission für die Gleichstellung, IFKG) supports the Medical Faculty in realizing measures ensuring effective equality of women and men. Together with the decision-makers of the institutes and clinics, the IFKG aims to improve conditions that facilitate the decision for women to pursue an academic career. The immediate aim is an increase of the number of women in leadership positions in the Medical Faculty. Among other measures, the IFKG aims to illustrate career options

that improve working conditions such that they allow both women and men to combine their family life with their academic career pathway.

To achieve these ambitious goals in an efficient way, the Medical Faculty has employed Mrs. Svea Lehmann as Coordinator for the Gender Equality Office since the end of 2017. In her work, she supports and coordinates the IFKG and works closely together with the different stakeholders in the gender equality field within the University of Bern and the Inselspital. To this end Mrs. Lehmann can make use of her 10 years' experience at the Inselspital, where together with the medical director, she has standardized the process established for the recruitment of clinical directors and professors.

Together with the Department of Gender Equality of the University Bern, an equality plan was developed in 2016. This Gender Equality plan contains a variety of measures, which are continuously completed and revised ([http://www.medizin.unibe.ch/unibe/portal/fak\\_medizin/content/e17216/e110779/e470466/Gleichstellungsplan\\_MedFak\\_2016-19\\_PUBLIC\\_ger.pdf](http://www.medizin.unibe.ch/unibe/portal/fak_medizin/content/e17216/e110779/e470466/Gleichstellungsplan_MedFak_2016-19_PUBLIC_ger.pdf)).

The Gender Equality plan allows a first impression of the daily business of the IFKG that extends beyond to additional activities not mentioned here.



## Highlights 2018

During 2018, the IFKG has taken the initiative to bring together different stakeholders responsible for gender equality of the University of Bern and the Inselspital to quarterly conversations. The overall goal of these “Quartalsgespräche” is to define and then eliminate the reasons leading to the significant lack of women in leading positions at the Inselspital and the Medical Faculty. The first meeting took place and was a success. In addition to exchanging information, participants initiated first actions aiming to optimize career tracks and to improve the establishment of gender mixed teams. The meetings will continue to take place in a quarterly rhythm allowing to control realization and success of each measure and to launch novel initiatives.

In response to an initiative of the medical students, the IFKG has set up a framework to revise the “Problem Based Learning” cases used in the preclinical teaching of the medical students, with regard to gender equality, language and modern gender relations. All reviewers received guidelines to support their work. In addition, Mrs. Kläger, the student representative of the IFKG, has taken over the final proofreading.

The year 2018 was again marked by successful continuation of the Mentoring for Women (M4W) program. Emphasis of M4W is the personal interaction of an experienced mentor with the mentee allowing for personalized advice with respect to the career stage of the respective mentee.



The M4W herewith takes into account the narrow time budget of the mentors and mentees and thus waives the requirement of completing additional courses and trainings. In addition, the mentees can choose the starting time of the program on an individual basis, further underlining the highly individual character of the program. At the same

time, the IFKG has intensified the interaction with the coordinators for other mentoring programs at the University of Bern, allowing to improve for all mentees the access to high quality training and career planning as well as to stimulate networking.

Another project of the IFKG, which has started during the past year, is informing the department heads and raising awareness on “unconscious gender bias”. The unconscious gender bias is a social stereotype that is still deeply anchored in our society and awareness of its existence needs to be raised to counteract its inhibitory effects on the career advancement of women. Together with the Office for Gender Equality of the University of Bern, the IFKG has therefore started a video project called “Professorin gesucht”, which will be implemented in 2019 ([https://www.unibe.ch/universitaet/portraet/selbstverstaendnis/gleichstellung/schwerpunkte/anstellungsverfahren/index\\_ger.html](https://www.unibe.ch/universitaet/portraet/selbstverstaendnis/gleichstellung/schwerpunkte/anstellungsverfahren/index_ger.html))



Video «Professorin gesucht»: In a promotion interview a female candidate was recently asked, if she wants to become a mother in the next few years. The supervisor would never have asked a man!

# ARTORG Center for Biomedical Engineering Research

Murtenstrasse 50  
3008 Bern



Prof. Stefan  
Weber  
IGT



Prof. Olivier  
Guenat  
OOC



Prof. Stavroula  
Mougialakou  
DTR



Prof. Laura  
Marchal-Crespo  
GER



Prof. Tobias  
Nef  
GER



Prof. Dominik  
Obrist  
CVE



Prof. Raphael  
Sznitman  
OTL



Dr. Wilhelm  
Wimmer  
HRL

## Research Partners

- Angiology (Iris Baumgartner)
- Cardiology (Stephan Windecker)
- Cardiovascular Surgery (Thierry Carrel)
- Diagnostic and Interventional Neuroradiology (Jan Gralla)
- Diagnostic, Interventional and Paediatric Radiology (Johannes Heverhagen)
- Intensive Care Medicine (Stephan Jakob, Jörg Schefold)
- Nephrology and Hypertension (Bruno Vogt)
- Neurology (René Müri, Claudio Bassetti, Julia Müllner)
- Neurosurgery (Andreas Raabe)
- Neuroradiology (Jan Gralla, Roland Wiest)
- Ophthalmology (Sebastian Wolf)
- Orthopaedics (Klaus Siebenrock)
- Otolaryngology, Head and Neck Surgery (Marco Caversaccio, Martin Kompis)
- Pulmonary Medicine (Thomas Geiser)
- Thoracic Surgery (Ralf Schmid)
- Visceral Medicine and Transplantation Surgery (Daniel Candinas, Guido Beldi,)
- Diabetes, Endocrinology, Nutritional Medicine and Metabolism (Christoph Stettler, Zeno Stanga)
- Psychiatry and Psychotherapy of Old Age (Stefan Klöppel)
- NeuroCenter Siloah (Jean-Marc Burgunder)
- Kantonsspital Luzern (Tim Vanbellingen)

## Structure and Research Profile

The ARTORG Center has seven research teams:

- OOC - Biomimetic Organs-On-Chip for preclinical and precision medicine applications
- DTR - AI for diabetes patient empowerment
- HRL - Diagnose and treat inner ear diseases
- IGT – Image-guided, robotics-enabled precision surgical and interventional therapies
- GER - Robotic training strategies for neuro-rehabilitation of brain injured patients; Virtual reality, tele-rehabilitation and assistive technologies for neurocognitive disorders
- CVE - Novel diagnostic and therapeutic approaches for cardiovascular diseases
- OTL - AI-enabled ophthalmic diagnostics and therapeutics

## Teaching Profile

The center contributes to the Master's degree program in Biomedical Engineering. The postgraduate program currently has 45 full-time PhD students at the interface between technical and medical disciplines.

## Highlights 2018

The Organs-on-Chip Technologies Group with its partners (Insel, Helmholtz Saarbrücken, Völklingen Heart Center,

University of Ulm and AlveoliX AG) reported a unique breathing lung-on-a chip, capable of maintaining functional primary alveolar cells from patients to predict efficacy and safety of drug candidates.



The lung-on-chip with 6 independent alveolar barrier systems filled with cell culture medium.

The Diabetes Technology Group develops AI-based nutrient calculation for diabetes management and detection of malnutrition during hospitalization. An AI-based, personalized insulin treatment was validated according to FDA standards.



The AI-based algorithm, integrated into a highly secured Android smartphone, takes input from either a blood glucose meter or a continuous glucose monitor, and outputs the daily insulin profile. The algorithm learns while used by the patient and is able to provide personalized advice on the insulin treatment.

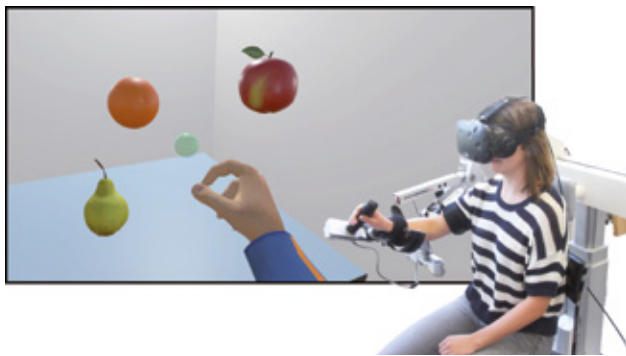
Cardiovascular Engineering continued a collaboration with CorFlow therapeutics AG towards a novel catheter-based approach for the diagnosis and treatment of microvascular obstructions of the heart muscle.

The Hearing Research Laboratory started two observational studies to investigate new diagnostic approaches for hearing

impaired patients and persons suffering from tinnitus in collaboration with leading industrial partners.

The Image-Guided Therapy group and its clinical partner Insel-ENT concluded the world's first clinical trial in robotic cochlear implantation (9 patients enrolled). A navigated positioning of ablation probes using intrahepatic tumour referencing and electromagnetic guidance was developed together with Insel Visceral Surgery (Prof. Dr. Daniel Candinas). Work towards Intelligent Sensor-enhanced Robotic Neurosurgery has started together with Insel Neurosurgery.

The GER group reported improvements of its exoskeleton ARMin technology (with Reha Rheinfelden) for use in patients at different stages of recovery. The use of AR and VR technology to reduce cognitive loads of stroke patients during robotic therapy with the ArmeoSpring device was investigated in collaboration with the Insel Neurology.



Subject performing arm training with support from the therapy robot Armeo®Spring (Hocoma, Switzerland). The training task is visualized in immersive virtual reality using a head-mounted display (HTC Vive, USA)

The clinical study "VR stimulation in the ICU" showed that VR stimulation is a safe and effective intervention for neurocognitive late effects in critically ill patients. The project "Puzzling the Mind" has entered testing phase in collaboration with the Swiss Huntington Center, NeuroCenter Siloah, Insel Neurology, and Kantonspital Luzern.



A patient receiving VR stimulation in an ICU setup. Physiological parameters are also measured in real-time to adapt the content of the stimulation thus influencing the visual attention of the patient.

The OTL group in collaboration with the Department of Ophthalmology has developed AI-based technology that analyzes optical coherence tomography data during retinal laser treatment to determine effective treatment dose for dosimetry control of novel laser technology that treat conditions like Diabetic Retinopathy.

### Selected Awards 2017-2018

- Silje Ekroll Jahren, Medtronic Young Investigators Award
- Rebecca Paladini, Clinical Neuroscience Bern Annual Meeting
- Stephan Gerber, Travel Grant, BME Club Bern
- Ya Lu, Travel Grant 4th International Workshop Multimedia Assisted Dietary Management
- Stergios Christodoulidis Free Communication Award, COST Action ENT-eR-child
- Stavroula Mougikakou Innovation prize, Diagnostic, Interventional & Pediatric Radiology, Inselspital
- Soheila Zeinali, Best Poster, IOOCS
- Pauline Zamprogno, Best Poster DBMR Research Day
- Giulia Raggi, Best MSc Thesis, Life Sciences & Technology Master, EPFL
- Nuria Roldan, Best Poster, Eurotox
- Pauline Zamprogno, Best Poster, MMB
- Olivier Guenat, Award of the Egon Naef foundation for in-vitro research
- Juan Anso, Best Video Award, Hamlyn Surgical Robot Challenge
- OTL IPCAI Best Paper Award runner-up, IPCAI
- Samuel Stucky, Best MSc Innovation Award

### Selected Competitive Grants

- H2020 ITN Marie Curie (EUROoC, 3.9€ Mio, O. Guenat)
- Novartis Foundation (kCHF 100, P. Urwyler)
- Innosuisse (Mio CHF 1'7, D. Obrist)
- Innosuisse (kCHF 425, J. Ànso)
- Innosuisse (kCHF 411, P. Urwyler)
- UniBE Initiator Grant (kCHF 19, P. Urwyler)
- UniBE ID Grant (kCHF 141, P. Urwyler)
- SNF PostDoc.Mobility Fellowship (kCHF 80, W. Wimmer)
- SNF Bridge (kCHF 112, S. Kucur)

### Selected Publications

- Stucki JD et al. Medium throughput breathing human primary cell alveolus-on-chip model. *Sci Rep.* 2018 Sep 25;8(1):14359. doi: 10.1038/s41598-018-32523-x
- Paladini RE et al. Attentional reorienting triggers spatial asymmetries in a search task with cross-modal spatial cueing. *PLoS One.* 2018 Jan 2;13(1):e0190677. doi: 10.1371/journal.pone.0190677
- Gerber SM et al. Visuo-acoustic stimulation that helps you to relax: A virtual reality setup for patients in the intensive care unit. *Sci Rep.* 2017 Oct 16;7(1):13228. doi: 10.1038/s41598-017-13153-1
- Hasler D, Obrist D. Three-dimensional flow structures past a bio-prosthetic valve in an in-vitro model of the aortic root. *PLoS One.* 2018 Mar 16;13(3):e0194384. doi: 10.1371/journal.pone.0194384
- Anthimopoulos M et al. Semantic Segmentation of Pathological Lung Tissue with Dilated Fully Convolutional Networks. *IEEE J Biomed Health Inform.* 2019 Mar;23(2):714-722. doi: 10.1109/JBHI.2018.2818620
- Vasiloglou MF et al. A Comparative Study on Carbohydrate Estimation: GoCARB vs. Dietitians. *Nutrients.* 2018 Jun 7;10(6). pii: E741. doi: 10.3390/nu10060741
- Ansó J et al. Neuromonitoring During Robotic Cochlear Implantation: Initial Clinical Experience. *Ann Biomed Eng.* 2018 Oct;46(10):1568-1581. doi: 10.1007/s10439-018-2094-7
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## Department for BioMedical Research (DBMR)

University of Bern  
Bern, Switzerland



Prof. Mark  
Rubin  
Director DBMR



Prof. Robert  
Rieben  
Directorate  
Coordinator  
Murtenstrasse  
40/50



Prof. Willy  
Hofstetter  
Directorate  
Coordinator  
MEM Building



Dr. Manfred  
Heller  
Coordinator  
Kinderklinik



Prof. Peter  
Vermathen  
Coordinator  
Erlachstrasse 9A



Dr. Monique  
Vogel  
Coordinator  
Sahli-Haus 1+2

### Structure Profile

The role of the Department for BioMedical Research DBMR is to provide its 48 research groups with optimal infrastructure and scientific support. The vast majority (43) of these groups are from clinics of the Inselspital, Bern University Hospital. The remainders (5) are internal DBMR groups, who are involved in the scientific support and coordination of equipment and infrastructure on a daily basis. Equally important, the DBMR is responsible for operating Technology and Animal Core Facilities. Furthermore, the groups of the department are supported by central services responsible for administration, informatics, technical support and bioinformatics.

### Research Partners

As research partners, we have the DBMR Research Groups:

- Anaesthesiology
- Angiology
- Audiology
- Bone Biology & Orthopaedic Research
- Cardiology
- Cardiovascular Research
- Cardiovascular Surgery
- Clinical Pharmacology (IFIK)
- Clinical Radiopharmacy
- Cranio-Maxillofacial Surgery
- Dermatology
- Endocrinology / Diabetology (Adults)
- Endocrinology / Diabetology / Metabolism (Paediatrics)
- Endocrinology of the Breast
- Endometriosis and Gynaecological Oncology
- Endometrium & Ovary
- Experimental Haemostasis
- Experimental Radiology
- Gastroenterology / Mucosal Immunology
- Hand Surgery
- Hematology (Adults)
- Hematology / Oncology (Paediatrics)
- Hepatology
- Human Genetics
- Intensive Care Medicine
- Magnetic Resonance Spectroscopy and Methodology (AMSM)
- Medical Oncology
- Molecular Biology

- Nephrology and Hypertension
- Neurology
- Neurosurgery
- Ophthalmology
- Orthopaedic Surgery
- Osteoporosis
- Pediatric Surgery
- Plastic Surgery
- Precision Oncology
- Prenatal Medicine
- Protein and Cell Biology
- Pulmonary Medicine (Adults)
- Pulmonary Medicine (Paediatrics)
- Radiation Oncology
- Rheumatology
- RNA & Cancer (NCCR RNA & Disease)
- Thoracic Surgery
- Tumor-Immunology
- Urology
- Visceral and Transplantation Surgery

### Research Profile

The Department for BioMedical Research (DBMR) of the Faculty of Medicine of the University of Bern, led by Prof. Mark Rubin, was established 25 years ago by the University of Bern and the Inselspital (Bern University Hospital). To realize its mission to bridge the gap between bench and bedside, the DBMR promotes an integrative perspective to clinical research with a strong emphasis in the development of translational approaches, the use of omics and other cutting-edge technologies, and extensive interaction and collaboration between laboratory-based and patient-oriented clinical research. The DBMR is also committed to fostering the careers of young academics.

### Teaching Profile

Most of the research groups of the department are hosting masters, PhD, MD-PhD-students, and post-doctoral fellows who are integrated in the research projects of the individual groups. PhD-students are generally enrolled in the graduate school of cellular and biomedical sciences of the University of Bern. The Department organizes progress reports, seminars, and conferences that can be credited by the PhD-students. Furthermore, all group leaders of the department participate in teaching activities.



## Highlights 2018

- In April 2018, the cornerstone of the new research building at Murtenstrasse 24 was laid during a ceremony. These premises are planned to open in 2021 and the DBMR and the Institute of Forensic Medicine of the University of Bern will co-occupy this building.
- The Johanna Dürmüller-Bol DBMR Research Award 2018 went to Dr. Stephanie Ganal-Vonarburg, Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital and Research Group Gastroenterology / Mucosal Immunology, Department for BioMedical Research, for the project „The role of maternal microbiota in durably shaping intestinal immunity and gene expression in the offspring through epigenetic mechanisms“.
- ESPE (European Society for Paediatric Endocrinology) gave an international Outstanding Clinician Award to Christa Flück of the Endocrinology / Diabetology / Metabolism (Paediatrics) group.
- Kellie Cotter from the Precision Oncology research group received a Prostate Cancer Foundation (PCF) 2018 Young Investigator Award.

## Selected Competitive Grants

- Joanna Triscott – Marie Skłodowska-Curie Individual Fellowship PCAPIP - Establishing the importance of non-canonical phosphatidylinositol kinases as cornerstones of prostate biology. MSCA EF
- SNF, Endothelial cell protection in ischemia / reperfusion injury: Investigation into the roles of the glycocalyx and the plasma cascade systems CHF 700'000, Robert Rieben
- SNF, Deciphering the Interplay of Regulatory T Cells and the Gut Microbiota in the Regulation of Myeloid Leukemia Stem Cells, CHF 663'406, Carsten Riether

## Selected Publications

- Shoag J, Liu D, Blattner M, Sboner A, Park K, Deonarine L, Robinson BD, Mosquera JM, Chen Y, Rubin MA, Barbieri CE. SPOP mutation drives prostate neoplasia without stabilizing oncogenic transcription factor ERG. *J Clin Invest.* 2018 Jan 2;128(1):381-386. doi: 10.1172/JCI96551. Epub 2017 Dec 4
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- Cotter K, Rubin MA. Sequence of events in prostate cancer. *Nature.* 2018 Aug;560(7720):557-559. doi: 10.1038/d41586-018-06029-5

- Triscott J, Rubin MA. Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression? *Cancer Discov.* 2018 Jun;8(6):682-685. doi: 10.1158/2159-8290.CD-18-0369
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- Hauser M, Siegrist M, Keller I, Hofstetter W. Bone. Healing of fractures in osteoporotic bones in mice treated with bisphosphonates - A transcriptome analysis. *Bone.* 2018 Jul;112:107-119. doi: 10.1016/j.bone.2018.04.017. Epub 2018 Apr 20
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- Riccardo Sfriso, Shengye Zhang, Colette Andrea Bichsel, Oliver Steck, Alain Despont, Olivier Thierry Guenat & Robert Rieben. 3D artificial round section microvessels to investigate endothelial cells under physiological flow conditions. *Sci Rep.* 2018 Apr 12;8(1):5898. doi: 10.1038/s41598-018-24273-7
- Längin M, Mayr T, Reichart B, Michel S, Buchholz S, Guethoff S, Dashkevich A, Baehr A, Egerer S, Bauer A, Mihalj M, Panelli A, Issl L, Ying J, Fresch AK, Buttgereit I, Mokelke M, Radan J, Werner F, Lutzmann I, Steen S, Sjöberg T, Paskevicius A, Qiuming L, Sfriso R, Rieben R, Dahlhoff M, Kessler B, Kemter E, Klett K, Hinkel R, Kupatt C, Falkenau A, Reu S, Ellgass R, Herzog R, Binder U, Wich G, Skerra A, Ayares D, Kind A, Schönmann U, Kaup FJ, Hagl C, Wolf E, Klymiuk N, Brenner P, Abicht JM. Consistent success in life-supporting porcine cardiac xenotransplantation. *Nature.* 2018 Dec;564(7736):430-433. doi: 10.1038/s41586-018-0765-z. Epub 2018 Dec 5
- Roccio M, Perny M, Ealy M, Widmer HR, Heller S, Senn P. Molecular characterization and prospective isolation of human fetal cochlear hair cell progenitors. *Nat Commun.* 2018 Oct 2;9(1):4027. doi: 10.1038/s41467-018-06334-7

## Microscopy Imaging Center (MIC)

c/o Theodor Kocher Institute  
Freiestrasse 1, 3012 Bern



Prof. Britta Engelhardt  
MIC Board  
President  
Representative of the Medical Faculty



Prof. Michael Stoffel  
MIC Board  
Representative of the Vetsuisse Faculty



Prof. Oliver Pertz  
MIC Board  
Representative of the Faculty of Science



PD Dr. Ruth Lyck  
MIC Coordinator



Dr. Guillaume Witz  
MIC Scientific Assistance  
Bioluminescence and  
BigData Specialist



Dr. Yury Belyaev  
MIC Scientific Assistance  
Light Microscopy Specialist

### Structure Profile

The MIC was founded in 2005 and has since developed into the University of Bern's center of excellence for high-end microscopy in the life sciences. Experts in microscopy from a total of 15 institutes from the Medical Faculty, the Faculty of Science and the Vetsuisse Faculty of the University of Bern and from the University of Fribourg have joined forces to provide central access to numerous high-end microscopes and imaging systems for all university members. The directive panel of the MIC is the MIC Commission, which in 2018 involved 32 representatives from the participating institutes. The steering panel of the MIC is the MIC Board consisting of the MIC chair, the representatives from the participating faculties and the MIC coordinator. In 2018, Olivier Pertz succeeded Volker Heussler as the MIC board representative of the Faculty of Science. The MIC oversees 52 instruments including 41 light microscopes, 8 electron microscopes, two atomic force microscopy systems and one micro computed tomography (micro-CT) instrument. In 2018, this equipment has benefitted 334 active users. Highly qualified scientists provide expert knowledge for a multitude of microscopic applications and support usage of the sophisticated instruments. MIC technical staff helps in choosing the appropriate instrument, offers sample preparation services and assists in handling of the microscopes. A specialist in bioimage analysis and processing of big image data gives advice on the appropriate data processing and image analysis strategy. The MIC is furthermore instrumental in identifying new technologies to be implemented at the University of Bern and thus in supporting strategic novel acquisitions for example through R'Equip programs. The service portfolio and teaching activities of the MIC as well as the yearly resources in terms of personal points are laid down in the performance mandate signed between the MIC board and the rector of the University of Bern.

### Research Partners

- Swiss Bioluminescence – Swiss Microscopy and Imaging Core Facility Network, [www.swissbioimaging.org](http://www.swissbioimaging.org)
- German Bioluminescence (GerBI) – German national network of microscopists and imaging specialists, [www.germanbioimaging.org](http://www.germanbioimaging.org)
- Euro-Bioluminescence – The European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences (Euro-Bioluminescence, EuBI or EuBI ERIC), [www.eurobioimaging.eu](http://www.eurobioimaging.eu)

- European Light Microscopy Initiative (ELMI)- Communication network between European scientists working in the field of light microscopy and the manufacturers of their equipment, [www.embl.org/elmi](http://www.embl.org/elmi)
- Neubias – The Network of European Bioluminescence Analysts, COST Action CA15124, [eubias.org/NEUBIAS](http://eubias.org/NEUBIAS)
- Science IT Support (SciTS, [www.scits.unibe.ch](http://www.scits.unibe.ch)), PD Dr. Sigve Haug, Mathematical Institute, University of Bern, Bern, Switzerland
- Prof. Paolo Favaro, Institute of Computer Science, University of Bern, Bern, Switzerland
- Prof. Raphael Sznitman, ARTORG Center, Ophthalmic Technology Lab, University of Bern, Bern, Switzerland
- Dr. Akitaka Ariga, Laboratory for High Energy Physics (LHEP), University of Bern, Bern, Switzerland

### Service Profile

As an inter-disciplinary organization, the MIC brings together researchers from various disciplines in the field of life sciences. They provide expert knowledge in microscopy to make the discipline «Microscopy» accessible to the researchers' community of the University of Bern at an uppermost expert level. The expertise ranges from live imaging of whole organisms to organs, cells and subcellular dynamics. High-throughput setups are available to screen large cohorts of living or fixed samples. The MIC portfolio provides imaging from 2D to 4D and from the mesoscopic scale to the ultra-structural level. Electron microscopy allows resolution up to the nanometer range in transmission or scanning mode and can be combined with serial block face sectioning. Atomic force microscopy allows for the analysis of surfaces of materials or organism with micrometer to nanometer resolution. For details of the full range of MIC activities and services, please visit the MIC homepage at [www.mic.unibe.ch](http://www.mic.unibe.ch).

### Teaching Profile

The MIC sustains a wide range of teaching activities. In 2018, the lecture series on Advanced Microscopy was attended by 56 students at the master and PhD level. MIC workshops on selected microscopy techniques are offered by MIC experts. MIC trainings cover a multitude of topics, ranging from basic wide-field microscopy to confocal microscopy and from software handling to writing own scripts for automated image acquisition or analysis. The MIC also offers a broad palette of activities in the frame of a PhD program in microscopy named Cutting Edge Microscopy (CEM),

which is offered to PhD students with a specific interest in in-depth knowledge of microscopy. In 2018, the MIC organized a 3-day summer school and a 2-day visit of the Nikon Imaging Center at the Institut Curie and the Institut Pasteur in Paris, France, for the 20 students enrolled in the CEM PhD program.

### Highlights 2018

In 2018, MIC has received funding from the University of Bern allowing for employment of an expert in Bioluminescence. On September 1<sup>st</sup> 2018, Guillaume Witz joined the MIC to play his specific part in supporting the MIC in the areas of Bioluminescence and Big Data in microscopy. After his graduation from physics, Guillaume joined the field of life science and became an imaging specialist with in-depth experience in multi-dimensional imaging and 4D image reconstruction. He further contributes to the MIC with his knowledge in developing software solutions and pipelines such as high-performance computing (HPC) and deep learning for the automated processing of large and complex microscopy datasets. Guillaume is localized with the Science IT Support at the Mathematical Institute (<http://www.scits.unibe.ch>). With his expert knowledge, Guillaume provides valuable input allowing to increase the quality of microscopic image analysis at the University of Bern.

On July 4<sup>th</sup>, 2018, the MIC organized the MIC Research Day in the lecture hall of the Department of Infectious Diseases and Pathobiology of the Vetsuisse Faculty. This afternoon event was attended by more than 100 researchers interested in microscopy-oriented scientific projects of colleagues at the University of Bern and the University of Fribourg. CEM PhD students who were perfectly up to the task chaired the presentations. Overall, the MIC Research Day provided the opportunity to acquire knowledge about new and sophisticated microscopy techniques at the University of Bern and to interact with local experts in the field.

The 2<sup>nd</sup> MIC Summer School took place from July 4<sup>th</sup> to 6<sup>th</sup>. On July 4<sup>th</sup>, the students actively participated in the MIC Research day. This event was followed by the Students' Day on July 5<sup>th</sup> and an introduction to the interconnection of microscopy-related problems and science IT solutions on July 6<sup>th</sup>. Overall, the MIC Summer School 2018 was a great success in terms of scientific discussions, sharing ideas and personal exchange.

On November 30, 2018, record high 185 participants from the University of Bern, from all over Switzerland, France and Germany attended the traditional MIC Symposium entitled *From Organoids to Organisms: Multiscale Imaging*. Nadia Mercader and Olivier Guenat as the scientific committee ensured a well-balanced and highly informative content. After the welcome addresses by Hans-Uwe Simon and Britta Engelhardt, six scientific talks of Swiss and internationally renowned scientists and two company presentations imparted their most recent achievements in the areas of intravital microscopy or *in vitro* imaging of organoids. The lunch break was intensely used as a platform for discussion and networking. Active participation of company representatives provided latest information on technology development at first hand. We thank the scientific committee for preparing the interesting program, the speakers for sharing their research results and enthusiasm for microscopy, the students of the PhD program Cutting Edge Microscopy for help in the

organization, all the participants for their interest in microscopy and the sponsors for the generous financial support of the symposium.



Impressions of the MIC Symposium 2018.

In 2018, the following colleagues were elected as new members of the MIC commission. Kerry Woods represents life science imaging expert knowledge at Vetsuisse. Giuseppe Locatelli is the Two-Photon microscopy expert at Theodor Kocher Institute. Sigve Haug contributes to the MIC commission with his expert knowledge on Science IT. Guillaume Witz started his position as the new Bioluminescence and Big Data specialist and is also a new member of the MIC commission.

### Selected Publications

Many important publications that have been realized with the help of the MIC cannot be listed due to space restrictions.

Please see the depository BORIS for a complete list of MIC affiliated publications (<https://boris.unibe.ch/>, institute section '09 Interdisciplinary Units').

- Mossu A, Rosito M, Khire T, Li Chung H, Nishihara H, Gruber I, Luke E, Dehouck L, Sallusto F, Gosselet F, McGrath J, Engelhardt B. A silicon nanomembrane platform for the visualization of immune cell trafficking across the human blood-brain barrier under flow. *J Cereb Blood Flow Metabol* 2018 Dec 19:271678X18820584. doi: 10.1177/0271678X18820584
- Sfriso R, Zhang S, Bichsel CA, Steck O, Despont A, Guenat OT, Rieben R. 3D artificial round section micro-vessels to investigate endothelial cells under physiological flow conditions. *Sci Rep*. 2018 Apr 12;8(1):5898. doi: 10.1038/s41598-018-24273-7
- Hlushchuk R, Zubler C, Barré S, Correa Shokiche C, Schaad L, Röthlisberger R, Wnuk M, Daniel C, Khoma O, Tschanz SA, Reyes M, Djonov V. Cutting-edge micro-angiography-CT: new dimensions in vascular imaging and kidney morphometry. *Am J Physiol Renal Physiol*. 2018 Mar 1;314(3):F493-F499. doi: 10.1152/ajprenal.00099.2017
- Bagonis MM, Fusco L, Pertz O, Danuser G. Automated profiling of growth cone heterogeneity defines relations between morphology and motility. *J Cell Biol*. 2019 Jan 7;218(1):350-379. doi: 10.1083/jcb.201711023
- V'kovski P, Gerber M, Kelly J, Pfaender S, Ebert N, Braga Lagache S, Simillion C, Portmann J, Stalder H, Gaschen V, Bruggmann R, Stoffel MH, Heller M, Dijkman R, Thiel V. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. *Elife*. 2019 Jan 11;8. pii: e42037. doi: 10.7554/eLife.42037



# Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel)

Freiburgstrasse 3 (building under construction)  
3010 Bern



Dr. Simon Rothen  
CEO and Director  
Network &  
Communication



Prof. Juergen Burger  
Director School

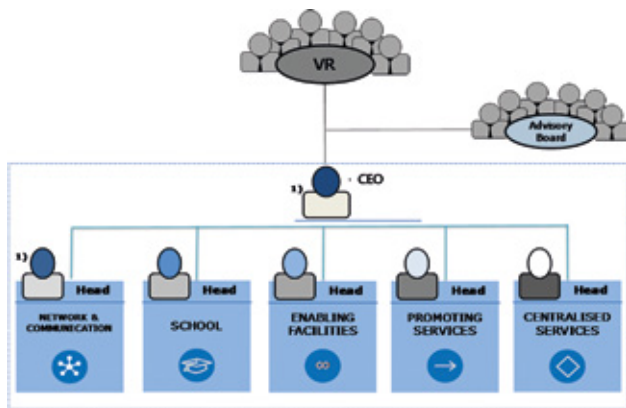


Prof. Rudolf Blankart  
Director Promoting  
Services



Dr. Christian Rosser  
Director Centralised  
Services

## Structure Profile



1) Personalunion

## Research Partners

- Clinical Anatomy, KARL STORZ SE & Co, Tuttlingen, Germany
- Dental Translational Research Center, Institut Straumann AG, Basel, Switzerland
- Translational Imaging Center, Siemens Healthcare AG, Zurich, Switzerland
- Diabetes Center Bern, Willy Michel, Solothurn, Switzerland
- Metabolomics Unit, Waters AG, Baden Dättwil, Switzerland
- CSL Biologics Research Center, CSL Behring AG, Bern, Switzerland
- Berner Fachhochschule, Bern, Switzerland
- Hamburg Center for Health Economics, Universität Hamburg, Hamburg, Germany
- Harvard T.H. Chan School of Public Health, Boston, USA
- Centre for Research on Health and Social Care Management (CERGAS), University of Bocconi, Milano, Italy

## Research Profile

sitem-insel was created to establish, operate, and develop a National Centre of Excellence for Translational Medicine and Entrepreneurship. Being organized as a non-profit oriented public private partnership, sitem-insel's mission is to create and foster an enhanced environment for translational medicine in Switzerland.



sitem-insel's strategy rests on three pillars:

- sitem-insel School offers university-level continuing professional development courses taught by university and private-sector lecturers.
- sitem-insel Enabling Facilities provides infrastructure to foster cooperation between industrial partners, basic scientists and clinicians on the Inselspital Campus with the ultimate goal to bring novel diagnostic and therapeutic products towards clinical application.
- sitem-insel Promoting Services aims to optimize the administrative-regulatory effort along the route from invention to commercialization.

## Teaching Profile

Collaboration with the University of Bern: In addition to lectures and seminars in the field "Medicine and Industry", "Regulatory Affairs and Health Technology Assessment", and "Intelligent Implants and Surgical Instruments", the directors of sitem-insel are currently supervising several Postdocs, PhD and master students at the University of Bern. Their theses are in the fields of regulatory affairs, health care management, strategy building for public private partnership organizations, and smart medical devices.

sitem-insel School: The sitem-insel School, which aims to promote young researchers and train executives in the fields of translational medicine and biomedical entrepreneurship, started in April 2018 with the second cohort of nine master students. Lecturers and supervisors of the school are representatives from private companies, scientists from universities, clinicians, collaborators from regulatory agencies, and financial experts. The program is certified by the University of Bern and participants may obtain the degrees of «Master of Advanced Studies» (MAS), «Diploma of Advanced Studies» (DAS) or «Certificate of Advanced Studies» (CAS).

## Highlights 2018

Governance of sitem-insel: sitem-insel's board of directors is implementing its long-term strategy for the management of the institute. On January 1, 2019 Prof. Dr. med. dent. Daniel Buser will take over the presidency of the board of directors, which Dr. h. c. Uwe E. Jocham had exercised ad interim since autumn 2017. In addition, Prof. Dr. Christian Leumann, Rector of the University of Bern, has joined the board of directors in September 2018. At the operational level, Dr. sc. nat. ETH Simon A. Rothen has in November 2018 taken over the newly created function of the CEO from the former managing director Prof. em. Dr. med. Felix Frey. Simon Rothen has many years of leadership experience in the biotechnology industry, including ten years as CEO in the field of laboratory diagnostics.



Subsidies and shareholders: Being approved by the Swiss Confederation to be of national importance, sitem-insel receives approximately 25 Mio CHF of subsidies from both the Swiss Confederation and the Canton of Bern (2017-2020). The share capital, which is distributed to shareholders from both the private sector (e.g. Diabetes Center Berne Foundation, CSL Behring AG, Energie Wasser Bern) and the public sector (e.g. University of Bern, Inselspital-Stiftung), amounts to 12.096 Mio CHF.

New Building on the Inselspital Campus: sitem-insel will be located at the entrance of the Insel campus. On May 31, 2018, the topping out ceremony of sitem-insel's new

building took place at the invitation of sole contractor HRS Real Estate AG. The new building's opening is planned for May 2019.

## Selected Competitive Grants

- HORIZON 2020 (H2020-SC1-2017): Pushing the boundaries of Cost and Outcome analysis of Medical Technologies (COMED).
- ONE-STEP BALLOON CATHETER, Innosuisse project.
- NRP74 SMARTER HEALTHCARE: Projecting the impact of health policy changes for Swiss patients with chronic conditions using simulation modeling (co-investigator)

## Selected Publications

- Bereuter L, Gysin M, Kueffer T, Kucera M, Niederhauser T, Fuhrer J, Zurbuchen A, Obrist D, Tanner H, Haeberlin A (2018). Leadless Dual-Chamber pacing - A Novel Communication Method for Wireless Pacemaker Synchronization. *Journal of the American College of Cardiology, Basic to Translational Science*, accepted.
- Blankart CR, Foster AD, Mor V (2018). The effect of political control on financial performance, structure, and outcomes of US nursing homes. *Health Serv Res.* 2018 Oct 8. doi: 10.1111/1475-6773.13061. [Epub ahead of print]
- Dams F, Gonzalez Rodriguez JL, Cheung KL, Wijnen BFM, Hiligsmann M (2018). Relevance of barriers and facilitators in the use of health technology assessment in Colombia. *J Med Econ.* 2018 May;21(5):510-517. doi: 10.1080/13696998.2018.1449751. Epub 2018 Mar 23
- Sager, F., Rosser, C., Mavrot, C., & Hurni, P. Y. (2018). *A Transatlantic History of Public Administration: Analyzing the USA, Germany and France.* Edward Elgar Publishing
- Tholl MV, Haeberlin A, Meier BK, Shaheen S, Bereuter L, Becsek B, Tanner H, Niederhauser T, Zurbuchen A. An intracardiac flow based electromagnetic energy harvesting mechanism for cardiac pacing. *IEEE Trans Biomed Eng.* 2018 Jun 22. doi: 10.1109/TBME.2018.2849868. [Epub ahead of print]

# University Neurocenter

University of Bern  
Bern, Switzerland



Prof. Claudio Bassetti (speaker)  
Neurology



Prof. Andreas Raabe  
Neurosurgery



Prof. Jan Gralla  
Neuroradiology



Prof. Maja Steinlin  
Neuropediatrics



Prof. Werner Strik  
Psychiatry



Rosmarie Wyss  
Neurology



Barbara Weiss-Zurschmiede  
Neurosurgery



Michela Mordasini  
Neuroradiology



Heidi Baumgartner  
Neuropediatrics



Philipp Meyer  
Psychiatry

## Structure Profile

The Neurocenter of Bern was founded in 2012. With > 400 beds, > 1'000 collaborators, > 60'000 ambulatory patients, > 8'000 stationary patients, and > 3'500 operations/intervention/angiographies each year and a budget of > 350 Mio CHF it is the largest of its kind in Switzerland and leading in Europe.

## Research Partners

- Alzheimer Research Center, Karolinska Institute, Stockholm, Sweden
- ARTORG Center, University of Bern, Bern, Switzerland
- Department of Informatics, TU Munich, Munich, Germany
- Department of Neurology, University of California, Los Angeles (UCLA), Los Angeles, USA
- Department of Neurology, McGill University, Montreal, Canada
- Department of Pediatric Neurology, Royals Children Hospital, Murdoch Research Institute, Melbourne Australia
- Faculty of Human Sciences, Department of Psychology, University of Bern, Bern, Switzerland
- Institute for Research in Biomedicine, Università della Svizzera italiana, Bellinzona, Switzerland
- Institute for Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
- Swiss Center for Electronics and Microtechnology, Neuchâtel, Switzerland

## Research Profile

Research areas with strong transdisciplinary approaches/interactions within the Neurocenter include the following:

- stroke\* (4 out of 5 departments), including complex neurovascular diseases
- sleep-wake-epilepsy\*, including epilepsy surgery (4/5)
- movement disorders, including functional neurosurgery for Parkinson's disease, neurological and psychiatric disorders (5/5)
- neurorehabilitation including computer-assisted systems and robotics (4/5)

- neuroimmunology\* (3/5)
- neurodegeneration\*/dementia (3/5)
- intraoperative imaging, neuromonitoring, augmented reality, navigation associated developments, targeted procedures and 3D printing and simulation techniques (2/5)
- systems neuroscience and psychopathology (3/5)

\*in these areas clinical/human and experimental/animal approaches are used

The research groups of the Neurocenter use the following common research platforms:

- neuro-clinical trial unit (in collaboration with the CTU Bern)
- human neurophysiological laboratories
- human neuroimaging facilities (including the neurointerventional lab)
- animal research facilities (ZEN, center for experimental neurology)
- technological facilities (ARTORG, ITEM)
- support center for advanced neuroimaging (SCAN)

## Teaching Profile

The following pre- and postgraduate events are jointly organized by different departments of the Neurocenter each year:

- Clinical Neuroscience Bern (CNB) meeting, brain week, and neuroscience slam (organizers: U. Fischer, T. Nef)
- stroke meeting, European Stroke Winter School, brain-heart symposium (M. Arnold, U. Fischer, J. Gralla)
- Bernese sleep-wake days, Winter Sleep Science and Summer Sleep Medicine Schools, BENESCO seminars (C. Bassetti, M. Gugger, K. Schindler, A. Adamantidis, C. Nissen)
- neuro-emergencies symposium (W. Z'Graggen, U. Fischer)

Following an initiative of the Neurocenter a new PhD program in Clinical Sciences was launched in October 2017 ([www.ghs.unibe.ch](http://www.ghs.unibe.ch)).



## Highlights 2018

- In 2018, 35 SNF (22 Neurology, 4 Neurosurgery, 3 Psychiatry, 6 Neuroradiology) projects were running and > 300 publications (whereof 144 in Neurology and 58 in Neurosurgery) were published in the Neurocenter
- The University of Bern granted 6 Mio CHF for an Interfaculty Cooperation Research (IRC) project (Caudio Bassetti, Fred Mast)
- Selma Aybek was awarded a SNSF Professorship
- Maxime Baud received a SNSF Ambizione Grant
- Paul Krack, joined as head physician of the movement disorders unit and was awarded the "Parkinson Schweiz" Professorship

## Selected Competitive Grants

Only the largest grants obtained are listed:

- Neurology: Decoding Sleep: (IRC-Grant; C. Bassetti; 6.2 Mio CHF); Sense of Agency and Stress in Functional Neurological Disorders (SNSF; S. Aybek; 1'583'722 CHF); Chronobiology of seizure risk in epilepsy (SNSF; M. Baud; 963'000 CHF); Synaptic dysfunction in motoneuron disease (SNSF; S. Saxena; 700'000 CHF)
- Neurosurgery: Resurge (314'088 CHF), Bridge (687'000 CHF), Craniospinal compliance (985'103 CHF), Implantable bioelectronics for wireless and high resolution monitoring of epilepsy in vivo. Part II (150'466 CHF)
- Neuroradiology: SENERGIA, PI R. Wiest) Predict and monitor epilepsy – the SWISS FIRST study, 2.66 Mio. CHF, EU Horizon 2020 Grant CI J. Slotboom 562'000 CHF, SNF Grant PI J. Slotboom 364'000, SPHN Grant R. Wiest (CI) 1'500'000
- Neuropediatrics: None
- Psychiatry: SNF (320030\_146789, 105319\_159286) Prediction in auditory hallucinations (T. Dierks, 499'000CHF), SNF 180022 (K. Stegmayer, 326'000); Klöppel S. und Nissen C. SNF Grant Nr. 2018-PI02, 300'000 CHF: „Improving slow wave sleep to enhance memory consolidation and new learning in individuals at risk for dementia.“

## Selected Publications

- Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, Jovic S, Jarrossay D, Mathis J, Zellini F, Becher B, Lanzavecchia A, Khatami R, Manconi M, Tafti M, Bassetti CL\*, Sallusto F\*. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*. 2018 Oct;562(7725):63-68. doi: 10.1038/s41586-018-0540-1 (\*co-shared senior authors)
- Gent TC, Bandarabadi M, Herrera CG, Adamantidis AR. Thalamic dual control of sleep and wakefulness. *Nat Neurosci*. 2018 Jul;21(7):974-984. doi: 10.1038/s41593-018-0164-7
- Seiffge DJ, Werring DJ, Paciaroni M, Dawson J, Warach S, Milling TJ, Engelter ST, Fischer U, Norrving B. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol*. 2019 Jan;18(1):117-126. doi: 10.1016/S1474-4422(18)30356-9
- Maier JG, Kuhn M, Mainberger F, Nachtsheim K, Guo S, Bucsenz U, Feige B, Mikutta C, Spiegelhalder K, Klöppel S, Normann C, Riemann D, Nissen C. Sleep orchestrates indices of local plasticity and global network stability in the human cortex. *Sleep*. 2018 Dec 22. doi: 10.1093/sleep/zsy263. [Epub ahead of print]
- Stegmayer K, Bohlhalter S, Vanbellingen T, Federspiel A, Wiest R, Müri R, Strik W, Walther S (2018). Limbic interference during social action planning in schizophrenia.

*Schizophr Bull*. 2018 Feb 15;44(2):359-368. doi: 10.1093/schbul/sbx059

- Kaess M, Whittle S, O'Brien-Simpson, Allen NB, Simmons JG (2018). Childhood maltreatment, early pituitary volume and adolescent hypothalamic-pituitary-adrenal axis – prospective evidence for a maltreatment-related attenuation. *Psychoneuroendocrinology*. 2018 Dec;98:39-45. doi: 10.1016/j.psyneuen.2018.08.004
- Koenig J, Westlund Schreiner M, Klimes-Dougan B, Ubani B, Mueller B, Kaess M, Cullen KR (2018). Brain Structural Thickness and Resting State Autonomic Function in Adolescents with Major Depression. *Soc Cogn Affect Neurosci*. 2018 Sep 4;13(7):741-753. doi: 10.1093/scan/ny046
- Klöppel S, Yang S, Kellner E, Reiser M, Heimbach B, Urbach H, Linn J, Weidauer S, Andres T, Bröse M, Lahr J, Lützen N, Meyer PT, Peter J, Abdulkadir A, Hellwig S, Egger K, Alzheimer's Disease Neuroimaging Initiative (2018). Voxel-wise deviations from healthy aging for the detection of region-specific atrophy. *Neuroimage Clin*. 2018;20:851-860. doi: 10.1016/j.nicl.2018.09.013
- Roccio, Marta; Perny, Michael; Ealy, Megan; Widmer, Hans Ruedi; Heller, Stefan; Senn, Pascal (2018). Molecular characterization and prospective isolation of human fetal cochlear hair cell progenitors. *Nat Commun*. 2018 Oct 2;9(1):4027. doi: 10.1038/s41467-018-06334-7
- Deletis, Vedran; Seidel, Kathleen; Sala, Francesco; Raabe, Andreas; Chudy, Darko; Beck, Jürgen; Kothbauer, Karl F (2018). Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. *J Neurol Neurosurg Psychiatry*. 2018 Jul;89(7):754-761. doi: 10.1136/jnnp-2017-317172
- Raabe, Clemens; Fichtner, Jens; Beck, Jürgen; Gralla, Jan; Raabe, Andreas (2018). Revisiting the rules for freehand ventriculostomy: a virtual reality analysis. *J Neurosurg*. 2018 Apr;128(4):1250-1257. doi: 10.3171/2016.11.JNS161765
- Bigi S, Dulcey A, Gralla J, Bernasconi C, Melliger A, Datta AN, Arnold M, Kaesmacher J, Fluss J, Hackenberg A, Maier O, Weber J, Poloni C, Fischer U, Steinlin M. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol*. 2018 Jun;83(6):1125-1132. doi: 10.1002/ana.25242
- Mürner-Lavanchy I, Rummel C, Steinlin M, Everts R. Cortical morphometry and cognition in very preterm and term-born children at early school age. *Early Hum Dev*. 2018 Jan;116:53-63. doi: 10.1016/j.earlhumdev.2017.11.003
- Whelan CD, et al. for the ENIGMA-Epilepsy Working Group. Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. *Brain*. 2018 Feb 1;141(2):391-408. doi: 10.1093/brain/awx341
- Kellner-Weldon F, El-Koussy M, Jung M, Jossen M, Klinger-Gratz PP, Wiest R. Cerebellar hypoperfusion in migraine attack: incidence and significance. *AJNR Am J Neuroradiol*. 2018 Jan 11. doi: 10.3174/ajnr.A5508. [Epub ahead of print]

# University Cancer Center (UCI)

Inselhospital, Bern University Hospital  
Freiburgstrasse 10, 3010 Bern



Prof. Daniel M. Aebersold  
Chairman and Board of Directors



Prof. Michael Müller  
Vice-Chairman and Board of Directors



Prof. Daniel Candinas  
Board of Directors



Prof. Adrian Ochsenbein  
Board of Directors



Prof. Aurel Perren  
Board of Directors



Prof. Andreas Raabe  
Board of Directors



Prof. George Thalmann  
Board of Directors



Prof. Jörg Beyer  
Managing Director



Nele Hardt  
Head Coordination and Quality Management

## University Cancer Center Inselhospital (UCI)

Insel Gruppe AG / University of Bern

### General Assembly

Representatives from organ-specific centers as well as from the Insel Gruppe AG & the University of Bern

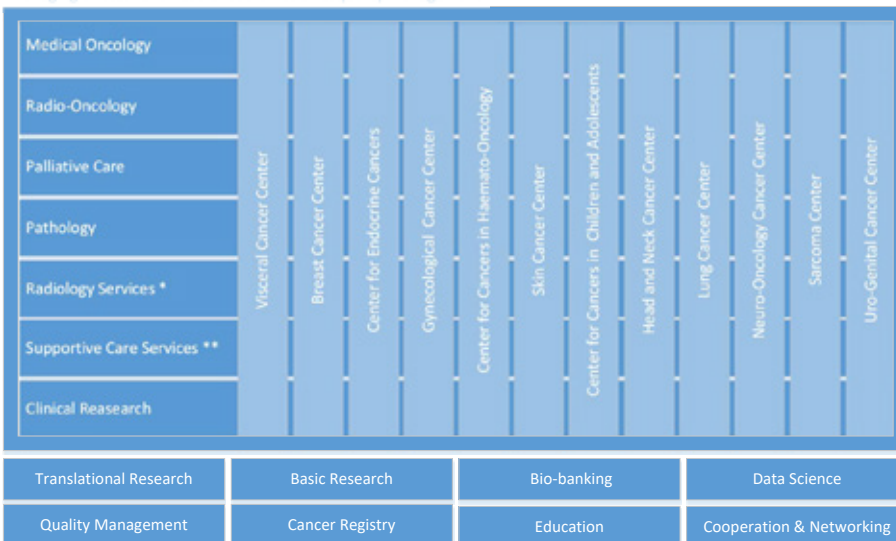
### Board of Directors

Seven elected representatives of the organ-specific centers

Advisory Board

### Management

Managing director and head of coordination & quality management



Interdisciplinary Expert Groups

Molecular Oncology

Immuno-Oncology

Genetics and Genetic Counseling

Cancer Survivorship

Young Adults

Geriatric Oncology

Cancer Surgery

\* Radiology, Neuroradiology, Nuclear Medicine  
\*\* Psycho-Oncology, Spiritual Care, Social Services, Nutritional Counseling

**Mission**

In an aging population, cancer is increasingly prevalent and constitutes the second leading cause of death in Switzerland as well as the main cause of potential years-of-life lost. The University Cancer Center Inselspital (UCI) aims at coordinating all activities in prevention, diagnosis, treatment and follow-up of cancer. It aims at being the reference center within the Canton of Bern and being among the top centers of excellence in Switzerland. The UCI coordinates activities and services relating to cancer within the Inselspital and offers outside services to institutions, physicians, patients and their relatives. It has a strong commitment to basic and translational research with active clinical trials across all cancer diagnoses.

**Structure**

The structure of the UCI is outlined in the graphic. Twelve organ-specific cancer centers constitute the core of the UCI supported by interdisciplinary services and expert groups focusing on special aspects of cancer care.

**Activities**

Highlights of 2018 were the establishment of the center for "Cancers in Hemato-Oncology" as a new "organ-specific" center within the UCI. The center is also the premier one in Switzerland to open a clinical trial on CAR T-cells as an innovative and promising treatment of refractory leukemias and lymphomas. Expert groups have constituted in molecular medicine and cancer survivorship care and a regular cancer survivorship clinic has opened as a cooperation between the departments of pediatrics and general medicine.

**Outreach**

The UCI has close ties with the University of Bern, the cancer registry of the Canton of Bern as well as with national and international research organizations. Referring institutions and practicing physicians can participate in one of 16 organ-specific interdisciplinary tumor boards that offer expert advice on newly diagnosed cancer patients as well as on individual difficult-to-treat cases. In addition, outpatient clinics are being offered at each of the organ-specific centers for second-opinion.

**Contact**

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## Clinical Trial Unit Bern (CTU)

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PD Dr. Sven  
Trelle  
Director



Prof. Urs  
Fischer  
Deputy Director



Christina  
Huf  
Head Quality  
Management



Muriel  
Helmers  
Head Data  
Management



Dr. Andreas  
Limacher  
Head Statistics  
and Methodology



Dr. Felix  
Rintelen  
Head Monitoring  
and Regulatory  
Affairs

### Research Partners

- All clinics at the Inselspital, University Hospital, University of Bern, Bern, Switzerland
- All institutes of the Medical Faculty, Bern, Switzerland
- University Hospital of Psychiatry, Bern, Switzerland
- All members of the Swiss Clinical Trial Organization CTU network, Switzerland
- Department of Internal Medicine, Kantonsspital Baden, Baden, Switzerland
- Brustzentrum Bern, Lindenhofgruppe, Bern, Switzerland
- Department of Infectious Diseases, Hôpitaux Universitaires de Genève, Genève, Switzerland
- Department of Plastic and Hand Surgery, University Hospital Zürich, Zürich, Switzerland

### Research Profile

CTU Bern supports and collaborates in clinical trials, epidemiological studies and meta-analyses in any clinical field to strengthen and expand the evidence base for health care nationally and internationally. It offers the scientific, regulatory and technical expertise needed to support patient-oriented clinical research at all stages, from conception to completion and dissemination. CTU Bern works according to established scientific standards. The services offered by the unit enable clinical researchers to comply with legal and regulatory requirements, and with international standards. Relevant expertise is provided within the unit itself or by facilitating and coordinating contact with outside experts. Services are provided in a modular fashion and range from advice and general support to full development of the design and conduct of clinical studies. The unit is organized in five divisions: Statistics & Methodology, Data Management, Project Coordination, Quality Assurance & Monitoring, and Clinical Investigation. Although the primary focus of CTU Bern lies on late phase clinical studies we have some expertise in early phase clinical trials including exploratory clinical trials.

### Teaching Profile

CTU Bern is involved in several undergraduate and postgraduate teaching activities. Staff contributes to undergraduate teaching for 3rd year medical and biomedical sciences students. Postgraduate teaching activities involve contribution to the Certificate of Advanced Studies course in Clinical Research (University of Bern) and the Certificate of Advanced Studies for Clinical Research Coordinators offered by the University of Applied Sciences Bern. Research ethics

and Good Clinical Practice training form an important part. The basic course uses blended learning with a self-learning part and a whole day face-to-face part consisting of lectures and workshops. The advanced course is a one day face-to-face course consisting of lectures and workshops. Both courses are recognised by swissethics. In addition, CTU Bern offers special courses such as GCP refresher course, software trainings (REDCap and Stata®), or a course on writing a study protocol. Once a month, a CTU lecture is dedicated to a specific topic of relevance to all persons involved in clinical research.

### Highlights 2018

#### *First audit – successfully passed*

Within the framework of a large European clinical trial, CTU Bern was externally audited. After two inspections by Swissmedic some years ago, this was the first formal audit. The audit lasted for two days and the focus was on processes related to data management, statistics, and monitoring services. It went very well and none of the findings was unexpected. The suggested corrective and preventive actions were all accepted by the auditor and have been implemented. This audit has been a good basis for the sought certifications in 2019 (ISO 9001 and ECRIN data centre).

#### *SCTO/SERI platform statistics and methodology*

In 2017, the Swiss network of clinical trial units received a four year grant from the State Secretariat for Education, Research, and Innovation to foster collaboration and improve the clinical research environment for multicentre clinical trials. Within this grant, CTU Bern is responsible for the statistics and methodology platform. This year, the first workshop, on adaptive designs and the use of historical information for clinical trials, was hosted in Bern. Statisticians from all CTUs participated.

#### *Completed research projects*

Several large clinical trials, mainly in cardiology, were finished this year. GLOBAL LEADERS was a mega trial that evaluated two different antiplatelet regimens in more than 15'000 patients who received a stent for an acute coronary syndrome. The trial provides solid evidence that the current regimen should remain the standard. CTU Bern was responsible for the statistical analysis. MATRIX was also a large European trial program in interventional cardiology. One of the trials evaluated whether radial access is superior to

femoral access in patients with coronary syndrome undergoing coronary angiography. The trial showed that radial access reduces the risk for net adverse clinical events. CTU Bern was again responsible for the statistical analysis. Also in 2018, several analyses using data from the SWITCO65+ cohort that had observed elderly patients with pulmonary embolism or deep vein thrombosis (<http://switco65.ctu.unibe.ch>) were supported by CTU Bern statisticians. The main focus in this year was on developing prediction models (e.g. for post-thrombotic syndrome or recurrent venous thromboembolism) or validating risk scores. A large collaborative project combining data from several cohort studies investigated the incidence of non-Hodgkin lymphoma in more than 200,000 HIV+ patients who started antiretroviral therapy. Incidence was similar for most population groups across the world but the study showed, that South African women had a particularly increased risk for this type of cancer.

#### *Consulting and project support*

Consulting and project support are one of the main objectives of CTU Bern. In 2018, CTU Bern conducted nearly 300 consultations, mainly for researchers from Inselspital Bern, and supported more than 100 projects.

#### **Selected Publications**

- AIDS-defining Cancer Project Working Group of leDEA and COHERE in EuroCoord (Bütikofer L). Non-Hodgkin lymphoma risk in adults living with HIV across five continents. *AIDS*. 2018 Nov 28;32(18):2777-2786. doi: 10.1097/QAD.0000000000002003
- Méan M, Limacher A, Alatri A, Aujesky D, Mazzolai L. Derivation and Validation of a Prediction Model for Risk Stratification of Post-Thrombotic Syndrome in Elderly Patients with a First Deep Vein Thrombosis. *Thromb Haemost*. 2018 Aug;118(8):1419-1427. doi: 10.1055/s-0038-1661392
- Pilgrim T, Piccolo R, Heg D, Roffi M, Tüller D, Müller O, Moarof I, Siontis GCM, Cook S, Weilenmann D, Kaiser C, Cuculi F, Hunziker L, Eberli FR, Jüni P, Windecker S. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. *Lancet*. 2018 Sep 1;392(10149):737-746. doi: 10.1016/S0140-6736(18)31715-X
- Studer P, Horn T, Haynes A, Candinas D, Banz VM. Quality of life after hepatic resection. *Br J Surg*. 2018 Feb;105(3):237-243. doi: 10.1002/bjs.10735
- Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet*. 2018 Sep 8;392(10150):835-848. doi: 10.1016/S0140-6736(18)31714-8

- Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018 Sep 15;392(10151):940-949. doi: 10.1016/S0140-6736(18)31858-0

# Institute of Anatomy

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Prof. Valentin Djonov  
Director



Prof. Annette Draeger  
Co-Director



Prof. Nadia Mercader Huber  
Co-Director



Prof. Benoît Zuber  
Co-Director



PD Dr. Stefan Tschanz  
Central Services  
Leader



PD Dr. Asparouh Iliev  
Group Leader



Prof. Marianne Geiser  
Group Leader



PD Dr. Gudrun Herrmann  
Group Leader



Prof. Johannes Schittny  
Group Leader

## Research Partners

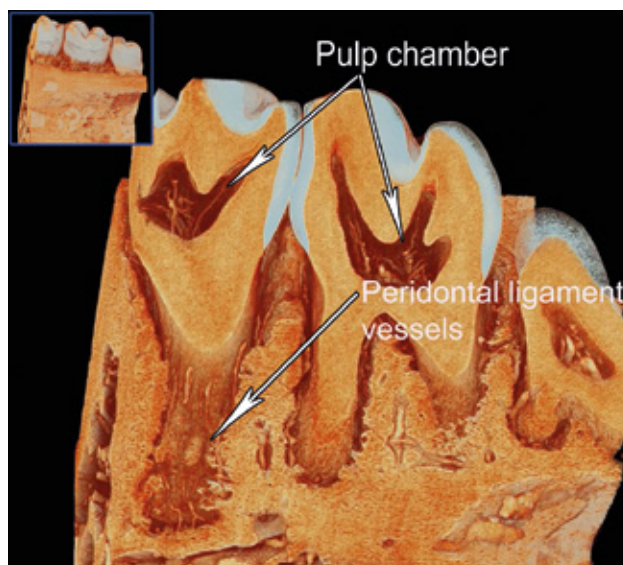
- Prof. Michael Stoffel, Dept. of Veterinary Anatomy, University of Bern, Switzerland
- Prof. Martin Frenz, Inst. of Applied Physics, University of Bern, Switzerland
- Prof. José Antonio Enriquez, Centro Nacional de Investigaciones Cardiovasculares CNIC, Madrid, Spain
- Prof. Julien Vermot, IGBMC, Strasbourg, France
- Prof. Gisou van der Goot, EPFL, Lausanne, Switzerland
- Prof. Abbas Ourmazd, University of Wisconsin-Milwaukee, USA
- Prof. Sibylle Schneider-Schaulies, Institute of Virology and Immunobiology, University of Würzburg, Germany
- Prof. Urs Baltensperger Paul Scherrer Institute, Villigen, Switzerland
- Prof. Marco Stampanoni, ETH Zürich, Switzerland
- Roland Nau, Neuropathologie, Universität Göttingen, Germany

## Research Profile

The Institute's research interests cover a variety of topics ranging from basic to applied science: cardiovascular development, repair and regeneration, fine structural investigation of neuronal synapses, research on the effect of bacterial toxins and the prevention of antimicrobial resistance, pulmonary development and function of cilia in the respiratory tract, as well as dangers of occupational exposure to inhaled particles. One of the Institute's expertise is imaging. We image tissues and organs at the macroscopic, microscopic and ultrastructural level using micro-CT, Synchrotron Radiation based X-ray Tomographic Microscopy, *in vivo* Confocal and Light Sheet Microscopy, cryo-Electron Microscopy and Serial Block Face Scanning Electron Microscopy. The Institute is part of the Microscopy Imaging Center (MIC) of the University. Our research models include cell culture, zebrafish, mice and patient samples. The Institutes also offers a Swiss-wide unique service in micro-morphological analysis of primary ciliary dyskinesia.

## Teaching Profile

The Institute of Anatomy is responsible for the comprehensive teaching of preclinical medical students (human, dentistry and veterinary medicine) and students of related paramedical fields (Biomedical Sciences, Bioengineering, Physiotherapy, Osteopathy) in subjects such as Gross Anatomy, Histology, Embryology and Cell Biology. In addition, postgraduate education and advanced surgical training is provided for medical graduates specializing in a large variety of surgical fields. 2 MD theses and 1 PhD Thesis were complete in 2018. Cedric Zubler was awarded the MD-thesis prize from the Swiss Society of Anatomists (SSGAHE/SSAHE).

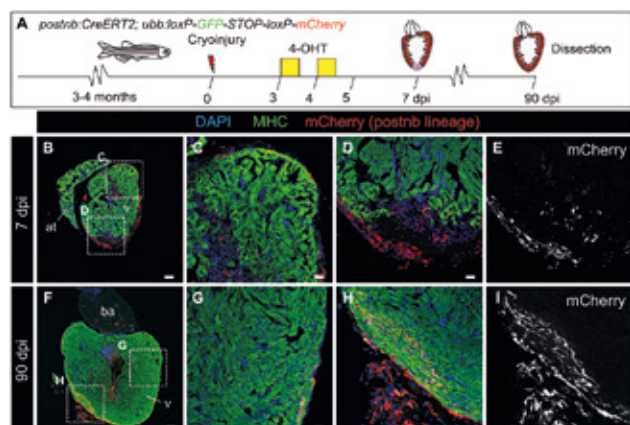


Microangiography of the murine mandibula with the use of  $\mu$ Angiofil. The microvasculature of the murine mandibula and the teeth (including vessels within the pulp chamber) can be clearly visualized even without the decalcification (courtesy Ruslan Hlushchuk).



## Highlights 2018

In 2018 the Institute of Anatomy was substantially involved into the “+100” initiative, which consisted in a 40% increase of students in the first year of medical education. One research focus of the Institute is cardiovascular development. The zebrafish is a model organisms on which this research is carried out, given its amenability to *in vivo* imaging and genetic manipulation. It also has an extraordinary capacity of regeneration, allowing to interrogate the mechanisms of natural organ regeneration in a vertebrate species. This year, the group of Nadia Mercader published an article reporting that the high degree of cellular plasticity contributes to heart regeneration in the zebrafish. Furthermore, in a second article, the group revealed their recent findings, showing that a fibrotic response that follows after injury also in this species, is actually not detrimental to regeneration but necessary for cardiomyocyte proliferation. Imaging at all scales is central to the Institute. This year, a new Digital Light Sheet confocal microscopes was acquired, which will be accessible through the MIC-Bern Microscopy Unit to the rest of the University. Researchers at the Institute were able to secure funding through several national and international calls including 13 SNF grants and EU or international grants such as Human Frontiers Science Program, ERA-NET NEURON as well as an ERC Consolidator grant.



Fate of fibroblasts during cardiac regeneration in the zebrafish. A, Genetic fate mapping was used to trace the fate of fibroblasts during heat regeneration. B-E, Fibroblasts (red) accumulate in response to cardiac injury. F-I, After complete regeneration of the myocardium, the fibroblasts are still present in the heart. Rather than getting eliminated they persist in an inactive form (Sánchez-Iranzo et al., 2018 PNAS).

## Selected Competitive Grants

- ERC Starting grant (337703)
- European Industrial Doctorate Program (H2020-MSCA-ITN-2016)
- European Research Area Network (ERA-NET) NEURON grant (32NE30\_185536)
- Swiss Cancer Research (KFS-4281-08-2017) HFSP OXPHOS (RGP0016/2018-4)

## Selected Publications

- Sánchez-Iranzo H, Galardi-Castilla M, Minguillón C, Sanz-Morejón A, González-Rosa JM, Felker A, Ernst A, Guzmán-Martínez G, Mosimann C, Mercader N. Tbx5a lineage tracing shows cardiomyocyte plasticity during zebrafish heart regeneration. *Nat Commun* 2018. 9:428. DOI: 10.1038/s41467-017-02650-6
- Köffel R, Wolfmeier H, Larpin Y, Besançon H, Schoenauer R, Babychuk VS, Drücker P, Pabst T, Mitchell TJ, Babychuk EB Draeger A. Host-Derived Microvesicles Carrying Bacterial Pore-Forming Toxins Deliver Signals to Macrophages: A Novel Mechanism of Shaping Immune Responses. *Front Immunol*. 2018 Jul 27;9:1688. doi: 10.3389/fimmu.2018.01688. eCollection 2018
- Kreyling, W.G., W. Möller, U. Holzwarth, S. Hirn, A. Wenk, C. Schleh, M. Schäffler, N. Haberl, N. Gibson, J.C. Schittny. Age-dependent rat lung deposition patterns of inhaled 20 nanometer gold nanoparticles and their quantitative biokinetics in adult rats. *ACS Nano*. 2018 Aug 28;12(8):7771-7790. doi: 10.1021/acsnano.8b01826. Epub 2018 Aug 15
- Maurer J, Hupp S, Pillich H, Mitchell TJ, Chakraborty T, Iliev AI. Missing elimination via membrane vesicle shedding contributes to the diminished calcium sensitivity of listeriolysin O. *Sci Rep*. 2018 Oct 26;8(1):15846. doi: 10.1038/s41598-018-34031-4
- Potez M, Bouchet A, Wagner J, Donzelli M, Bräuer-Krisch E, Hopewell JW, Laissue J, Djonov V. Effects of Synchrotron X-Ray Micro-beam Irradiation on Normal Mouse Ear Pinnae. *Int J Radiat Oncol Biol Phys*. 2018 Jul 1;101(3):680-689. doi: 10.1016/j.ijrobp.2018.02.007. Epub 2018 Feb 13

# Institute of Biochemistry and Molecular Medicine (IBMM)

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Prof. Hugues Abriel  
Co-Director  
Head NCCR  
TransCure



Prof. Jürg Gertsch  
Deputy &  
Co-Director



Prof. Christine Peinelt  
Co-Director



Prof. Dimitrios Fotiadis  
Managing  
Director



Prof. Christiane Albrecht



Prof. Peter Bütikofer



Dr. Jin Li Ambizione  
Group Leader



Prof. Matthias Hediger



Dr. Martin Lochner  
Lecturer



Prof. Charles Roch-Philippe  
Lecturer

## Research Partners

- DCB, DBMR, Inselspital, Institutes of Physiology, Pathology, Urology, University of Bern, Bern, Switzerland
- D-BSSE & D-CHAB, ETH Zürich, Zürich, Switzerland
- Swiss Institute of Bioinformatics, University of Geneva, Geneva, Switzerland
- School of Medicine, University of Nottingham, Nottingham, UK
- Department of Pharmacology, University of Cambridge, Cambridge, UK
- Novartis Institutes of Biomedical Research, Basel, Switzerland
- Max-Planck- Institute, Munich, Germany
- Laboratory of Molecular Electron Microscopy, The Rockefeller University, New York, USA
- PeterMac Institute, Melbourne, Australia
- NIH, NIAAA, Rockville, USA

## Research Profile

The research activities at the Institute of Biochemistry and Molecular Medicine (IBMM) focus on the structure, function, and pharmacology of membrane proteins like transporters, ion channels, and membrane receptors. A strong emphasis is put on the roles of these membrane proteins in human diseases such as cancer, neuropsychiatric and cardiac disorders, pre-eclampsia and pathogen infections. Currently, more than 100 scientists, of whom many are Ph.D. students and post-doctoral fellows, belong to one of the currently ten multidisciplinary groups of the IBMM. The IBMM hosts most of the Bernese groups of the Swiss National Science Foundation-funded National Center of Competence in Research (NCCR) TransCure that was established in 2010 at the University of Bern. In addition to basic science, the IBMM promotes expertise in drug discovery and development.

## Teaching Profile

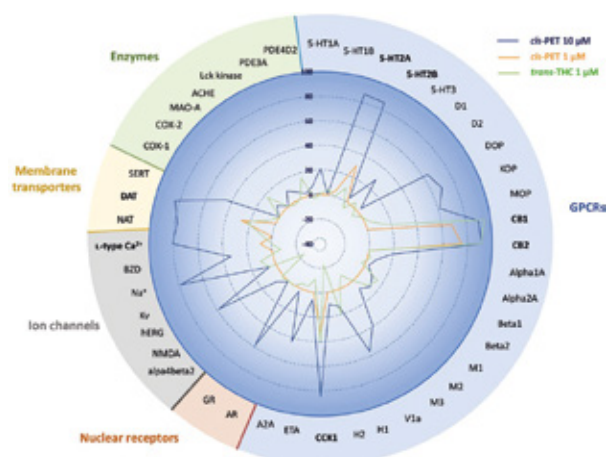
The institute provides basic and specialized teaching at both, pregraduate and postgraduate levels in the faculties of Medicine, Natural Sciences and VetSuisse. In addition, the

IBMM is actively involved in the GCB graduate school and the reorganization of the pre-clinical curriculum for medical students and the new full Pharmacy curriculum at the University of Bern. The teaching activities at the IBMM are at the interface of the natural and medical sciences, focusing on the molecular mechanisms of life.

## Highlights 2018

*Uncovering the psychoactivity of a cannabinoid from liverworts associated with a legal high*

Phytochemical studies on the liverwort *Radula* genus have previously identified the bibenzyl (-)-cis-perrottetene (cis-PET), which structurally resembles (-)- $\Delta^9$ -trans-tetrahydrocannabinol ( $\Delta^9$ -trans-THC) from *Cannabis sativa* L. *Radula* preparations are sold as cannabinoid-like legal high on the internet, even though pharmacological data are lacking. Herein, we describe a versatile total synthesis of (-)-cis-PET and its (-)-trans diastereoisomer and demonstrate that both molecules readily penetrate the brain and induce hypothermia, catalepsy, hypolocomotion, and analgesia in a CB1 receptor-dependent manner in mice. The natural

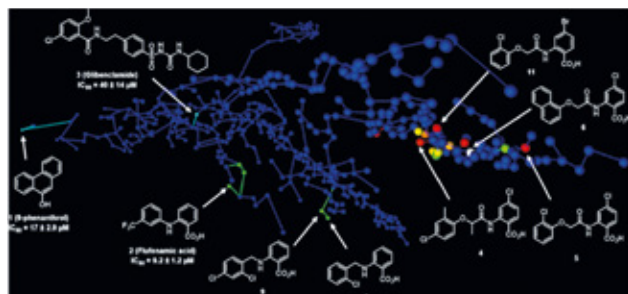


Receptor profiling of novel cannabinoids from *Radula* liverworts shows selective interaction with cannabinoid receptors.

product (-)-cis-PET was profiled on major brain receptors, showing a selective cannabinoid pharmacology. This study also uncovers pharmacological differences between  $\Delta^9$ -THC and PET diastereoisomers. Most notably, (-)-cis-PET and (-)-trans-PET significantly reduced basal brain prostaglandin levels associated with  $\Delta^9$ -trans-THC side effects in a CB1 receptor-dependent manner, thus mimicking the action of the endocannabinoid 2-arachidonoyl glycerol. Therefore, the natural product (-)-cis-PET is a psychoactive cannabinoid from bryophytes, illustrating the existence of convergent evolution of bioactive cannabinoids in the plant kingdom. (Science Advances 2018, 4(10):eaat2166).

#### Identification of potent and selective small molecule inhibitors of the cation channel TRPM4

TRPM4 (Transient receptor potential melastatin-4), is a calcium-activated nonselective cation channel expressed in different cell types including cardiac tissue and different types of cancer cells. Recently genetic variants of TRPM4 have been described in families with cardiac conduction disorders. Given its impact in human cardiac physiology, it is important to characterize the functional role of TRPM4 in cardiac electrical activity using either genetic or pharmacological tools. Unfortunately, the lack of availability of a potent and selective modulator of TRPM4 the physiological role remains unclear. Here in our lab, we developed a high throughput screening assay to record TRPM4-mediated sodium influx in cells to screen a small set of compounds selected by ligand-based virtual screening using previously known weakly active ( $IC_{50} = 30 \mu M$ ) and non-selective TRPM4 inhibitors as seed molecules. Combining these approaches we identified a potent and selective inhibitors of TRPM4 in the nanomolar range. (British Journal of Pharmacology, 2018, DOI:10.1111/bph.14220).



Chemical space analysis of the known and novel TRPM4 inhibitors. Selected view of an interactive 3D map of substructure fingerprint similarity representing each of the 470 compounds tested in the study as one sphere. The map is colour-coded by  $pIC_{50}$  value from blue (lowest value) to red (highest value). Map generated by the group of Prof. J.L. Reymond, DCB, University of Bern.

#### The LAT1 inhibitor JPH203 reduces growth of thyroid carcinoma in a fully immunocompetent mouse model

The L-type amino acid transporter 1 (LAT1/SLC7A5) transports essential amino acids across the plasma membrane. While LAT1 is overexpressed in a variety of human neoplasms, its expression and its role in thyroid cancer is currently unknown. Anaplastic thyroid carcinoma (ATC) is a highly aggressive malignancy for which no effective therapy exists. The purpose of this study was to explore whether the inhibition of LAT1 in ATC would affect tumor growth. LAT1 was pharmacologically inhibited by JPH203 in human ATC and papillary thyroid cancer (PTC) cell lines. The effects on

proliferation and mTORC1 activity were addressed in vitro. A genetically engineered mouse model of ATC was used to address the effects of inhibiting LAT1 on tumor growth in vivo. SLC7A5 transcription was measured in patient-derived ATC samples to address the clinical relevance of the findings. LAT1 inhibition by JPH203 reduced proliferation and mTORC1 signaling in human thyroid cancer cell lines. SLC7A5 transcription was upregulated in ATC tissues derived from a genetically engineered mouse model and in ATC samples recovered from patients. JPH203 treatment induced thyroid tumor growth arrest in vivo in a fully immunocompetent mouse model of thyroid cancer. Additionally, analysis of publicly available datasets of thyroid carcinomas revealed that high LAT1 expression is associated with potentially untreatable PTC presenting reduced NIS/SLC5A5 transcription and with ATC. (J Exp Clin Cancer Res. 2018 Sep 21;37(1):234.)

#### Selected Competitive Grants

- Swiss National Science Foundation NCCR TransCure (leading house)
- NCCR Molecular Systems Engineering
- SNSF project grants No. 31003A\_173155, 310030\_165741, 31003A\_162581, 31003A\_176175, 31003A\_146722, 31003A\_149958, 31003A\_156376
- SNSF Sinergia grants: CR33I3\_156233, CRSII3\_160782, CRSII5\_183481/1
- SNSF Ambizione Fellowship: PZ00P3\_173961
- Swiss Heart Foundation
- CTI Grant Feasibility Study
- MS Foundation
- Lindenhof Foundation Bern
- Swiss Cancer League
- BaseLaunch

#### Selected Publications

- Ilgü H, Jeckelmann JM, Colas C, Ucurum Z, Schlessinger A, Fotiadis D. Effects of Mutations and Ligands on the Thermostability of the L-Arginine/Agmatine Antiporter AdiC and Deduced Insights into Ligand-Binding of Human L-Type Amino Acid Transporters. Int J Mol Sci. 2018 Mar 20;19(3). pii: E918. doi: 10.3390/ijms19030918
- Jack T, Leuenberger M, Ruepp MD, Vernekar SKV, Thompson AJ, Braga-Lagache S, Heller M, Lochner M. Mapping the Orthosteric Binding Site of the Human 5-HT3 Receptor Using Photo-cross-linking Antagonists. ACS Chem Neurosci. 2018 Sep 11. doi: 10.1021/acscchemneuro.8b00327. [Epub ahead of print]
- Huang X, Anderle P, Hostettler L, Baumann MU, Surbek DV, Ontsouka EC, Albrecht C. Identification of placental nutrient transporters associated with intrauterine growth restriction and pre-eclampsia. BMC Genomics. 2018 Mar 2;19(1):173. doi: 10.1186/s12864-018-4518-z
- Wang L, Iwasaki Y, Andra KK, Pandey K, Menon AK, Bütikofer P. Scrambling of natural and fluorescently tagged phosphatidylinositol by reconstituted G protein-coupled receptor and TMEM16 scramblases. J Biol Chem. 2018 Nov 23;293(47):18318-18327. doi: 10.1074/jbc.RA118.004213
- ElMokh O, Taelmann V, Radojewski P, Roelli MA, Stooss A, Dumont RA, Dettmer M, Phillips W, Walter MA, Charles RR. MEK inhibition induces therapeutic iodine uptake in a murine model of anaplastic thyroid cancer. J Nucl Med. 2018 Nov 21. pii: jnumed.118.216721. doi: 10.2967/jnumed.118.216721. [Epub ahead of print]



## Institute for the History of Medicine (IMG)

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Prof. Hubert  
Steinke  
Director



Prof. Martina  
King



Dr. Pascal  
Germann



Stefan  
Hächler  
Head of Archive



Dr. Dorothe  
Zimmermann  
Head of Collection



Bruno  
Müller  
Head of Library

### Research Partners

- Institute of History, University of Bern, Bern, Switzerland
- Institute of Germanic Languages and Literatures, University of Bern, Bern, Switzerland
- School of Liberal Arts, Indiana University, Bloomington, USA
- Center for African Studies, University of Florida, Gainesville, USA
- Department of History, University of Montréal, Montréal, Canada
- Institute for History and Ethics of Medicine, University of Köln, Köln, Germany
- Institute for History and Ethics of Medicine, University of Heidelberg, Heidelberg, Germany
- Institute of History, University of Zürich, Zürich, Switzerland
- Institute of Biomedical Ethics and History of Medicine, University of Zürich, Zürich, Switzerland
- Institute for the History of Medicine and Health, University of Lausanne, Lausanne, Switzerland

### Research Profile

The Institute for the History of Medicine, founded in 1963, is a small institution with a single professorship and a single research assistant position. In addition, a number of researchers are employed in externally funded projects. We have a long tradition of research on Albrecht von Haller, the Republic of Letters and the production of knowledge in the 18th century. Another broad focus is the theory and practice of Western medicine from the 18th to the 20th century. There is also a general interest in all studies related to the local history of medicine and health. A further area of expertise is the history of pharmacy. We are particularly keen to develop research projects based on unexplored archival material allowing for new medicohistorical perspectives. A central source for current and future projects is our own expanding archive. The institute owns also a rich library of 100,000 volumes and maintains a collection of 10,000 medical objects. Our collections are accessible to the general public and are important resources for research and teaching.

### Teaching Profile

Members of the institute teach history of medicine, theory of medicine and medical humanities within the teaching programs for students of medicine. We are also teaching medical students at the Universities of Basel and Fribourg. In addition, we offer seminars to history students at the Philosophical Faculty of our University.

### Highlights 2018

*Medical practice and international networks. Albert Schweitzer's Hospital in Lambarene, 1913-1965*

In this SNSF project we provide a first thorough historical study of Schweitzer's hospital, using a praxeological approach based on an exceptionally rich and hitherto unstudied corpus of archival material. In 2018, Tizian Zumthurn defended his PhD thesis on the biomedical practice at the hospital and wrote chapters of a book for a broader audience.

*Health and welfare after the boom: a history of the quality of life concept, 1965-2000*

This is a new SNSF Mobility Project which investigates the social, political, and epistemic conditions under which the quality of life concept gained acceptance and wielded influence. In 2018, Dr. Pascal Germann stayed at Johns Hopkins University (January to April) and the University of Manchester (Mai to December).



The Bernese polymath Albrecht von Haller (1708-1777) received 13,231 letters from hundreds of scholars all over Europe (map by Richard Stuber). His letters and book reviews will be published in an open access online edition.

*Online-edition of Albrecht von Haller's book reviews and letters: expertise and communication in the emerging scientific community*

This is a large editorial project (2018-2023) developed together with the Institute of History and the Institute of Germanic Languages and Literatures at our University. It is funded through the new SNSF program Edition projects in

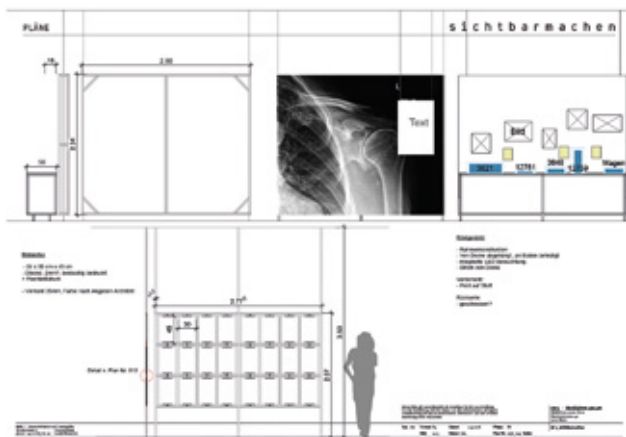
the humanities. It started in January 2018 and will in the end present – among others – an open access edition of 7,000 letters and 9,000 book reviews.

*From ergot to LSD. Materiality, local and global knowledge in the agricultural, industrial and scientific production of psychotropic substances*

This is a SNSF project based partly on the papers of Albert Hofmann at our Institute. In 2018, Dr. Beat Bächli visited several archives in Mexico to enrich his study of the transformation of the sacred Mexican mushrooms into marketable substances and organised the international conference “How Psychotropic Substances Transformed the World: Harvesting, Producing and Consuming LSD, Psilocybin and Mescaline” at our Institute.

*Medical Museum Bern*

After more than two years of intensive preparation the opening of the museum was scheduled for October 2018. The museum would have presented major aspects of modern medicine using the extensive collections of the Inselspital. It would have offered a space for temporary exhibition and critical reflection. Surprisingly, the new management of the hospital decided in June not to open the museum. The Institute will continue to be responsible for the collections.



Design of the museum section on visualization in medicine.

*Clinical trials in psychopharmacology*

In the last few years, public reports have shed critical light on the clinical trials in the early years of psychopharmacology in Switzerland. In 2018, Dr. Urs Germann analysed the context and the practices at the University Hospital of Psychiatry Zurich and Julia Manser started her MD thesis on clinical trials at the University Hospital of Psychiatry Bern 1950 to 1970.

*New project on the history of biomedical ethics in Switzerland*

Based on the archive of the Swiss Academy of Medical Sciences at our Institute, Dr. Magaly Tornay developed the research proposal “Governing by Values: On the History of Medical Ethics and Bioethics in Switzerland”, submitted to the SNSF in October 2018.

**Selected Competitive Grants**

- Swiss National Science Foundation (grants No. 100011\_149880; 100011\_159614; 10FE15\_157963; P2ZHP1\_174862).

**Selected Publications**

- T. Rietmann, U. Germann, F. Condrau: «Wenn Ihr Medikament eine Nummer statt einen Markennamen trägt». Medikamentenversuche in der Zürcher Psychiatrie 1950–1980, in: B. Gnädinger, V. Rothenbühler (Hg.): Menschen korrigieren. Fürsorgliche Zwangsmassnahmen und Fremdplatzierungen im Kanton Zürich bis 1981 (Zürich: Chronos, 2018)
- Mabika, Hines (ed.): Principes éthiques d’Albert Schweitzer en Afrique: le respect de la vie (Paris: L’Harmattan, 2018)
- Zumthurn, Tizian: Ideas and Improvisations: Biomedical Practices at the Hôpital Albert Schweitzer, Lambaréné 1913-1965 (PhD Dissertation, University of Bern, 2018)

## Institute of Pharmacology (PKI)

Inselspital, INO-F  
3010 Bern



Prof. Hans-Uwe  
Simon  
Director



Prof. Andrea  
Huwiler  
Deputy Director



Prof. Thomas  
Kaufmann



SNF Prof. Georgia  
Konstantinidou



Prof. Stephan  
von Gunten



Prof. Shida  
Yousefi



Prof. Uwe  
Zangemeister-Wittke

### Research Partners

- Institute of Biochemistry, University of Zürich, Zürich, Switzerland
- Institute of Experimental Immunology, Laboratory of Neuroinflammation, University of Zürich, Zürich, Switzerland
- Department of Pharmacology, Toxicology and Clinical Pharmacy, Institute of Pharmacy, University of Tübingen, Tübingen, Germany
- Pharmazentrum Frankfurt/ZAFES, University Hospital and Goethe University, Frankfurt/Main, Germany
- Department of Medicine, University of Toronto and Centre for Innovation, Canadian Blood Services, Toronto, Ontario, Canada
- Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
- Center of Laboratory Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Department of Clinical Immunology and Allergology, Sechenov University, Moscow, Russia
- Swiss EoE Research Group, Olten, Switzerland

### Research Profile

The Institute of Pharmacology was founded in 1885. Seven research groups are involved in the investigation of pathophysiological processes that contribute to inflammation and tumor diseases with the aim of discovering new drug targets. Several diseases serve as models to study such processes. The interdisciplinary approach includes different fields, including immunology, cell biology, molecular biology and pathology. Besides the pathogenic aspects of our research, we have developed several in vitro and in vivo test systems to determine potential effects of a given drug on the immune system. The spectrum of research ranges from fundamental research to clinical trials in which the efficacy of new drugs in humans is tested. The research requires a network of physician-scientists from many different clinics. For example, we are interested in the role of apoptosis and autophagy in inflammatory diseases and cancer, as well as in the role of lipids, including sphingolipids, eicosanoids, and free fatty acids in pathophysiological processes. In particular, we investigate pathogenic mechanisms of the following diseases: Atopic dermatitis, hypereosinophilic syndromes, eosinophilic esophagitis, sepsis, chronic kidney diseases, as well as malignant melanoma and lymphomas. We receive clinical samples for our research and are involved in several clinical drug studies.

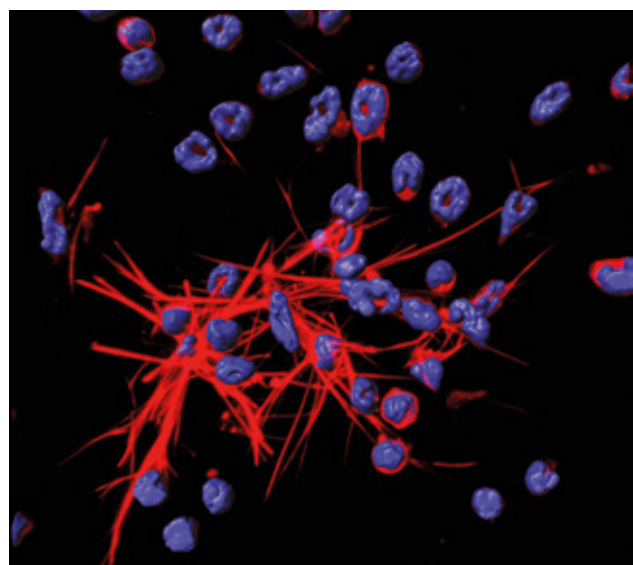
### Teaching Profile

The institute participates in University teaching programs for students of medicine, dental medicine, pharmacy, biomedicine and biology. We also teach students of medicine and biomedicine of the University of Fribourg. In addition, we are involved in teaching programs for graduate students within the Graduate School for Cellular and Biomedical Sciences (GCB).

### Highlights 2018

#### *Neutrophil extracellular trap formation requires OPA1-dependent glycolytic ATP production*

Optic atrophy 1 (OPA1) is a mitochondrial inner membrane protein that has an important role in mitochondrial fusion and structural integrity. Dysfunctional OPA1 mutations cause atrophy of the optic nerve leading to blindness. Here, we show that OPA1 has an important role in the innate immune system. Using conditional knockout mice lacking *Opa1* in neutrophils (*Opa1<sup>NA</sup>*), we report that lack of OPA1 reduces the activity of mitochondrial electron transport complex I in neutrophils. This then causes a decline in adenosine-triphosphate (ATP) production through glycolysis due to lowered NAD<sup>+</sup> availability. Additionally, we show that OPA1-dependent ATP production in these cells is required for microtubule network assembly and for the formation of neutrophil extracellular traps. Finally, we show that *Opa1<sup>NA</sup>* mice exhibit a reduced antibacterial defense capability against *Pseudomonas aeruginosa*.

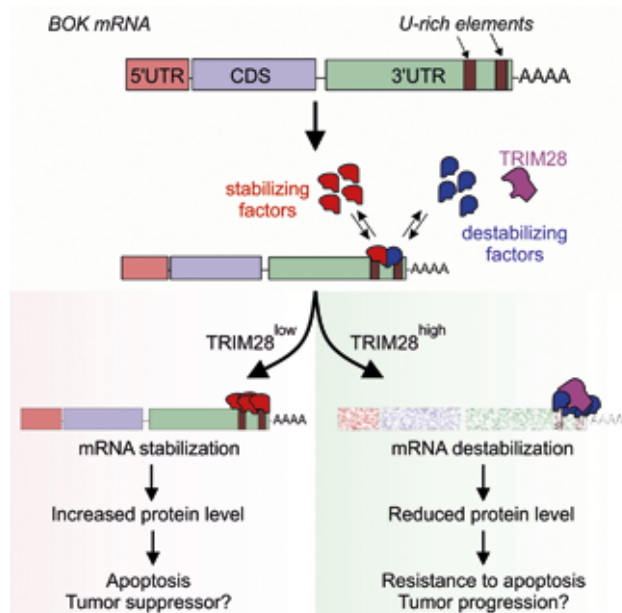


mtDNA nets (red) are released from activated human neutrophils. Nuclear DNA is stained by Hoechst 33342 (blue). Scale bar, 10  $\mu$ m.



*Negative regulation of BOK expression by recruitment of TRIM28 to regulatory elements in its 3' untranslated region*

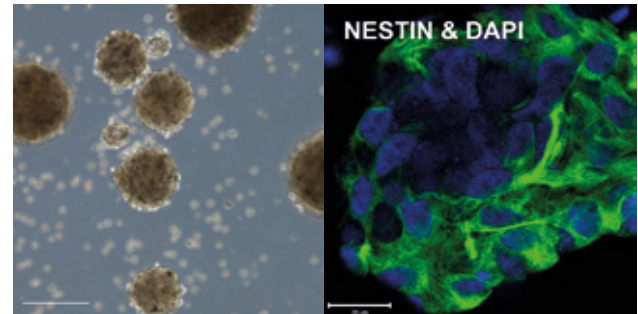
BCL-2-related ovarian killer (BOK) is a proapoptotic BAX-like member of the BCL-2 family with suggested tumor suppressor activity. The molecular mechanisms regulating BOK expression are poorly understood and fail to explain a frequent lack of concordance between protein and transcript levels. We discovered a potent post-transcriptional mechanism that negatively regulates BOK expression mediated by conserved (AU/U)-rich elements within the 3' untranslated region (3'UTR) of its mRNA transcript. Using proteomics approaches (mass spectrometry) we identified the pleiotropic Sumo E3 ligase TRIM28 as a key component associating with U-rich elements in the human BOK 3'UTR, resulting in a dramatic reduction of BOK expression. Whereas TRIM28 is overexpressed in several cancers, correlating with poor patient outcome, the BOK locus is frequently deleted, or its expression downregulated in human cancers. Data mining indicate that, for certain cancers, high TRIM28 and low BOK expression are significantly correlated in the stratum of patients with the worst survival, suggesting that this mechanism might be of potential therapeutic value.



*Biochemical re-programming of human dermal stem cells to neurons by increasing mitochondrial membrane potential*

Stem cells are generally believed to contain a small number of mitochondria, thus accounting for their glycolytic phenotype. We demonstrate here, however, that despite an indispensable glucose dependency, human dermal stem cells (hDSCs) contain very numerous mitochondria. Interestingly, these stem cells segregate into two distinct subpopulations. One exhibits high, the other low mitochondrial membrane potentials ( $\Delta\psi_m$ ). We have made the same observations with mouse neural stem cells (mNSCs) which serve here as a complementary model to hDSCs. Strikingly, pharmacologic inhibition of phosphoinositide 3-kinase (PI3K) increased the overall  $\Delta\psi_m$ , decreased the dependency on glycolysis and led to formation of TUJ1 positive, electrophysiologically functional neuron-like cells in both mNSCs and hDSCs, even in the absence of any neuronal growth factors. Furthermore, of the two, it was the  $\Delta\psi_m$ -high subpopulation which produced more mitochondrial reactive oxygen species (ROS) and showed an enhanced neuronal differentiation capacity

as compared to the  $\Delta\psi_m$ -low subpopulation. These data suggest that the  $\Delta\psi_m$ -low stem cells may function as the dormant stem cell population to sustain future neuronal differentiation by avoiding excessive ROS production. Thus, chemical modulation of PI3K activity, switching the metabolic type of hDSCs to neurons, may have potential as an autologous transplantation strategy for neurodegenerative diseases.



hDSC are characterized by sphere formation and the expression of the neuronal progenitor marker NESTIN (scale bar: 20  $\mu$ m).

### Selected Competitive Grants

- Swiss National Science Foundation (grant No. 310030-166473; 310030-153346; 31003A\_173215; 31003A\_149387; 310030\_162552; 310030-146215; 310030E-132762; 310030A-138201; 31003A\_173006)
- Swiss Cancer League (KFS-3703-08-2015; KFS-3941-08-2016)
- HORIZON 2020 (Marie Skłodowska-Curie Action): MEL-PLEX
- Novartis Foundation for Biological-Medical Research
- SNSF Professorship (PP00P3\_163929)

### Selected Publications

- Amini P, Stojkov D, Felser A, Jackson CB, Courage C, Schaller A, Gelman L, Eugenia Soriano M, Nuoffer JM, Scorrano L, Benarafa C, Yousefi S, Simon HU: Neutrophil extracellular trap formation requires OPA1-dependent glycolytic ATP production. *Nat Commun.* 2018 Jul 27;9(1):2958. doi: 10.1038/s41467-018-05387-y
- Liu H, He Z, April SL, Trefny MP, Rougier JS, Salemi S, Olariu R, Widmer HR, Simon HU: Biochemical re-programming of human dermal stem cells to neurons by increasing mitochondrial membrane potential. *Cell Death Differ.* 2018 Aug 28. doi: 10.1038/s41418-018-0182-8. [Epub ahead of print]
- Fernandez-Marrero Y, Bachmann D, Lauber E, Kaufmann T: Negative regulation of BOK expression by recruitment of TRIM28 to regulatory elements in its 3' untranslated region. *iScience.* 2018 Nov 10;9:461-474. doi: 10.1016/j.isci.2018.11.005
- Rabachini T, Fernandez-Marrero Y, Montani M, Loforese G, Sladky V, He Z, Bachmann D, Wicki S, Villunger A, Stroka D, Kaufmann T: BOK promotes chemical-induced hepatocarcinogenesis in mice. *Cell Death Differ.* 2018 Mar;25(4):706-718. doi: 10.1038/s41418-017-0008-0
- Blanchard O, Stepanovska B, Starck M, Erhardt M, Römer I, Meyer zu Heringdorf D, Pfeilschifter J, Zangemeister-Wittke U, Huwiler A: Downregulation of the S1P transporter Spinster homology protein 2 (Spns2) exerts an anti-fibrotic and anti-inflammatory effect in human renal proximal tubular epithelial cells. *Int J Mol Sci.* 2018 May 17;19(5). pii: E1498. doi: 10.3390/ijms19051498

# Institute of Physiology

University of Bern  
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Prof. Thomas Nevian  
 Managing Director



Prof. Walter Senn  
 Codirector



Prof. Stephan Rohr  
 Codirector



Prof. Ernst Niggli  
 Codirector



Prof. Marcel Egger



Prof. Stéphane Cioocchi  
 (SNF)



Prof. Jan Kucera



Prof. Jürg Streit



PD Dr. Sonja Kleinlogel



Prof. Jean-Pascal Pfister  
 (SNF)



Dr. Shankar Sachidhanandam

## Research Partners

- Humboldt University, Neurocure Cluster of Excellence, Berlin, Germany
- Brain Research Institute and Institute of Neuroinformatics, University of Zurich/ETH, Zurich
- Brain Mind Institute, EPFL, Lausanne, Switzerland
- Department of Pharmacy and Drug Science, University of Bari Aldo Moro, Bari, Italy
- Department of Medicine, Wisconsin Institutes for Medical Research, University of Wisconsin, USA
- Kirchoff Institute of Physics, University of Heidelberg, Heidelberg, Germany
- Medizinische Hochschule Hannover, Germany

## Research Profile

The Department of Physiology performs basic preclinical and translational research in cardiac- and neurophysiology. The five groups in cardiac physiology investigate the conditions that lead to heart failure and arrhythmias. They use electrophysiological and imaging techniques as well as computer simulations to elucidate the mechanisms of action potential propagation and excitation-contraction coupling on the subcellular, cellular and organ levels. In particular, two-photon uncaging combined with confocal microscopy is used to investigate calcium dynamics in cardiomyocytes. Finally, the role of myofibroblasts in cardiac arrhythmogenesis is investigated using novel imaging techniques and optogenetic tools.

Six groups conduct research in neurophysiology. The common theme is to understand neuronal network dynamics in the brain in health and disease. Strategies to cure retina degeneration are devised as well as developing new treatment strategies for chronic pain or spinal cord regeneration. The formation of emotional memories, anxiety, depression and perceptual vision are studied from molecules, over single cells to neuronal networks with electrophysiological, two-photon imaging, optogenetics and behavioural approaches. Two computational neuroscience groups develop probabilistic models of brain function at different levels, from single synapses to cognition.

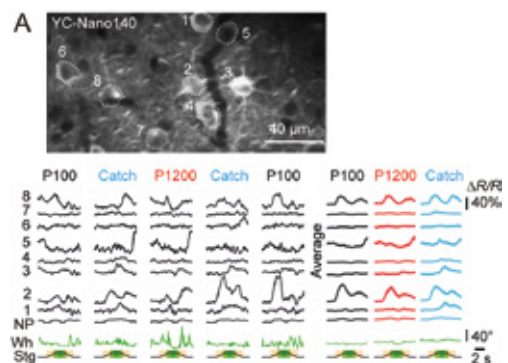
## Teaching Profile

The Department of Physiology is predominantly engaged in the education of students of human and dental medicine (Bachelor, years 1 to 3). The Department is responsible for the entire field of physiology, covering all lectures and practical courses and we supervise medical as well as natural science master and PhD theses. Lecturers of our institute participate in the training of students in veterinary medicine, pharmacy and the “Master in Biomedical Engineering” program. Our institute coordinates the master program in Biomedical Sciences (BMSc).

## Highlights 2018

*H. Mohan, Y. Gallero-Salas, S. Carta, J. Sacramento, B. Laurenczy, L.T. Sumanovski, C.P.J. de Kock, F. Helmchen & S. Sachidhanandam (2018) Sensory representation of an auditory cued tactile stimulus in the posterior parietal cortex of the mouse. Sci Rep 8:7739*

Sensory association cortices receive diverse inputs, from primary sensory and higher order cortical areas to generate a more comprehensive representation of the outside world. Here we examined the neuronal correlates of an

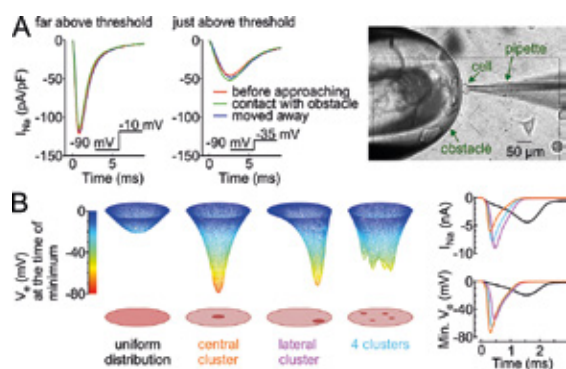


Neural dynamics of sensory representation in the PPC. (A) Top, 2-photon imaging of neurons expressing a genetically encoded calcium indicator. Bottom, calcium transients from the ROIs selected in the top panel in response to the presented auditory cues and textures, along with the neuropil (NP) signals and the corresponding whisker angles (Wh) in green. The transients represent the very first 5 trials that the mouse has been exposed to.

auditory-tactile stimulus sequence in the posterior parietal cortex (PPC) using 2-photon calcium imaging in awake mice. We find that PPC neurons were able to discriminate not only tactile stimulus features (i.e., texture graininess) but also reliably report the omission of the texture stimulus (Catch trials), as predicted by the auditory cues. These findings indicate that neuronal populations in PPC encode correlates of expectancy, potentially functioning as an integration site for top-down and bottom-up inputs within the framework of predictive coding.

*E. Hichri, H. Abriel & J. Kucera (2018) Distribution of cardiac sodium channels in clusters potentiates ephaptic interactions in the intercalated disc. J Physiol, 596:563-589*

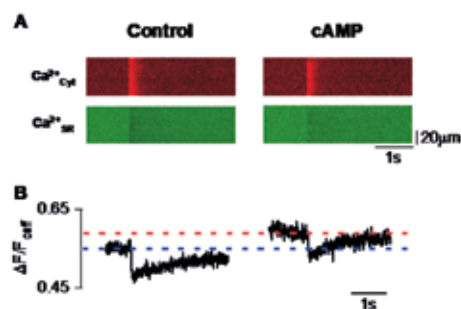
Ephaptic coupling is a controversial cardiac conduction mechanism that involves narrow extracellular large  $I_{Na}$  current ( $I_{Na}$ ) through the membrane on one side of the intercalated disc causes a negative extracellular potential which depolarizes the membrane on the other side, where it activates the  $Na^+$  channels. We demonstrated using patch clamp experiments that confining the extracellular space next to cells expressing  $Na^+$  channels alters  $I_{Na}$  in agreement with the ephaptic coupling mechanism. Using computational simulations, we showed that clustering of  $Na^+$  channels increases extracellular potentials and reinforces ephaptic coupling.



(A)  $I_{Na}$  in a HEK cell expressing  $Na^+$  channels during voltage steps far above ( $-10$  mV) and just above ( $-35$  mV) the  $I_{Na}$  activation threshold, before approaching the cell to a non-conductive obstacle, in contact with the obstacle, and after having moved it away. Restricting the extracellular space decreased  $I_{Na}$  at  $-10$  mV but increased it at  $-35$  mV, demonstrating ephaptic interactions. (B) Simulations showing that  $Na^+$  channel clustering increases the extracellular potential ( $V_e$ ) and accelerates the time course of  $I_{Na}$ .

*M. Fernandez-Tenorio & E. Niggli (2018) Stabilization of  $Ca^{2+}$  signaling in cardiac muscle by stimulation of SERCA. J Mol Cell Cardiol. 119; 87-95.*

In cardiac muscle, the  $Ca^{2+}$  signal responsible for contraction

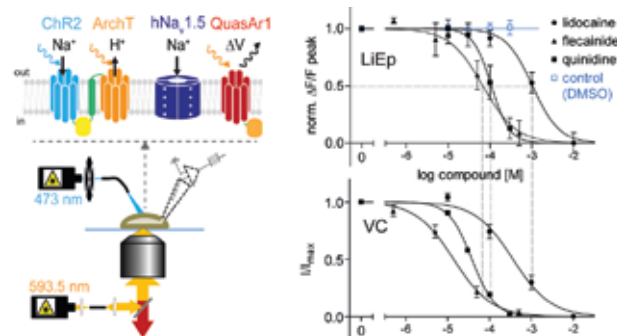


(A) Cytosolic (red) and intra-SR (green)  $Ca^{2+}$  signals visualized as confocal line-scan images. (B) Time-resolved profiles showing intra-SR  $Ca^{2+}$  drop during a wave. In the presence of cAMP, the SERCA stimulation leads to an elevated wave threshold (red dashed line).

is controlled by  $Ca^{2+}$  release from an intracellular store, the sarcoplasmic reticulum (SR). Refilling of the SR after each heartbeat is governed by the SR  $Ca^{2+}$  pump (SERCA). Using specific SERCA stimulation in isolated cardiomyocytes, we made the surprising observation that isolated SERCA stimulation actually stabilized  $Ca^{2+}$  signaling by elevating the wave threshold, therefore essentially being antiarrhythmic, opposite to previous expectations. This mechanism is presumably relevant during ongoing trials treating HF patients with SERCA gene therapies or small molecule SERCA stimulators.

*J. Streit & S. Kleinlogel (2018). Dynamic all-optical drug screening on cardiac voltage-gated ion channels. Scientific Reports, 8:1153*

Voltage-gated ion channels are prime targets for the pharmaceutical industry, but drug profiling is challenging since drug interactions are confined to specific conformational channel states mediated by changes in transmembrane potential. Here we combined various optogenetic tools – genetically encoded light-activated ion channels (channelrhodopsins, i.e. ChR2) and ion pumps (archaerhodopsins, i.e. ArchT) as well as genetically encoded light-emitting activity sensors (voltage sensors, i.e. QuasAr1) – to develop a “hands-free”, all-optical, high-throughput drug profiling assay to interrogate voltage-gated ion channel states on a millisecond timescale. Our novel technology that we termed light-induced electrophysiology (LiEp) yields high-quality pharmacological data with exceptional screening windows.



The LiEp system exemplified for  $hNa_{v1.5}$  screening. Top left: Schematic depiction of the cellular expression system and the imaging set-up. Top right: Comparison of dose-response curves of drugs acting on  $hNa_{v1.5}$  generated by LiEp (top) or by conventional voltage-clamp (VC, bottom).

### Selected Competitive Grants

- ERC Consolidator Grant (Nevian)
- ERC Starting Grant (Ciocchi)
- SNF Professorship Grant (Pfister)
- Bertarelli Foundation Catalyst Grant (Kleinlogel)

### Selected Publications

- J. Blanch, M. Egger (2018) Obstruction of ventricular  $Ca^{2+}$ -dependent arrhythmogenicity by IP- triggered SR- $Ca^{2+}$  release. *J. Physiol.* 596.18:4323–4340
- A. Buccarello, M. Azzarito, F. Michoud, S.P. Lacour, J.P. Kucera (2018) Uniaxial strain of cultured mouse and rat cardiomyocyte strands slows conduction more when its axis is parallel to impulse propagation than when it is perpendicular. *Acta Physiologica* 223:e13026
- D.M. Potenza, R. Janicek, M. Fernandez-Tenorio, E. Camors, R. Ramos-Mondragón, H.H. Valdivia, E. Niggli (2018) Phosphorylation of the ryanodine receptor 2 at serine 2030 is required for a complete  $\beta$ -adrenergic response. *J. Gen. Physiol.* online



# Institute of Social and Preventive Medicine (ISPM)

Mittelstrasse 43  
3012 Bern



Prof. Thomas Abel  
Head of  
Research Group



PD Dr. Christian Althaus  
Head of  
Research Group



PD. Dr. Julia Bohlius  
Head of  
Research Group



Prof. Matthias Egger  
Head of  
Research Group



Prof. Oscar Franco  
Director



Prof. Claudia Kuehni  
Head of  
Research Group



Prof. Nicola Low  
Head of  
Research Group



Prof. Stefan Reichenbach  
Head of  
Research Group



Luciano Ruggia  
Head of  
Research Group



Prof. Georgia Salanti  
Head of  
Research Group



Dr. Adrian Spoerri  
Head of  
Research Group



PD Dr. Ben Spycher  
Head of  
Research Group



Brigitte Wanner  
Head of Central  
Services



Prof. Marcel Zwahlen  
Deputy Director

## Project Websites

- CANUPIS, Childhood Cancer and Nuclear Power Plants in Switzerland
  - ESTHER Switzerland, Network for the Promotion of Institutional Health Partnerships
  - leDEA-SA, International epidemiologic Databases to Evaluate AIDS
  - MIWOCA, Migrant Women's Health Care Needs for Chronic Illness Services in Switzerland
  - Leicestershire Cohort Studies, The Leicestershire & Rutland Cohort Studies
  - STROBE, Strengthening the Reporting of Observational Studies in Epidemiology
  - SCCR, Swiss Childhood Cancer Registry
  - SHCS, Swiss HIV Cohort Study
  - SNC, Swiss National Cohort
  - SwissRDL, Medical Registries and Data Linkage
  - TB-Network, TB-Network - Molecular and clinical epidemiology of tuberculosis in Switzerland
  - ZOAP, Zika Open Access Project
- 18 national and international registries

## Research Profile

The institute of Social and Preventive Medicine (ISPM) at the University of Bern conducts interdisciplinary research in social and behavioral health, clinical epidemiology and biostatistics, and international and environmental health to promote health, prevent disease, and advance knowledge of health and disease at the population level.

## Teaching Profile

The institute teaches courses for University of Bern students of Medicine, Biomedicine, and Biomedical Engineering; University of Fribourg students of Biomedicine; and PhD and postgraduate programs of the Swiss School of Public Health.

## Highlights 2018

*New Director: Prof. Oscar Franco*

In June 2018, Prof. Oscar Franco assumed the directorship of ISPM. Prof. Franco obtained his MD at Pontificia Universidad Javeriana, Bogotá (1998), and MSc and DSc degrees in clinical epidemiology and a PhD in public health and cardiovascular disease prevention (2005) at the Erasmus University Medical Center in the Netherlands. Following a postdoc there, he was a senior public health epidemiologist at Unilever England, assistant professor of public health at the University of Warwick, and then director of the MPhil program and clinical lecturer in public health at the University of Cambridge.

In 2012 Prof. Franco returned to Erasmus University Medical Center as a professor of preventive medicine and the



principal investigator of the cardiovascular epidemiology group. He also founded and directed the Rotterdam Intergenerational Ageing Research Center ([www.erasmusage.com](http://www.erasmusage.com)), and is a cofounder and the CEO of Erasmus Epidemiology Resources ([erasmusepidemiologyresources.com](http://erasmusepidemiologyresources.com)).

*New CAS courses in Clinical Research and Managing Medicine*  
Clinical research determines the safety and efficacy of medications, medical devices, diagnostic procedures, and treatments. In the CAS in Clinical Research, participants learn to plan and conduct clinical research projects and communicate their results.

Medical care is planned, designed, and delivered – in short, it is managed. Managing Medicine means balancing patient needs with the requirements of service delivery and the dynamics and progress of medicine in a changing health care system. ISPM offers the CAS Managing Medicine in Health Care Organisations in close collaboration with college M and the Department of Management and Entrepreneurship, University of Berne.

#### *New premises at Mittelstrasse 43*

ISPM moved from four different locations to the newly renovated former SBB building at Mittelstrasse 43 in Bern.



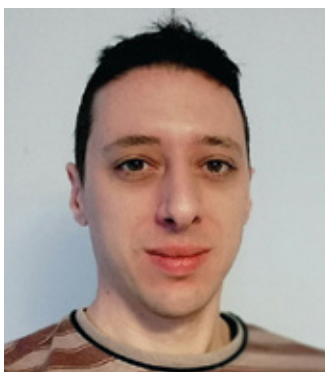
#### *National Registry for Childhood Cancer at ISPM*

The Swiss Childhood Cancer Registry (SCCR) at the University of Bern has collected data on children and adolescents with cancer in Switzerland for over 40 years. Now, the registry will be converted into a federal registry to further improve the documentation, diagnosis, and treatment of cancer in the young. The Registry is directed by Claudia Kuehni (left) and Verena Pfeiffer (right).



#### *Ambizione grant*

Orestis Efthimiou was awarded an Ambizione grant to develop methods for personalizing treatment choices. The project "Predicting the real-world effectiveness and safety of medical interventions" (REFINE) will develop new methods to personalize treatment and accommodate the individual characteristics, needs, and preferences of patients using evidence from randomized clinical trials and clinical practice.



#### **Selected Competitive Grants**

- SNF (IZ07ZO\_160909, 32473B\_160153, 407440\_167428, 32FP30\_174281, 320030\_173044, 320030\_169967, 320030\_176233, 320030\_176218, 320030\_179158, IZ08ZQ\_177319, PZ00P3\_180083)
- Krebsforschung (KFS-4157-02-2017, KFS-4156-02-2017, KLS-3886-02-2016)
- EU : PanCareLife (<http://www.pancarelife.eu/>)

#### **Selected Publications**

- Rohner, Eliane; Bütikofer, Lukas; Schmidlin, Kurt; Sengayi, Mazvita; Maskew, Mhairi; Giddy, Janet; Moore, Richard D; Goedert, James J; Gill, John M; Silverberg, Michael J; Patel, Pragna; Castilho, Jessica; Hoy, Jennifer; Sohn, Annette; Bani-Sadr, Firouze; Taylor, Ninon; Pappas, Vassilios; Le Moing, Vincent; Bonnet, Fabrice; Verbon, Annelies; ... (2018). Non-Hodgkin lymphoma risk in adults living with HIV across five continents: a multicohort study. *AIDS*. 2018 Nov 28;32(18):2777-2786. doi: 10.1097/QAD.0000000000002003
- Hocking, Jane S; Temple-Smith, Meredith; Guy, Rebecca; Donovan, Basil; Braat, Sabine; Law, Matthew; Gunn, Jane; Regan, David; Vaisey, Alaina; Bulfone, Liliana; Kaldor, John; Fairley, Christopher K; Low, Nicola; Consortium, ACCEPT (2018). Population effectiveness of opportunistic chlamydia testing in primary care in Australia: a cluster-randomised controlled trial. *Lancet*. 2018 Oct 20;392(10156):1413-1422. doi: 10.1016/S0140-6736(18)31816-6
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- Chowdhury, Rajiv; Ramond, Anna; O'Keefe, Linda M; Shahzad, Sara; Kunutsor, Setor K; Muka, Taulant; Gregson, John; Willeit, Peter; Warnakula, Samantha; Khan, Hassan; Chowdhury, Susmita; Gobin, Reeta; Franco, Oscar H; Di Angelantonio, Emanuele (2018). Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2018 Aug 29;362:k3310. doi: 10.1136/bmj.k3310
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# Institute for Surgical Technology and Biomechanics (ISTB)

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Prof. Philippe  
Büchler



Prof. Benjamin  
Gantenbein



Prof. Mauricio  
Reyes



Prof. Guoyan  
Zheng

## Research Partners

- Department of Orthopaedic, Plastic and Hand Surgery, University Hospital of Bern, Bern, Switzerland
- Department of Neurology, University Hospital of Bern, Bern, Switzerland
- Department of Radiology, Neuroradiology and Nuclear Medicine, University Hospital of Bern, Bern, Switzerland
- Institute for Biomechanics, Swiss Federal Institute of Technology Zürich, Zürich, Switzerland
- Laboratory for Mechanics of Materials, Swiss Federal Laboratories for Materials Science and Technology (EMPA), Thun, Switzerland
- Computer-Aided Medical Procedures & Augmented Reality, Technical University München, München, Germany
- Department of Orthopaedic Surgery, Surgical Science and Research Centre for Regenerative Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan
- Imaging-based Computational Biomedicine Lab, Nara Institute of Science and Technology, Nara, Japan
- Beckman Research Institute, City of Hope, California, USA
- Centre for Advanced Orthopaedic Studies, Harvard Medical School, Boston, USA

## Research Profile

The ISTB emerged from the Maurice E. Müller Institute for Biomechanics founded in 1981. Five research groups contribute to the development of novel diagnostic and surgical technologies with an emphasis on the musculoskeletal system. Basic and applied research are conducted for the prevention or treatment of disease, working from the cell to organs. The focus is on developing solutions that address particular clinical problems or unmet clinical needs. Tissue and organ mechano-biology aims at understanding cellular response to biomechanical stimuli and how cellular communities develop in 3D tissue and organ cultures. Medical image analysis employs image-based models to quantify and support the decision-making process of clinicians for diseases of the central nervous system. Computational bioengineering exploits modern simulation tools such as finite element analysis to resolve practical and fundamental clinical questions. Information processing in medical interventions involves pre-operative planning, intra-operative treatment and post-operative control of challenging surgeries such as peri-acetabular osteotomy or femoro-acetabular impingement treatment. Musculoskeletal biomechanics focuses on multi-scale structure-function relationships of bone tissue from the extra-cellular matrix to the organ level. Together with ARTORG, the ISTB also manages a machine shop supporting construction and production of various parts for experimental set-ups in biomedical engineering.

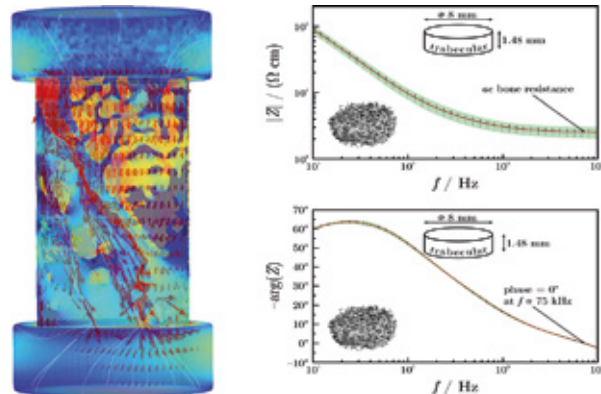
## Teaching Profile

The institute coordinates the master program for biomedical engineering in cooperation with the Bernese university of applied sciences. Within this program, the researchers of ISTB contribute substantially to the basic modules as well as to the specialization modules in biomechanical systems and image guided therapy. Supervision of master and doctoral theses represents an important part of the teaching activity.

## Highlights 2018

### *Characterization of the electrical conductivity of bone and its correlation to osseous structure*

The interaction of osseous tissue with electric fields has many potential applications; electrical bone stimulation is thought to promote osteogenesis, while bone impedance has been proposed to measure osteoporosis, to follow fracture healing, or to improve safety of surgical procedures. However, an accurate characterization of the electrical bone properties is required to establish these techniques in clinics. We developed new methods to precisely quantify bone impedance and determined the relationship between the measured conductivity and the bone volume fraction ( $R^2=0.83$ ). Our results also showed that a map describing bone resistivity can be directly derived from clinical images.

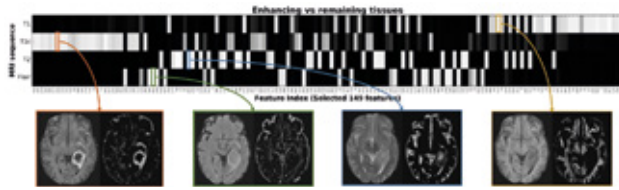


### *Efficient Focused Active Learning for Evolutive Deep Learning in Medical Image Analysis*

A novel technique for focused active learning was developed, enabling fast learning rates of deep learning technologies for image segmentation and image classification. The approach utilizes measures of uncertainty of computer-generated results to focus on difficult learning areas of an image. The focused learning is coupled with smart data augmentation approach that synthetically generates similar data samples around the data point of current focus. Experimental results on medical images show the ability of the approach to learn at faster rates than traditional active

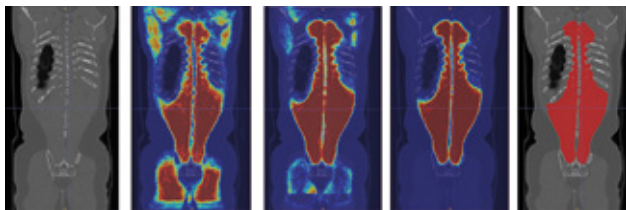


learning systems, while enabling a better usage of the available training set.



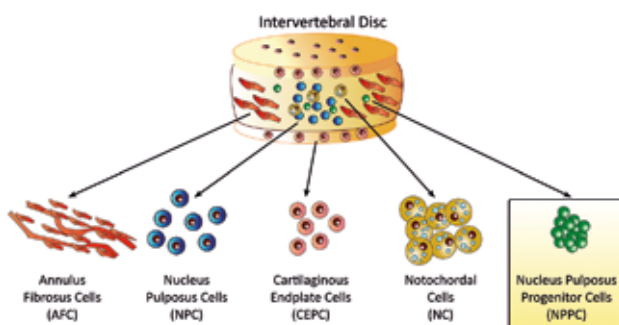
### Soft and Hard Tissue Segmentation from CT and MRI Data for Computer Assisted Interventions

The IPMI group successfully developed novel machine learning and deep learning methods for segmenting both soft and hard tissues from CT and MRI data, which is crucial for many clinical applications including disease diagnosis, surgical planning and computer assisted interventions. For example, bone and cartilage segmentation from hip MR images will greatly facilitate the applications of MR images for hip preservation surgical planning and simulation; segmentation of lumbar intervertebral discs from 3D MR data is a step prior to the quantitative assessment of IVD abnormalities for the diagnosis of spinal disease; accurate muscle segmentation from CT data is a prerequisite for characterizing muscle atrophy for patients with chronic obstructive pulmonary disease (COPD).



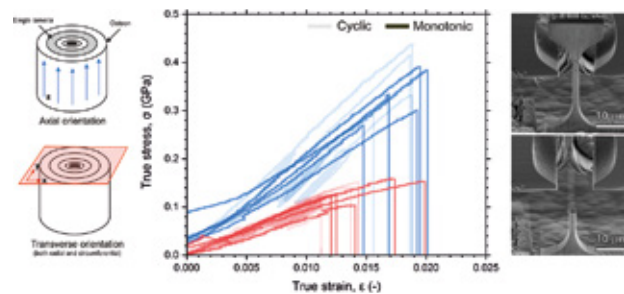
### Tissue-engineered strategies for intervertebral disc repair: on fibre-reinforced hydrogel and silk and on "fishing" of tissue-specific progenitor cells

The TOM group successfully completed and reported novel results of a tissue engineering study using a functionalized biomaterial of a genipin-fibre reinforced fibrin hydrogel for intervertebral disc repair in a mechanobiological relevant organ culture model (DOI: 10.3390/jfb9030040). Furthermore, the group reported how to "fish" a recently identified population of tissue-specific progenitor cells positive for the endothelial marker angiopoietin receptor-1 from the intervertebral disc across a wide range of species, i.e. mouse, canine, bovine and human (DOI: 10.1002/jsp2.1018). These progenitor cell population could be highly valuable as a cell source for regenerative therapy involving iPS cell technology (see figure). Finally, molecular investigations on the mechanisms of expression of BMP inhibitors for non-unions in spinal fusion have been reported (DOI: 10.3390/ijms19041195).



### Micro-meso scale transition of bone strength (SNF grant 165510 with EMPA)

A micromechanical tensile setup was designed to test focused ion beam (FIB) fabricated osteonal bone samples in tension inside a scanning electron microscope (SEM). Misalignment errors were carefully minimized using finite element analysis and both axial and transverse mechanical properties were measured at the scale of single lamellae (3-7  $\mu\text{m}$ ). These unique microtensile tests revealed a strong size effect and anisotropy of the mechanical properties at this lower length scale. Both axial and transverse samples revealed higher strengths from the ones found in macroscale experiments by a factor of 2.5, highlighting the effect of the hierarchical organization of bone tissue.



### Selected Competitive Grants

- Swiss National Science Foundation (grant no 157207; 163224; 165510; 169607; 173130; 170060)
- Innosuisse (grant no 18193.1 PFLS-LS; 27450.1 PFLS-LS; T-2017-023; 31274.1 IP-LS)
- Swiss Cancer League (grant no KFS-3979-08-2016)
- Center for Applied Biotechnology and Molecular Medicine (CABMM) University of Zürich, start-up grants
- HansJörg Wyss Medical, USA
- Horizon 2020 - Marie Skłodowska-Curie Global Fellowship GlimS (grant no 753878) and MIMetiCO (grant no 786692)

### Selected Publications

- Balmer TW, Vesztorgom S, Broekmann P, Stahel A, Büchler P: Characterization of the electrical conductivity of bone and its correlation to osseous structure. *Sci Rep.* 2018 Jun 5;8(1):8601. doi: 10.1038/s41598-018-26836-0
- Li X, Hao Chen QD, Fu CW, Qi X, Belavý DL, Armbrecht G, Felsenberg D, Zheng G, Heng PA: 3D multi-scale FCN with random modality voxel dropout learning for intervertebral disc localization and segmentation from multi-modality MR images. *Med Image Anal.* 2018 Apr;45:41-54. doi: 10.1016/j.media.2018.01.004
- May RD, Frauchiger DA, Albers CE, Benneker LM, Kohl S, Gantenbein B: Inhibitory Effects of Human Primary Intervertebral Disc Cells on Human Primary Osteoblasts in a Co-Culture System. *Int J Mol Sci.* 2018 Apr 13;19(4). pii: E1195. doi: 10.3390/ijms19041195
- Ovesy M, Voumard B and Zysset P: A non-linear homogenized finite element analysis of the primary stability of the bone-implant interface. *Biomech Model Mechanobiol.* 2018 Oct;17(5):1471-1480. doi: 10.1007/s10237-018-1038-3
- Pereira S, Meier R, McKinley R, Wiest R, Alves V, Silva C and Reyes M: Enhancing interpretability of automatically extracted machine learning features: application to a RBM-random forest system on brain lesion segmentation. *Med Image Anal.* 2018 Feb;44:228-244. doi: 10.1016/j.media.2017.12.009



## Theodor Kocher Institute (TKI)

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Prof. Britta Engelhardt  
Director and Group Leader



PD Dr. Ruth Lyck  
Group Leader



Prof. Jens V. Stein  
Group Leader  
(until 30.6.2018)



Dr. Giuseppe Locatelli  
Group Leader



Dr. Urban Deutsch  
Group Leader



PD Dr. Marlene Wolf  
Group Leader

### Research Partners

- Laboratory for High Energy Physics (LHEP), University of Bern, Bern, Switzerland
- Institute for Research in Biomedicine, Bellinzona, Switzerland
- Centre de Physiopathologie de Toulouse-Purpan, INSERM UMR1043, Toulouse, France
- Karolinska Institutet, Huddinge, Sweden
- Centre de Recherche, Laboratoire de la barrière hémato-encéphalique, Université d'Artois, Lens, France
- Department of Neuropathology, University of Freiburg, Freiburg im Breisgau, Germany
- Department of Biomedical Engineering, University of Rochester Medical Center, NY, USA
- KU Leuven, Leuven, Belgium
- Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

### Research Profile

Founding of the TKI in 1950 was made possible by a donation of the Bernese Nobel laureate Theodor Kocher in 1912. Current research at the TKI is to a large part dedicated to investigate cellular and molecular mechanisms involved in neuroinflammation as they occur in multiple sclerosis or in stroke. A special focus hereby lies on studying immune cell migration into the central nervous system (CNS) during immune surveillance and neuroinflammation employing cutting-edge 3D in vitro and in vivo live cell imaging methodologies and targeted transgenic mouse models. Research competence at the TKI allows for the coordination of the Microscopy Imaging Center (MIC, [www.mic.unibe.ch](http://www.mic.unibe.ch)) and the heading of the Mouse Cryoconservation and Mouse Transgenic and Genetic Engineering Facility, a member of the transgenesis platform of the Swiss Animal Facilities Network (SAFN).

### Teaching Profile

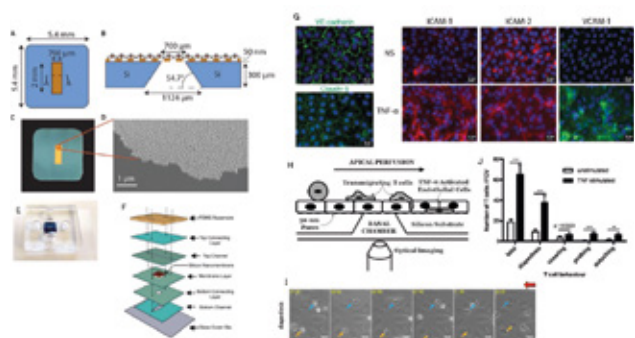
The TKI is involved in local, national and international teaching efforts providing a large portfolio of lectures and practical classes in immunology, microscopy, vascular cell biology, transgenic mouse technologies, inflammation and high end in vitro and in vivo live cell imaging for bachelor, master and graduate students in the Medical, Science and Vetsuisse Faculties. The TKI hosts the two interfaculty Graduate Schools (Graduate School for Cellular and Biomedical Sciences ([www.gcb.unibe.ch](http://www.gcb.unibe.ch)) & Graduate School for Health Sciences ([www.ghs.unibe.ch](http://www.ghs.unibe.ch))). In addition, coordination of the Swissuniversities supported PhD programs "Cell Migration" and "Cutting Edge Microscopy" are localized at

the TKI. Britta Engelhardt is coordinator of the Horizon2020 funded international PhD student training program BtRAIN (<http://www.btrain-2020.eu>).

### Highlights 2018

#### *Development of a breakthrough microfluidic human in vitro cerebrovascular barrier (CVB) model*

In collaboration with Dr. McGrath (University of Rochester, NY, USA), Dr. Gosselet (Université d'Artois, Lens, France) and Dr. Sallusto (IRB, Bellinzona) we have developed a microfluidic human in vitro cerebrovascular barrier (CVB) model featuring stem cell derived brain like endothelial cells (BLECs) and nanoporous silicon nitride (NPN) membranes ( $\mu$ SiM-CVB). The nanoscale thinness of NPN membranes combined with their high permeability and optical transparency make them an ideal scaffold for the assembly of a two-chamber in vitro microfluidic model of the blood-brain barrier (BBB). With the benefit of physiological flow and superior imaging quality, the  $\mu$ SiM-CVB allows to image each phase of the multi-step T-cell migration across the BBB by live cell imaging. The small scale of the  $\mu$ SiM-CVB allows for in vitro investigations of rare patient derived immune cells with the human BBB. We expect the  $\mu$ SiM-CVB to become a valuable new tool for the study of cerebrovascular pathologies ranging from neuroinflammation to metastatic cancer.

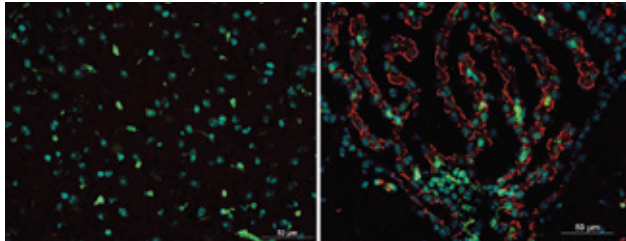


$\mu$ SiM-CVB: (A) Schematic of the NPN membrane. (B) The cross-sectional schematic of the membrane. (C) Optical micrograph of the chip. (D) Scanning electron micrograph of the NPN membrane. (E, F) Flow chamber configuration. (G) Immunofluorescence staining of BLECs. (H) Schematic of the flow settings. (I) Snapshots illustrating the multi-step interaction of T cells with BLECs. (J) Analysis of T-cell interactions with BLECs.

#### *Claudin-3 is not expressed at the blood-brain barrier*

The tight junction protein claudin-3 has been proposed to play a central role in regulating integrity of brain barriers' tight junctions. By establishing and analysing claudin-3<sup>-/-</sup> C57BL/6J mice using bulk and single cell RNA sequencing

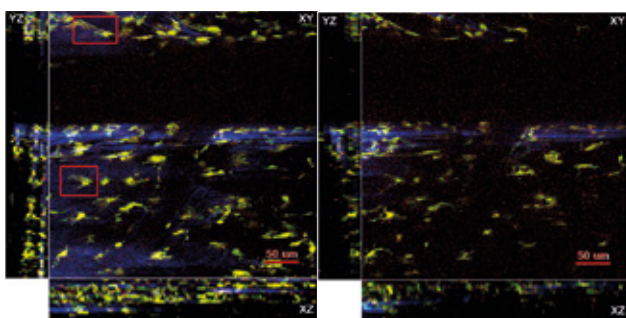
and direct comparative qRT-PCR analysis, we found that brain endothelial cells do not express claudin-3 mRNA. Detection of claudin-3 protein at the BBB in vivo and in vitro is rather due to junctional reactivity of anti-claudin-3 antibodies to an unknown antigen still detected in claudin-3<sup>-/-</sup> brain endothelium. At the same time our study did confirm expression and junctional localization of claudin-3 at the epithelial blood-cerebrospinal fluid barrier (BCSFB) of the choroid plexus. Absence of claudin-3 did however not impair brain barriers function during health and neuroinflammation in C57BL/6J mice (Dias, Coisne et al., Sci Reports, 2019, 9(1):203).



Claudin-3 is localized to tight junctions of the BCSFB. Immunofluorescent staining of frozen brain sections from WT C57BL/6, showing absence and presence of claudin-3 from the BBB (left) and the BCSFB (right), respectively. Red = claudin-3; green = endothelial cells, blue = nuclear staining. Scale bar = 50μm.

#### *Employing real-time data processing for movement correction and cell tracking during image acquisition*

Funding Unibern ID grant allowed for a collaboration of the Engelhardt group with Dr. Ariga from High Energy Physics of the University of Bern. Making use of his expertise in real-time data processing in microscopy employing parallel computing with GPUs, we established a powerful novel controllable synchronization tool allowing to use twophoton-intravital microscopy (2P-IVM) to image the cervical spinal cord, an area subjected to periodic movement due to animal breathing. The novel tool implements distortion correction in acquired images, thus enabling precise measurement of cellular motility parameters. The technology sets the stage for studying the cellular pathway of T-cell diapedesis across the BBB in vivo by 2P-IVM.



Example of the cervical spinal cord leptomeninges imaging in CX3CR1-GFP knock-in mice. Left: without synchronization tissue movement causes distortion in the acquired 3D volume. Fine structures appear as duplicates in XY projection (highlighted), and structural information in depth is lost (XZ, YZ projections). Right: with synchronization the fine cellular protrusions and the structural information is restored. Myeloid-cells (green) and collagen (blue, second harmonic generation).

*Chemokines and integrins independently tune actin flow and substrate friction during intranodal migration of T cells*  
Although much is known about the physiological framework of T cell motility, and numerous rate-limiting molecules have been identified through loss-of-function approaches, an integrated functional concept of T cell motility is

lacking. The Stein group used in vivo precision morphometry together with analysis of cytoskeletal dynamics in vitro to deconstruct the basic mechanisms of T-cell migration within lymphatic organs. In collaboration with Dr. Sixt (Vienna), we showed that the contributions of the integrin LFA-1 and the chemokine receptor CCR7 are complementary rather than positioned in a linear pathway, as they are during leukocyte extravasation from the blood vasculature. Our data demonstrate that CCR7 controls cortical actin flows, whereas integrins mediate substrate friction that is sufficient to drive locomotion in the absence of considerable surface adhesions and plasma membrane flux.

#### *VLA-4 mediated adhesion of melanoma cells on the blood-brain barrier is a critical cue in brain metastasis formation*

Melanoma is the most aggressive skin cancer in humans. One severe complication is the formation of brain metastasis. Employing live cell imaging of melanoma cells during their interactions with a mouse BBB model in vitro, we revealed a critical role of the integrin VLA-4 on melanoma cells for shear resistant arrest on and intercalation into the BBB. A tissue microarray revealed that indeed a majority of 92% of all human melanoma brain metastases stained VLA-4 positive. In conclusion, we propose VLA-4 as a target for the inhibition of brain metastasis formation in the context of personalized medicine.

#### **Selected Competitive Grants**

- Swiss National Science Foundation (31003A\_170131, CRSII3\_154483, 31003A\_172994, 16CRSII5\_170969).
- European Union: (FP7 MCA-ITN 607962nEUROinflammation; H2020-MSCA-ITN-2015 675619)
- Fidelity International Foundation, Swiss Multiple Sclerosis Society, Theodore Ott Fund, Bangerter-Rhyner Foundation, Foundation for Clinical-Experimental Cancer Research

#### **Selected Publications**

- Locatelli G, Theodorou D, Kendirli A, Jordão MJC, Staszewski O, Phulphagar K, Cantuti-Castelvetri L, Dagkalis A, Bessis A, Simons M, Meissner F, Prinz M, Kerschensteiner M. Mononuclear phagocytes locally specify and adapt their phenotype in a multiple sclerosis model. *Nat Neurosci.* 2018 Sep;21(9):1196-1208
- Tietz S, Périnat T, Greene G, Enzmann G, Deutsch U, Adams R, Imhof B, Aurrand-Lions M, Engelhardt B. Lack of Junctional Adhesion Molecule (JAM)-B ameliorates experimental autoimmune encephalomyelitis. *Brain Behav Immun.* 2018 Oct;73:3-20
- Mossu A, Rosito M, Khire T, Li Chung H, Nishihara H, Gruber I, Luke E, Dehouck L, Sallusto F, Gosselet F, McGrath JL, Engelhardt B. A silicon nanomembrane platform for the visualization of immune cell trafficking across the human blood-brain barrier under flow. *J Cereb Blood Flow Metab.* 2018 Dec 19:271678X18820584
- García-Martín AB, Zwicky P, Gruber T, Matti C, Moalli F, Stein JV, Francisco D, Enzmann G, Levesque MP, Hewer E, Lyck R. VLA-4 mediated adhesion of melanoma cells on the blood brain barrier is the critical cue for melanoma cell intercalation and barrier disruption *J Cereb Blood Flow Metab.* 2018 May 15
- Hons M, Kopf A, Hauschild R, Leithner A, Gaertner F, Abe J, Renkawitz J, Stein JV, Sixt M. Chemokines and integrins independently tune actin flow and substrate friction during intranodal migration of T cells. *Nat Immunol.* 2018 Jun;19(6):606-616

# Institute for Infectious Diseases (IFIK)

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Prof. Andrea Endimiani



PD Dr. Lucy Hathaway



PD Dr. Markus Hilty



Prof. Parham Sendi



PD Dr. Andreas Kronenberg  
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Dr. Alban Ramette



Dr. Peter Keller  
Head Innovation  
and Development



PD Dr. Christoph Niederhauser

## External Research Partners

- Environmental Engineering Institute, Environmental Microbiology Laboratory, and Interfaculty Institute for Bioengineering, Laboratory of Metabolic Signaling, EPFL, Lausanne, Switzerland
- Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, South Africa
- Swiss Tropical and Public Health Institute, Basel, Switzerland
- Department of Genetics, University of Leicester, UK
- Spiez Laboratory, Swiss Federal Office for Civil Protection, Spiez, Switzerland

## Institute Profile

The Institute for Infectious Diseases (IFIK) is the only Swiss university institute that covers the entire spectrum of microbiology, including virology, bacteriology, mycology, parasitology, molecular diagnostic and infection serology, integrated in comprehensive diagnostic services, research, and education. We provide diagnostic services recognized by Swissmedic and ISO/IEC 17025 (STS 0363) accredited for patient care in public hospitals including the Insel Group. The IFIK is home to the Swiss National Reference Centre for Pneumococci and to the Swiss National Centre for Antibiotic Resistance (anresis.ch) mandated by the Federal Office of Public Health. These activities are complemented by strategic and investigator-driven research projects in academic research laboratories working in the fields of antimicrobial resistance, central nervous system infection, diagnostic innovation, microbial genomics and host-microbiota interaction, and mucosal infections. Specific research topics in 2018:

- Research and diagnostic applications of 3<sup>rd</sup>-generation nanopore sequencing
- Characterization and rapid detection of clinically relevant and emerging antimicrobial resistance mechanisms and modes of transmission, including One-Health aspects
- Pathophysiology and therapy of central nervous infections including tick-borne encephalitis and bacterial meningitis and associated neurofunctional sequelae
- Streptococcal biofilm formation, molecular pathogenesis,

vaccination and bacteria-bacteria signaling

- Gut and airway microbiomes and their in-vivo modeling
- Microbiota-mediated effects of environmental chemicals on soil, crop, domestic animal and human health along the food chain

## Teaching Profile

The IFIK provides teaching programs for students of human medicine, dental medicine, pharmacology, biomedical sciences, and biology. The IFIK accepts applications for master, MD and PhD doctoral theses, and research postdoc fellowships. We are actively involved in the FAMH postgraduate training in Clinical Microbiology.

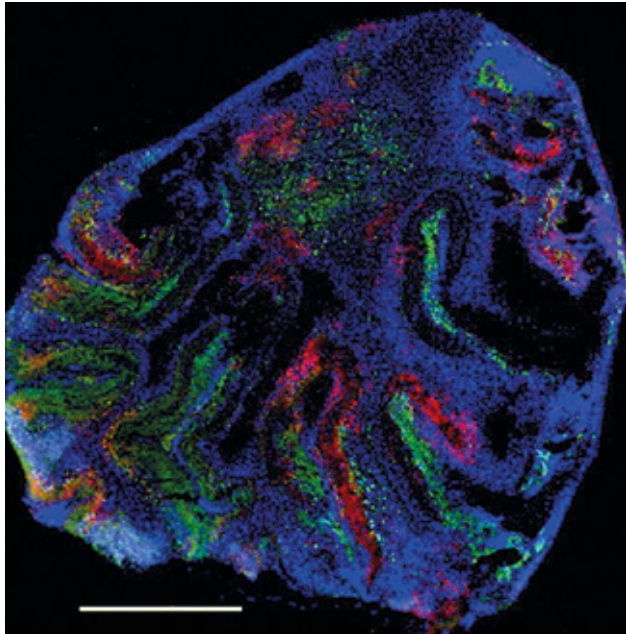
IFIK is part of the HONOURS consortium, an EU-funded Marie Skłodowska-Curie Action early-career scientist training network on host-switching pathogens, infectious outbreaks and zoonosis. This consortium consists of 10 high-profile universities, research institutions and companies located in Belgium, Germany, the Netherlands, Spain, Switzerland and the United Kingdom.

## Highlights 2018

In 2018 we celebrated the kick-offs of 2 Interfaculty Research Cooperation (IRC) projects with IFIK participation, "One-Health: Cascading and Microbiome-Dependent Effects on Multitrophic Health" and "Decoding Sleep: From Neurons to Health and Mind". IFIK continues to have a leading role in Swiss antimicrobial resistance research: Epidemiological data from anresis were published in the Swiss Antibiotic Resistance Report and broadly communicated during the Antibiotic Awareness Week. In addition, the first calculation of the associated disease burden in Switzerland was published in *Lancet Infectious Diseases*, and IFIK researchers received 3 new grants of the renowned SNF NRP-72 National Antibiotic Resistance Research Program. Supported by an SNF Sinergia grant with IFIK as leading house, an interdisciplinary research collaboration with EPFL and University of Nottingham was launched to study the bile-acid-mediated regulation of metabolism and immunity

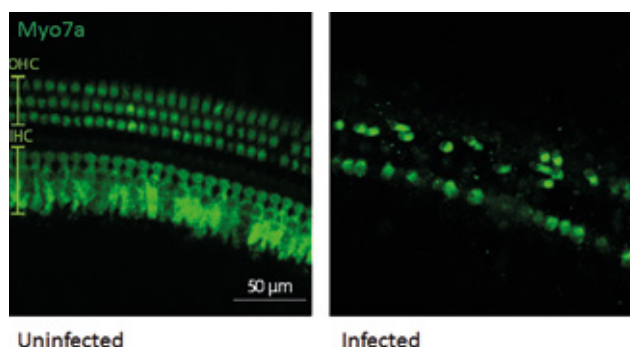


by the gut microbiota. As a result of our investments in next-generation sequencing technology the IFIK became the first certified service provider in Switzerland for DNA, cDNA, RNA and 1D2-based sequencing processes using Nanopore Sequencing Technologies.



Immunofluorescence microscopy of an organotypic rat cerebellar slice infected with tick borne encephalitis virus (TBEV) 3 days post infection. Blue DAPI staining, red =TBEV and green= Purkinje cells (image: N. Lenz, IFIK and Spiez Laboratory) (Reference: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0205294>).

Two major improvements of the IFIK microbiology laboratory diagnostic service were successfully implemented in 2018: First, the IFIK established a 24/7 service with dedicated on-site IFIK personnel providing accelerated bacterial blood culture, Gram staining, and Influenza diagnostic services. Second, in response to the 2018 outbreak of VRE involving Insel Group Hospitals the IFIK rapidly developed, validated and implemented an innovative molecular methodology with higher throughput, flexibility and scalability than conventional culture-based methods for the detection of VRE.



Immunofluorescence microscopy of an Organ of Corti whole mount from a healthy young rat (uninfected) or 3 weeks after experimental pneumococcal meningitis (infected). Numerous outer hair (OHC) and inner hair cells (IHC) died upon infection (image: Silvia Erni, IFIK).

### Selected Competitive Grants

- SNF NRP-72, National Research Program Antimicrobial Resistance grant 407240\_177378. Whole Genome and Plasmid Sequencing for MDR Enterobacteriaceae Simultaneously Isolated from Multiple Human and Non-Human Settings: Deciphering Impact, Risks, and Dynamics for Resistance Transmission and Spread to Andrea Endimiani (PI), Alban Ramette (Co-PI). 2018-2021
- SNF NRP-72 National Research Program, Antimicrobial Resistance grant 407240\_177452. Resistome in the pig farms: Comparison of the breeding and fattening units with a One Health approach." to Markus Hilty (PI). 2018-2021
- SNF NRP-72 National Research Program, New drugs and faster diagnostic techniques grant 407240\_177368. Rapid diagnostics of blood stream infections using synthetic nanobodies. to Markus Seeger (PI, UZH), Peter Keller (Co-PI). 2018-2021
- University of Bern Interfaculty Research Cooperation: Decoding Sleep: From Neurons to Health and Mind (total budget: CHF 6,000,000) CHF 280,000 to Stephen Leib (PI). 2018-2022
- SNF Sinergia grant 180317. Bacteria-host interactions through bile acid 7-dehydroxylation. CHF 827,000.- (total budget: CHF 2,988,000) to Siegfried Hapfelmeier-Balmer (Coordinating PI), R. Bernier-Latmani (EPFL, Co-PI), K. Schoonjans (EPFL, Co-PI), N. Minton (Univ. Nottingham, Co-PI), 2018-2022

### Selected Publications

- Donà V, Smid JH, Kasraian S, Egli-Gany D, Dost F, Imeri F, Unemo M, Low N, Endimiani A. Mismatch Amplification Mutation Assay (MAMA)-Based Real-Time PCR for Rapid Detection of *Neisseria gonorrhoeae* and Antimicrobial Resistance Determinants in Clinical Specimens. *J Clin Microbiol.* 2018; 56:e00365-18. doi: 10.1128/JCM.00365-18
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- Ruppen C, Mercier T, Grandgirard D, Leib SL, El Haj C, Murillo O, Decosterd L, Sendi P. Is Penicillin Plus Gentamicin Synergistic Against Sessile Group B Streptococcal Isolates? An in Vivo Study With an Experimental Model of Foreign-Body Infection. *Front Microbiol.* 2018; 9:919. doi: 10.3389/fmicb.2018.00919
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# Institute of Pathology

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Aurel Perren  
Director



Prof.  
Christoph Müller  
Experimental  
Pathology



Prof.  
Alessandro Lugli  
Clinical  
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Prof.  
Inti Zlobec  
TRU

## Research Partners

- Department of Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland
- ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland
- Institute of Pathology, University Hospital Basel, Basel, Switzerland
- Radboud University, Nijmegen, Netherlands
- Helmholtz Zentrum München, Neuherberg, Germany
- Institute of Medical Microbiology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
- Australian Pancreatic Cancer Genome Initiative (APGI), Garvan Institute, Sydney, Australia
- Department of Neurology, School of Medicine, Stanford University, Stanford, CA, USA
- Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, CA, USA
- Germany Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT, USA

## Research Profile

In addition to its diagnostic service, the Institute of Pathology is active in clinical, translational and basic science. Pathologists and researchers focus on the areas of tumor immunology, inflammation, autophagy as well as on prognostic/predictive biomarkers and molecular pathogenesis of various tumor types. In twelve research groups we address questions related to the etiopathogenesis of neoplastic or inflammatory disorders, but also to the identification of clinically relevant biomarkers in inflammatory disorders and to the development of vaccination strategies against solid tumors. We contribute actively to WHO classifications of tumors, ICCR guidelines, clinical guidelines and improvement of histopathological diagnostics. Furthermore, the Translational Research Unit (TRU) manages services of the Tissue Bank Bern (TBB) and supports tissue-based research by providing histology, tissue visualization, tissue microarraying and digital pathology expertise.

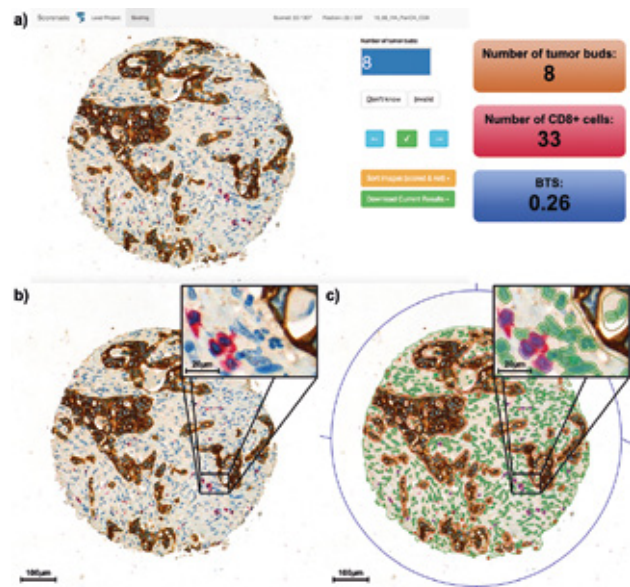
## Teaching Profile

The Institute of Pathology is active in teaching across different faculties and departments at the University of Bern, including the disciplines of Medicine, Cell Biology, Biomedical Sciences, and Bioinformatics, and participates with standard lectures, Problem Based Learning tutorials and workshops. The Institute hosts 10-15 new Medical Master students per year as well as numerous MSc (Cell Biology), and PhD students under the umbrella of the Graduate School of Cellular and Biomedical Sciences, University of Bern.

## Highlights 2018

### *Digital pathology helps to unravel the tumor microenvironment in colorectal cancer*

We set out to investigate the relative contribution of an “attacker-defender” model of the tumor microenvironment and prognosis in colorectal cancer. On the one hand, tumor buds, representing the attacker, are counted on digitally scanned slides of tissue microarrays with the help of a homegrown scoring tool “Scorenado”. On the other, CD3, CD8 and CD45RO positive lymphocytes, representing the defender, were quantified using digital image analysis after training classifiers in open-source software QuPath. Through bioinformatics pipelines, both sets of scores are linked to the clinicopathological data of each patient. Indeed, the combination of tumor buds and T-lymphocytes reveals improved prognostic stratification than either tumor buds or lymphocyte counts separately, suggesting that a “Budding T-cell Score” (BTS) should be considered as a prognostic biomarker.



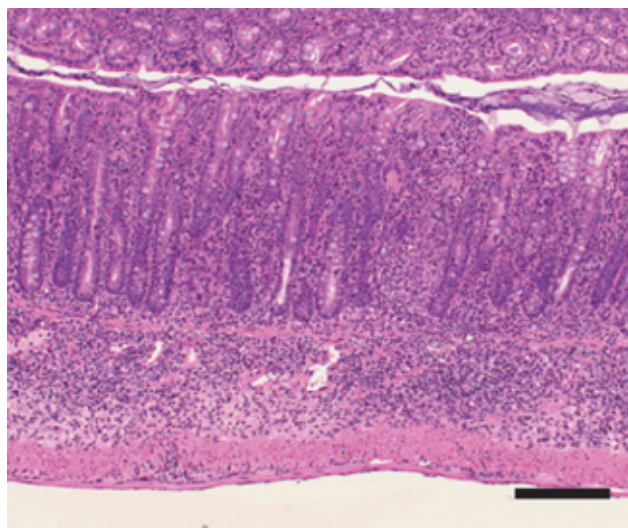
### *PathoLINK: Development of a Swiss standard for structured tumor data*

Research using biological materials is critically dependent on good clinical annotations. With evolving diagnostic precision cancers are subdivided into an increasing number of

sub-entities, some of them genetically defined. This allows more targeted treatments, but makes individual entities very rare and therefore difficult to study. Sharing samples and data becomes more important. The Swiss Biobanking Platform (SBP) has the task to harmonize technical sample collection aspects including pre-analytics. To also improve annotations of tumor samples all five University Hospital Pathology Institutes of Switzerland joined forces in the PathoLINK project. In the last two years, we have agreed on data-points to be recorded in a structured reporting system for 5 tumor entities and are in the process of implementation into clinical routine in all 5 University hospitals. These data-points are based on international standards such as the ones defined by ICCR. This will allow to have Swiss-wide detailed phenotypes of these tumors from next year onward, a crucial basis to be able to use samples from several centers in one study on one hand, and on the other, a basis to link these data to structured clinical outcomes and genomic data that is developed in two running SPHN projects.

*Experimental Pathology: CD4 T cell-derived IL17A/F compensates for the absence of interferon- $\gamma$  in experimental colitis*

The relevance of interferon- $\gamma$  secretion by T cells and innate lymphoid cells for the induction of experimental colitis in mice has been controversially discussed, and discrepant findings in the literature were often ascribed to differences in the intestinal microbiota. Using two different, but microbiota-stabilized, mouse models of colitis, i.e. the anti-CD40 induced colitis in lymphopenic RAG1<sup>-/-</sup> mice, and the CD4 T cell transfer model of colitis in RAG1<sup>-/-</sup> mice, we demonstrated that interferon- $\gamma$  produced by innate lymphoid cells (ILC) upon anti-CD40 stimulation in vivo is essential for colitis induction in the absence of CD4 T cells, whereas in the CD4 T cell transfer model, colitis develops even in the complete absence of interferon- $\gamma$ . In this case IL17A and IL17F, produced by CD4 T cells, are the critical disease inducing factors. These experiments also provide an explanation for the failed attempts to control inflammatory bowel diseases in patients by blocking interferon- $\gamma$ .



### Selected Competitive Grants

- Swiss National Science Foundation (grant No.310030\_152872; 314730\_163086; 310030\_170084; 33CS30\_177523; 320030\_176083; 33CS30\_148422; 31003A\_173219; 31003A\_175656)
- Peter Hans Hofschneider - Stiftung für Experimentelle Biomedizin
- Free Novation (Novartis)
- Swiss Cancer Research/Swiss Cancer League (KLS-3408-02-2014; KFS-3409-02-2014; KFS 4162-02-2017-R; KFS-4227-08-2017)
- Wilhelm Sander-Stiftung Nr. 2017.073.1

### Selected Publications

- Graule J, Uth K, Fischer E, Centeno I, Galván JA, Eichmann M, Rau TT, Langer R, Dawson H, Nitsche U, Traeger P, Berger MD, Schnüriger B, Hädrich M, Studer P, Inderbitzin D, Lugli A, Tschan MP, Zlobec I. CDX2 in colorectal cancer is an independent prognostic factor and regulated by promoter methylation and histone deacetylation in tumors of the serrated pathway. *Clin Epigenetics*. 2018 Sep 26;10(1):120. doi: 10.1186/s13148-018-0548-2
- Wartenberg M, Cibir S, Zlobec I, Vassella E, Eppenberger-Castori S, Terracciano L, Eichmann MD, Worni M, Gloor B, Perren A, Karamitopoulou E. Integrated Genomic and Immunophenotypic Classification of Pancreatic Cancer Reveals Three Distinct Subtypes with Prognostic/Predictive Significance. *Clin Cancer Res*. 2018 Sep 15;24(18):4444-4454. doi: 10.1158/1078-0432.CCR-17-3401
- J Brasseit, CKC Kwong Chung, M. Noti, D. Zysset, N. Hoheisel-Dickgreber, V. Genitsch, N. Corazza, Christoph Mueller. Divergent roles of interferon- $\gamma$  and innate lymphoid cells in innate and adaptive immune cell-mediated intestinal inflammation. *Front Immunol*. 2018 Jan 24;9:23. doi: 10.3389/fimmu.2018.00023. eCollection 2018



## Institute of Forensic Medicine (IRM)

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Director



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Deputy Director  
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Matthieu Glardon  
Forensic Physics and Ballistics



Prof. Michael Liebreuz  
Forensic Psychiatric Services



Dr. Sandra Lösch  
Physical Anthropology



Dr. Matthias Pfäffli  
Traffic Medicine



PD Dr. Antoine Roggo  
Medical Law



PD Dr. Christian Schyma  
Forensic Medicine and Imaging



Dr. Silvia Utz  
Forensic Molecular Biology

### Research Partners

- Institute of Legal Medicine, University of Bonn, Bonn, Germany
- Institute of Legal Medicine, University of Schleswig-Holstein, Kiel, Germany
- Center for Medical Image Science and Visualization, CMIV, Linköping University, Linköping, Sweden
- Department of Diagnostic, Interventional and Pediatric Radiology, Bern University Hospital and University of Bern, Bern, Switzerland
- Institute of Pathology, University of Bern, Bern, Switzerland
- Institute of Forensic Medicine, University Medical Center Freiburg, Freiburg, Germany
- Department of Chemistry and Biochemistry, University of Bern, Bern, Switzerland
- Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Zürich, Switzerland
- Department of Prehistory, Institute of Archaeological Sciences, University of Bern, Bern, Switzerland
- Netherlands Forensic Institute, Den Haag, The Netherlands

### Research Profile

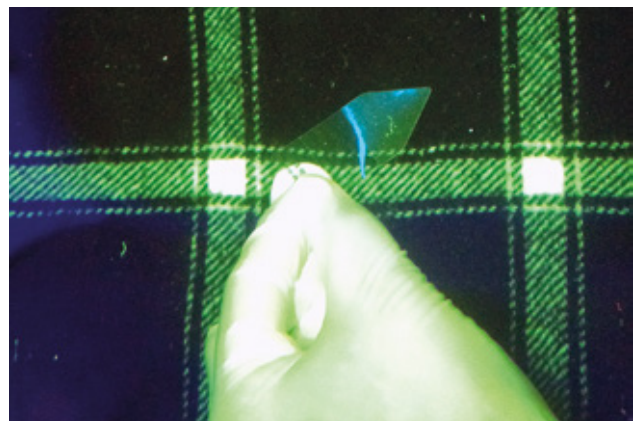
The Institute of Forensic Medicine consists of eight departments. Each department conducts research projects within the context of forensic sciences. The department of Forensic Medicine and Imaging, the department of Forensic Toxicology and Chemistry and the department for Physical Anthropology received external fundings. The Institute of Forensic Medicine in Bern is world leading in forensic physics and ballistics, forensic imaging and alcohol consumption markers. Furthermore forensic psychiatric projects, forensic genetics projects and traffic medicine projects have been successfully performed.

### Teaching Profile

On behalf of the University of Bern, the Institute of Forensic Medicine in Bern (IRM) is responsible for the training and continuing education of students of medicine and jurisprudence, medical personnel and the institutions of the administration of justice and the police.

### Highlights 2018

*Optimizing the sampling procedure for touch DNA recovery*  
The vast majority of biological traces analyzed in forensic labs today do not involve any detectable body fluids and consist of only minute amounts of DNA from a couple of cells. To recover such traces efficiently, it is crucial to select the right sampling protocol. In collaboration with the Bern Cantonal Police, DNA sampling from clothes by tape lifting was evaluated and the extraction protocol for tapes optimized. It could be demonstrated that tape-lifting, when combined with the right extraction protocol, is significantly more efficient than the conventional sampling by swab.



DNA sampling by forensic lifting tape under UV light.

*Multidisciplinary research approach to the Swiss Oberbipp dolmen in the context of Neolithic revolution in Central Europe (SNF CR3113L\_157024)*

Dolmen are stone monuments that were used as collective graves during the Late Neolithic period in Europe. In 2012, an intact dolmen burial was excavated in Oberbipp, followed by an interdisciplinary research project. The human remains were subjected to morphological, biochemical and paleogenetic analyses in order to reconstruct the composition, diet, origins and relationships of the buried individuals. A minimum number of 42 men, women and children were buried in the dolmen during two occupation phases between 3400 and 2800 BCE, representing a Neolithic population with immediate families and terrestrial diet.



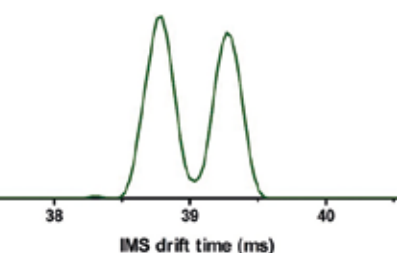
Excavation of the dolmen before the removal of the top stone.



Skull of a male burial found in the dolmen.

*Ion-Mobility Mass Spectrometry for differentiation of THC and CBD*

In a collaboration with TOWERK AG (Thun) we developed a method for the differentiation of the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) and their precursor acids by use of an ion mobility cell coupled to a high-resolution mass spectrometer (IMS-HR-MS). CBD-marijuana is a legal tobacco substitute in Switzerland, as long as its total THC-content is below 1%. With this new technique and an additional calibration it is possible to differentiate between legal CBD-containing and illegal mainly



THC-containing marijuana in a few minutes, even though the molecular weights of CBD and THC and their respective precursor acids are identical.

*Switzerland cuts drug-related deaths by acting outside of box*

Heroin is one of the substances highly prevalent in prison settings globally. Especially in the USA experts speak of a true "opioid epidemic". In Switzerland, people with an opioid dependence are treated with methadone maintenance treatment (MMT) or heroin-assisted treatment (HAT). HAT is available for those who fail MMT and have a long history of dependence. So far, little is known about outcomes related to HAT in the prison setting. We evaluated data from Realta prison (2005-2015) and did not find evidence for increased abuse or lethal overdose. Furthermore, the high working rate of inmates supports HAT's utility with respect to functioning and rehabilitation even in a prison setting.



Diaphan® is only prescribed to patients within the framework of heroin-assisted treatment in appropriately equipped institutions approved by the FOPH and only delivered under visual control of treatment personnel.

**Selected Competitive Grants**

- Swiss National Science Foundation (grant No. CR3113L\_157024; 320030\_179466/1; IZK0Z1\_175400; IZSEZO\_180184/1)

**Selected Publications**

- Hädener M, Kamrath MZ, Weinmann W, Groessl M (2018). High-Resolution Ion Mobility Spectrometry for Rapid Cannabis Potency Testing. *Anal Chem.* 2018 Aug 7;90(15):8764-8768. doi: 10.1021/acs.analchem.8b02180
- Luginbühl M, Willem S, Schürch S, Weinmann W (2018). Formation of phosphatidylethanol from endogenous phosphatidylcholines in animal tissues from pig, calf, and goat. *Forensic Sci Int.* 2018 Feb;283:211-218. doi: 10.1016/j.forsciint.2017.12.030
- Riva F, Mattijssen EJAT, Kerkhoff W (2018). Rifle bullet deflection through a soft tissue simulant. *Forensic Sci Int.* 2018 Oct;291:199-206. doi: 10.1016/j.forsciint.2018.08.024
- Siebke I, Campana L, Ramstein M, Furtwängler A, Hafner A, Lösch S (2018). The application of different 3D-scan-systems and photogrammetry at an excavation – A Neolithic dolmen from Switzerland. *Archaeology and Cultural Heritage*, 10(2018) e00078
- Stoop B, Defaux PM, Utz S, Zieger M. Touch DNA sampling with SceneSafe Fast™ minitapes. *Leg Med (Tokyo).* 2017 Nov;29:68-71. doi: 10.1016/j.legalmed.2017.10.006

# Institute of Dental Medicine (ZMK)

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Prof. Anton Sculean  
Executive Director and Director of the Clinic of Periodontology



Prof. Daniel Buser  
Director of the Clinic of Surgery and Stomatology



Prof. Hendrik Meyer-Lückel  
Director of the Clinic of Restorative, Preventive and Pediatric Dentistry



Prof. Christos Katsaros  
Director of the Clinic of Orthodontics and Dentofacial Orthopaedics



Prof. Urs Brägger  
Director of the Clinic of Reconstructive Dentistry and Gerodontology



Prof. Martin Schimmel  
Head of the Division of Gerodontology

## Research Partners

- Clinic of Rheumatology, Clinical Immunology and Allergology, University of Bern, Bern, Switzerland
- Institute for Surgical Technology and Biomechanics (ISTB), University of Bern, Bern, Switzerland
- Department of Operative Dentistry, Periodontology and Preventive Dentistry RWTH Aachen, Aachen, Germany
- Fraunhofer Institute for Cell Therapy and Immunology IZI-MWT, Halle/Saale, Germany

## Research Profile

The research profile is translational and clinical focusing on caries and tooth erosion, in vitro and in vivo evaluation of novel antimicrobials with potential effects for the treatment of dental related infections (e.g. caries, periodontitis and peri-implantitis), novel biomaterials for hard and soft tissue regeneration around teeth and dental implants, and on the mechanisms involved in craniofacial growth and lip-palate clefts involving basic researchers and clinicians from the various clinics from the School of Dental Medicine, medical hospital and numerous international centers.

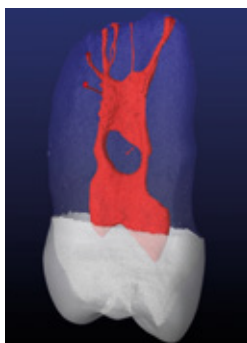
## Highlights in Research

### Practice-based research

Besides pre-clinical studies in cariology and dental materials we are performing practice-based research in conjunction with private practitioners. Diagnosis and treatment of root caries, together with long-term evaluation of dental restorations are primary goals.

### Endodontology

We are currently conducting research referring the internal morphology of teeth using micro-computer tomography. After scanning and processing analyzed data is visualized with a 3D software-imaging. This cooperation project with



Maxillary first premolar by  $\mu$ -Ct with complicated root canal system (pulp: red, enamel: white, dentine: transparent grey) showing various accessory root canals/foramina and an anastomosis in the middle and apical third of the root.

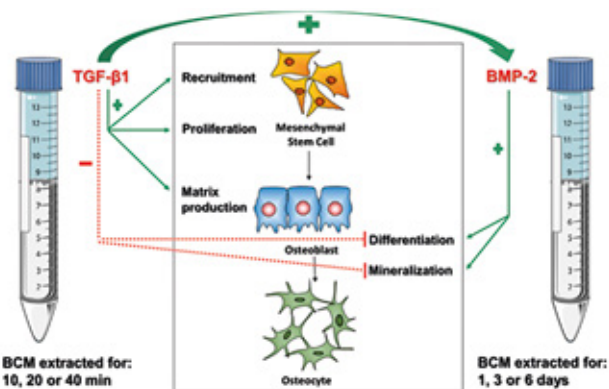
the Universities of Mainz (Germany) and Zurich (Switzerland) is to provide the clinician with guidance and additional information to identify difficulties before and during endodontic treatment.

### Oral microbiology

The presence of periodontal pathogens and the intrathecal generation of pathogen-specific antibodies was verified in patients with Alzheimer's disease and with other forms of dementia and was shown that periodontal destruction and inflammation were omnipresent.

### Bone and soft tissue regeneration research at the Laboratory of Oral Cell Biology

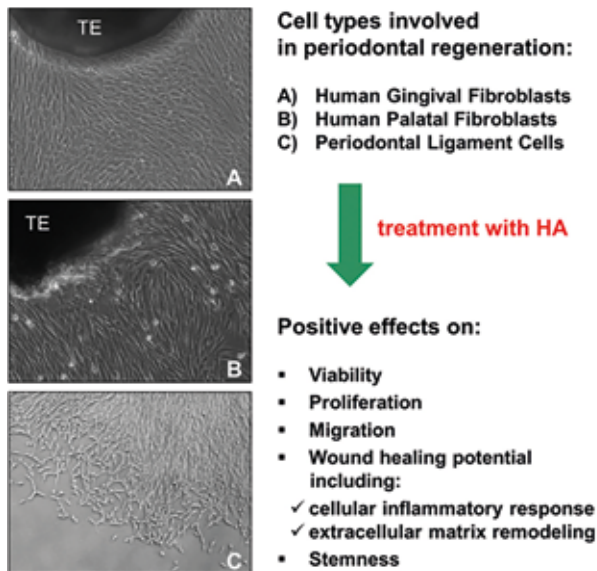
Bone Conditioning Media (BCM) obtained during surgical procedure causes increased proliferation of mesenchymal stem cells, thus expanding the pool of osteoblast progenitors and has the potential to stimulate the production of bone matrix. BCM released from the autograft in situ and, the BMP-2 contained in this medium stimulates the late stages of osteoblast differentiation and mineralization, thus contributing to the progression of osteogenesis (Asparuhova MB, et al. Int J Oral Sci. 2018; 10(2):20).



Schematic representation of the biological activity of bone-conditioned medium (BCM), derived from autologous bone grafts, on the osteogenic potential of mesenchymal stem cells. A complex interplay between two growth factors, TGF- $\beta$ 1 and BMP-2 contained in the BCM, is depicted.

A series of in vitro studies have shown findings that HA influences the cellular inflammatory response and extracellular matrix remodeling by affecting pro-inflammatory cytokine and matrix metalloproteinase gene expression (Asparuhova MB, et al. J Periodontal Res. 2018; 00:1-13).

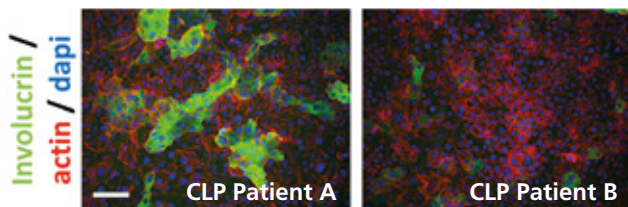




Schematic representation of the biological activity on the wound healing properties of primary cell types involved in periodontal regeneration (TE: tissue explant).

#### Research on craniofacial growth and lip-palate clefts

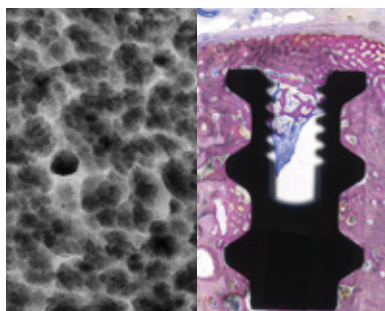
To better understand the complex cellular and molecular processes underlying cleft lip/palate (CLP), we established a unique human cell bank, consisting of keratinocytes and corresponding fibroblasts from individual CLP patients. In an initial study, we detected great variations between individual keratinocyte cultures in regard to their terminal differentiation potential. Our results suggest that some of the genetic predispositions causing CLP might also lead to deficiencies in keratinocyte differentiation manifested in in vitro assays.



Staining for the differentiation marker involucrin in two confluent CLP patient-derived keratinocyte cultures. While the keratinocytes of patient A induce involucrin (green) and differentiate, cells of patient B display deficiencies in involucrin induction and differentiation. Scale bar: 50µm.

#### Research on osseointegration of ultrafine-grained titanium with a hydrophilic nano-patterned surface

A new ultra-fine grained titanium (ufgTi) implant material with a hydrophilic nano-patterned surface was compared to commercially pure titanium (cpTi). Histomorphometric and biomechanical torque out analysis revealed no significant



The ufgTi viewed in the laser confocal microscope (left). Excellent osseointegration after 8 weeks (right).

differences between ufgTi and cpTi thus suggesting that ufgTi has therapeutic potential for less invasive treatments.

#### Teaching Profile

The School of Dental Medicine is providing both undergraduate and postgraduate training. In 2018, the undergraduate dental curriculum was reaccredited by the Swiss Accreditation Council.

The postgraduate teaching encompasses 3–4 year postgraduate programs leading to specialty and / or MAS degrees in Preventive Dentistry and Cariology, Periodontology, Oral Surgery, Reconstructive Dentistry and Orthodontics.

#### Public Service

The School of Dental Medicine provides a wide range of treatment encompassing all fields of dentistry. Difficult and complex cases, in most cases referred by colleagues from private practices, are treated on the various speciality clinics or teams of different specialists, thus providing a high quality care.

#### Highlights 2018

- Top ranking for the School of Dental Medicine (rank N° 7 according to QS World University Rankings by Subject 2018. Most importantly, the School of Dental Medicine ranked second in terms of H-Index and citation per paper according to QS World University Rankings 2018 and was ranked n° 1 among all German speaking dental schools.
- Reaccreditation of the Undergraduate Dental Curriculum by the Swiss Accreditation Council.

#### Selected Competitive Grants

- Swiss Society for Endodontology, Project, Root Canal Morphology and Configuration by Micro-CT
- Innosuisse (Number 26940.1 PFLS-LS) Evaluierung vom potentiellen Inhaltsstoffen für Mundpflegeprodukte zur Anwendung bei Patienten mit Parodontitis

#### Selected Publications

- Asparuhova MB, Kyriak D, Eliezer M, Mihov D, Sculean A. Activity of two hyaluronan preparations on primary human oral fibroblasts. *J Periodontol Res.* 2019 Feb;54(1):33-45. doi: 10.1111/jre.12602. Epub 2018 Sep 27
- Buser R, Ziltener, V., Samietz, S., Fontollet, M., Nef, T. & Schimmel, M. Validation of a Purpose-Built Chewing Gum and Smartphone Application to Evaluate Chewing Efficiency. *J Oral Rehabil.* 2018 Nov;45(11):845-853. doi: 10.1111/joor.12696. Epub 2018 Aug 3 (Advancement Award of the Senior Citizens' University, M Dent Med)
- Degen M, Wiederkehr A, La Scala GC, Carmann C, Schnyder I, Katsaros C. Keratinocytes isolated from individual Cleft Lip/Palate patients display variations in their differentiation potential in vitro. *Front Physiol.* 2018 Nov 29;9:1703. doi: 10.3389/fphys.2018.01703. eCollection 2018
- Schnider N, Forrer FA, Brägger U, Hicklin SP. Clinical Performance of One-Piece, Screw-Retained Implant Crowns Based on Hand-Veneered CAD/CAM Zirconia Abutments After a Mean Follow-up Period of 2.3 Years. *Int J Oral Maxillofac Implants.* 2018 Jan/Feb;33(1):188-196. doi: 10.11607/jomi.5929
- Wierichs RJ, Kramer EJ, Wolf TG, Naumann M, Meyer-Lueckel H. Longevity of composite build-ups without posts-10-year results of a practice-based study. *Clin Oral Investig.* 2018 Jul 25. doi: 10.1007/s00784-018-2565-0. [Epub ahead of print]

# Institute of Primary Health Care (BIHAM)

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Dr. Martin Feller  
Research Coordination



Dr. Roman Hari  
Teaching



Prof. Sven Streit  
Career Development and Networking

## Research Partners

- Departments of General Internal Medicine, of Cardiology & of Neurology, Inselspital, University of Bern, Switzerland
- Institute of Social and Preventive Medicine (ISPM) & Clinical Trial Unit (CTU), University of Bern, Switzerland
- Department of Primary Care and Public Health, Leiden University Medical Center, The Netherlands
- Department of Medicine & of Epidemiology and Biostatistics, UCSF, CA, USA
- Department of Epidemiology, McGill University, Montreal, Canada
- Institute of Health Policy, Management and Evaluation University of Toronto, Canada
- The Thyroid Studies Collaboration on 5 continents
- Institute of Social and Preventive Medicine (IUMSP), Policlinique Médicale Universitaire (PMU), Institut de Santé au Travail (IST), Lausanne University, Switzerland
- Institute of Primary Care Zurich, University of Zurich, Switzerland
- Italian Cochrane Centre, University of Modena and Reggio Emilia, Modena, Italy

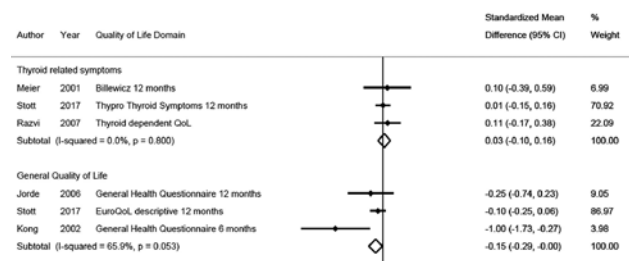
## Research Profile

The Institute of Primary Health Care of the University of Bern (BIHAM) trains and fosters primary care physicians and carry out research in primary health care, epidemiology and public health. It offers an interdisciplinary environment with excellent methodological support and access to a large network of practicing primary care physicians. Research projects are conducted about, e.g., multimorbidity, overdiagnosis, de-prescribing, screening, smoking, hypertension and variation in care, with grants notably from the Swiss National Science Foundation (SNSF) and European Union. Systematic reviews are also conducted. Several MD and PhD students are part of the team of researchers.

## Highlights 2018

*No benefit of thyroid hormone replacement therapy in sub-clinical hypothyroidism also among younger adults*  
Subclinical hypothyroidism is a mild dysfunction of the thyroid gland affecting one in ten adults. It has been associated with unspecific but common symptoms such as tiredness and weight gain. It is often treated with thyroid hormone therapy, despite weak evidence of benefits. In a systematic review and meta-analysis including all 21 RCTs and more than 2'000 participants, published in JAMA, we found no clinical benefit of thyroid hormone therapy in patients with subclinical hypothyroidism. These findings (i) should finally

lead to an adaptation of international guidelines on the management of subclinical hypothyroidism, generally recommending against thyroid hormone therapy, and (ii) implicate that millions of patients with subclinical hypothyroidism are spared from taking a daily therapy.



Positive standardized mean differences indicate benefit of levothyroxine; 0.2, 0.5 and 0.8 represent small, moderate and large effects, respectively (JAMA 2018).

## Efficacy and tolerability of medications for attention-deficit hyperactivity disorder (ADHD)

We performed a systematic review of randomised controlled trials comparing medications for ADHD with each other or placebo in children, adolescents, and adults. Based on data from 133 RCTs, and taking into account efficacy (change in severity of ADHD core symptoms based on clinicians' ratings) and tolerability (dropouts due to adverse events), our results supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD.

## E-cigarettes as potential aid for smoking cessation?

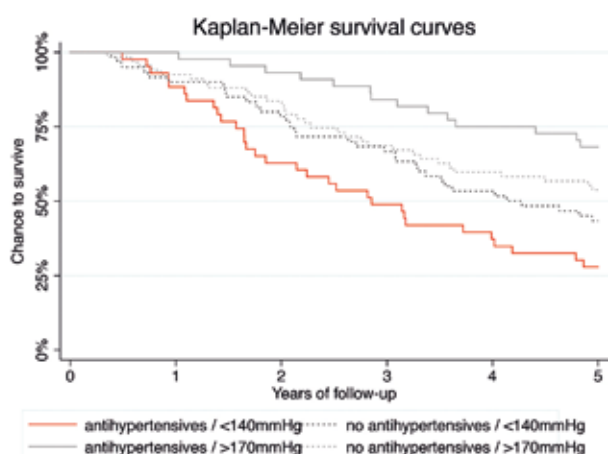
Primary health care physicians are on the front line to help smokers quit. Recently, e-cigarettes, i.e. nicotine vaporizers, have become popular. We have launched a multicentre randomized controlled trial (RCT) funded by the Swiss National Science Foundation to test the efficacy of vaporizers for



cigarette smoking cessation, test the safety of vaporizers on reducing adverse events and the effect of vaporizers on reducing exposure to inhaled toxic compounds as well as on health-related outcomes (respiratory symptoms, oxidative stress, risk factors for heart disease). Over the next 2 years, 1173 participants will be randomized in RCT that will add vaporizers to smoking cessation counselling (SCC), and compare vaporizers to SCC alone.

#### Blood Pressure Medication can be detrimental in Old Age

Using data from the Leiden 85-plus Study, a population-based prospective cohort study of 599 inhabitants of Leiden age 85 years or more, we found that low blood pressure was associated with increased all-cause mortality followed-up to a maximum of 5 years. Among treated participants, low blood pressure was associated with a cognitive decline. Frailty modified this association, with participants with a weak hand grip strength having an accelerated cognitive decline. In participants not treated for hypertension, we found no relationship between blood pressure and mortality and cognitive function.



Survival by treatment and quintile of blood pressure (Age and Ageing 2018).

#### Teaching in Primary Care

Medical students are trained within our clerkships “Berner Hausarztpraktika”, where they spend time in a private practice during their whole medical training. In parallel, we teach primary care in lectures and workshops with a special focus on communication skills and clinical examination. We lead interdisciplinary teaching task forces in communication and diagnostic ultrasound. In 2018, we successfully



implemented a new assessment format in year one with a strong focus on formative feedback. We were also able to upscale the workshop series “HAMMER-Seminare” to now include 24 half days of interdisciplinary case discussions with GPs and specialists. In November 2018, we inaugurated the new ultrasound skills lab with eight ultrasound work stations within the new skills center at the UniZiegler and started the first mandatory ultrasound course.

#### Selected Competitive Grants

- OPERAM – European Union’s Horizon 2020 (grant agreement 634238)
- Thyroid – SNSF (320030\_172676)
- OPTICA – SNSF (NFP74;407440-167465)
- LESS – SGAIM Foundation
- ESTxENDS – SNSF (IICT 33IC30\_173552)
- SDM in CRC – SNSF (NFP74;407440\_167519)
- Claims data colorectal cancer – Swiss Cancer League (HSR-4366-11-2017)

#### Selected Publications

- Feller M, Snel M, Moutzouri E, Bauer DC, de Montmollin M, Aujesky D, Ford I, Gussekloo J, Kearney PM, Mooijaart S, Quinn T, Stott D, Westendorp R, Rodondi N, Dekkers OM. Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism: A Systematic Review and Meta-analysis JAMA. 2018;320(13):1349-1359
- Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old – data from the Leiden 85-plus Study. Age Ageing. 2018 May 8. doi: 10.1093/ageing/afy072
- Anker D, Santos-Eggimann B, Santschi V, Del Giovane C, Wolfson C, Streit S, Rodondi N, Chiolerio A. Screening and treatment of hypertension in older adults: less is more? Public Health Rev. 2018;39:26
- Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, Atkinson LZ, Tessari L, Banaschewski T, Coghill D, Hollis C, Simonoff E, Zuddas A, Barbui C, Purgato M, Steinhausen HC, Shokraneh F, Xia J, Cipriani A. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5(9):727-738
- Auer R, Sidney S, Goff D, Vittinghoff E, Pletcher MJ, Allen NB, Reis JP, Lewis CE, Carr J, Rana JS. Lifetime marijuana use and subclinical atherosclerosis: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Addiction. 2018;113(5):845-856
- Blum MR, Gencer B, Adam L, Feller M, Collet TH, da Costa BR, Moutzouri E, Dopheide J, Depairon M, Sykiotis GP, Kearney P, Gussekloo J, Westendorp R, Stott DJ, Bauer DC, Rodondi N. Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly with Subclinical Hypothyroidism, A Randomized Trial. J Clin Endocrinol Metab. 2018;103(8):2988-2997



# Institute of Complementary and Integrative Medicine (IKIM)

Inselspital, Freiburgstrasse 46, 3010 Bern  
von Roll Campus, Fabrikstrasse 8, 3012 Bern



Prof. Ursula  
Wolf  
Director



Dr. Martin  
Frei-Erb



Dr. Johannes  
Fleckenstein



Prof. Lorenz  
Fischer

## Research Partners

- Swiss Group for Clinical Cancer Research SAKK, Breast Cancer Group, Switzerland
- Hospital of Fribourg (HFR), Fribourg, Switzerland
- Paracelsus Spital Richterswil, Switzerland
- Medical University of Vienna, Department of Medicine I, Clinical Division of Oncology, Vienna, Austria
- University Children's Hospital, Inselspital, Bern, Division of Pediatric Hematology/Oncology, Switzerland
- University Hospital Inselspital, Bern, Department of Radiooncology, Switzerland
- ISS Inc., Champaign, IL, USA
- University Clinic of Obstetrics and Gynecology, Inselspital, Bern, Department of Gynecologic Endocrinology and Reproductive Medicine
- Bern University of Applied Sciences, Health Professions, Physiotherapy, Bern, Switzerland

## Research Profile

Group Wolf: The focus lays on patient centered translational and clinical research. In a large study, effects of colored light on brain and systemic physiology are investigated. Clinical trials on e.g. the treatment of radiation dermatitis, cancer related fatigue and chemotherapy associated neuropathy are running or in the planning phase.

Group Frei-Erb: Topics are systematic reviews (e.g. on clinical effects of homeopathically potentized substances), surveys (e.g. job satisfaction of Swiss GPs), development of a tool for GPs to reduce the use of antibiotics in acute cystitis, basic research on high dilutions and follow-up of individual treatment in children with ADD/ADHD or cancer.

Group Fleckenstein: The integration of acupuncture in clinical routine is the main research objective in Traditional Chinese Medicine TCM/acupuncture. In a clinical study, the add-on effect of acupuncture in the treatment of menopause is evaluated. Additionally, mechanisms of action (e.g. peripheral neurophysiology) of acupuncture are researched.

Group Fischer: The main research topic in neural therapy continues to be the clinical presentation and neurophysiology of sympathetically maintained pain and inflammation. We work on new mechanisms of action (positive feedback loops) and carry out clinical studies. Studies on efficacy and costs are ready for publication.

## Teaching Profile

The institute participates with lectures and courses in the curricula for medical students at the University of Bern. Additionally, lectures on homeopathy are given for pharmacology students at ETH Zurich, lectures on neural therapy at the University of Zurich and lectures on TCM/acupuncture at the University of Basel. Two medical doctoral theses and two master theses were successfully completed (Group Wolf).

## Highlights 2018

Hamoon Zohdi, PhD candidate (Group Wolf) received the prestigious Dietrich W. Lübbers Award of the International Society of Oxygen Transport to Tissue (ISOTT) in Seoul, South Korea, for his oral presentation „Absolute values of tissue oxygenation and hemoglobin concentration in the human cerebral cortex during resting-state: dependence on individual subject and measurement location“.

The work of Prof. Fischer and his group on Neural Therapy in Chronic Pelvic Pain Syndrome published in 2018 generated worldwide response and Prof. Fischer received the BNR-NAZLIKUL Award at the IV. World Neural Therapy IFMANT Congress & VII. International Neural Therapy BNR Congress, Istanbul, Turkey. In recognition of his research merits, he also became an honorary member of the Italian Neural Therapy association Neuralia.

Felix Scholkmann, PhD (Group Wolf) was rewarded with an invited oral presentation and gave the presentation entitled “Systemic-physiology-augmented functional near-infrared spectroscopy (SPA-fNIRS) neuroimaging” at the congress of the Society for functional near infrared spectroscopy fNIRS in Tokyo, Japan.

### **Selected Competitive Grants**

- Bridge-Discovery, SNSF (20B2-1\_180983/1)
- Software AG Foundation (BA-P11425, SE-P12117, BA-P12916)
- University of Bern, UniBE Initiator Grant

### **Selected Publications**

The complete publication list can be found at:

[www.ikim.unibe.ch/research/publications](http://www.ikim.unibe.ch/research/publications)

- Kloter E, Barrueto K, Klein SD, Scholkmann F, Wolf U (2018). Heart rate variability as a prognostic factor for cancer survival – A systematic review. *Front Physiol.* 2018 May 29;9:623. doi: 10.3389/fphys.2018.00623. eCollection 2018
- Schitter AM, Fleckenstein J (2018). Passive hydrotherapy WATSU (WaterShiatsu) in the rehabilitation of a severely traumatized accident survivor - A prospective case report. *Complement Med Res.* 2018;25(4):263-268. doi: 10.1159/000487768
- Gaertner K, Lürer SC, Frei-Erb M, von Ammon K (2018). Complementary individual homeopathy in paediatric cancer care: A case series from a University Hospital, Switzerland. *Complement Ther Med.* 2018 Dec;41:267-270. doi: 10.1016/j.ctim.2018.10.010
- Nasser N, Caicedo A, Scholkmann F, Zohdi H, Wolf U (2018). Impact of changes in systemic physiology on fNIRS/ NIRS signals: Analysis based on oblique subspace projections decomposition. *Adv Exp Med Biol.* 2018;1072:119-125. doi: 10.1007/978-3-319-91287-5\_19
- Kronenberg RM, Ludin SM, Fischer L (2018). Severe case of chronic pelvic pain syndrome: recovery after injection of procaine into the vesicoprostatic plexus — case report and discussion of pathophysiology and mechanisms of action. *Case Rep Urol.* 2018 Jun 26;2018:9137215. doi: 10.1155/2018/9137215. eCollection 2018

# Institute for Medical Education (IML)

University of Bern, Medical Faculty  
Mittelstrasse 43, 3012 Bern



Prof. Sissel  
Guttormsen  
Director IML



Prof. Sören  
Huwendiek  
Department Head  
AAE



Dr. Philippe  
Zimmermann  
Department Head  
ASCII



Dr. Sandra  
Trachsel  
Department Head  
MME



Dr. Kai  
Schnabel  
Department Head  
AUM

## Research Partners

- Federal Office of Public Health, Switzerland
- Medical Faculty Zürich, Switzerland
- Medical Faculty Lausanne, Switzerland
- Medical Faculty Geneva, Switzerland
- University Hospital Bern (Inselspital), Switzerland
- University Hospital Zürich, Switzerland
- LMU München, Klinikum der Universität München, Germany
- Universitätsklinikum Hamburg-Eppendorf, Germany

## Research Profile

Interdisciplinary research in Medical Education and related fields, both quantitative, qualitative and mixed method research.

### Summative assessment

Scoring and pass-fail decision in multiple choice exams; assessment of communication skills in OSCE; development of innovative assessment formats.

### Formative Assessment

Workplace-based assessment, multisource feedback, Virtual Patients, various self-assessments.



Entrance at "UniZiegler", new faculty Skillslab und Learning Centre.

### E-Learning

Research on the impact of cognitive load for learning with multimedia applications, on-line learning of communication skills, blended learning.

### Teaching

Understanding and improving various teaching formats: Interprofessional teaching; Peer Teaching, Communication training.

### Human-Computer Interaction

New technologies in educational settings, digital transformation in education, mobile educational technologies, interface design of educational applications.



IML's new Video-Studio at the new location at Mittelstrasse 43, in Bern.

## Teaching Profile

*Undergraduate training at the Medical Faculty in Bern*  
PBL, Clinical skills trainings, communication trainings, inter-professional trainings, Peer-Teaching, eLearning.

### Postgraduate training

Program leadership and teaching in the international Master of Medical Education (MME) of the University of Bern. Postgraduate teaching activities includes also the Master of Medical education in Germany, Harvard Macy Institute Program for Leading Innovation in Healthcare and Education at Harvard Medical School; invited workshops national and international; Faculty development, Clinical Teaching and Feedback trainings, Courses and trainings for exam authors, Communication trainings.



## Highlights 2018

*SAMW Award for interprofessional teaching 2018, the third year in a row*

K. Feller (Oberärztin), L. Remund (Psychologin), S. Stocker (Diabetesfachberaterin), M. Müller (Ernährungsberaterin), Ch. Berendonk (IML. Clinical assessment). Project: "Interprofessionelle Arbeitsplatz-basierte Assessments in der Diabetologie am Universitätsspital Bern".

### 3 Medical-Education PhD's Projects successfully finished

- February: Andrea Lörwald, "Mini-CEX and DOPS: educational impact and influencing factors". Thesis advisor S. Huwendiek
- March: Felicitas Lahner "Influence of different scoring algorithms for multiple true-false items on the measurements precision of multiple-choice exams". Thesis advisor S. Huwendiek
- May: Felix Schmitz "Fostering communication skills in undergraduate health profession students". Thesis advisor S. Guttormsen

### IML eAssessment tools continuously disseminate

Further organisations decided to use the IML tools from the Examic® Assessment Suite for their written and practical exams. Also, the federal exam of human medicine will run on tablets with Examic Measured® in the future.

### New skills training centre at the old Zieglerspital

Opening of the UniZiegler as a new skills training centre at the old Zieglerspital in September 2018. Head: K. Schnabel, AUM, IML. <https://www.iml.unibe.ch/en/topics/overview/stories-en/new-location-for-the-biss>

### New Location for the IML

The IML moves into the new location at the Mittelstrasse 43 in Bern together with 9 other university institutions. We now have an excellent infrastructure, a new research-lab and a IML-video-studio.



The digital Transformation in medical assessment is advancing.

## Selected Competitive Grants

- University of Bern, "Förderung innovative Lehre (FIL)", support of the project: „Improvement of the competency of medical students in the treatment of interdisciplinary Pediatric emergency patients via Blended Learning with Virtual Patients and practical work under supervision“, I. Steiner & S. Huwendiek
- University of Bern, "Förderung innovative Lehre (FIL)" support of the project: „Development of a Blended-Learning Curriculum for medical students regarding motivational interviewing in the psychiatry clerkship“, S. Pinilla & S. Huwendiek
- University of Bern, Förderung innovative Lehre (FIL), support of the project: "Basic Trauma Management (BTM) a mandatory course for 3rd year Medical Students: Curriculum-Revision." J. Berger-Estillita\*, R. Greif\* (\*Department of Anesthesia, Insel University hospital), K. Schnabel

## Selected Publications

- Lörwald AC, Lahner FM, Nouns ZM, Berendonk C, Norcini J, Greif R, Huwendiek S. The educational impact of Mini-Clinical Evaluation Exercise (Mini-CEX) and Direct Observation of Procedural Skills (DOPS) and its association with implementation: A systematic review and meta-analysis. PLoS One. 2018 Jun 4;13(6):e0198009. doi: 10.1371/journal.pone.0198009. eCollection 2018
- Lörwald AC, Lahner FM, Mooser B, Perrig M, Widmer MK, Greif R, Huwendiek S. Influences on the implementation of Mini-CEX and DOPS for postgraduate medical trainees' learning: A grounded theory study. Med Teach. 2018 Oct 28;1-9. doi: 10.1080/0142159X.2018.1497784. [Epub ahead of print]
- Schmitz FM, Schnabel K, Bauer D, Bachmann C, Woermann U, Guttormsen S (2018). The learning effects of different presentations of worked examples on medical students' breaking-bad-news skills: A randomized and blinded field trial Patient Educ Couns. 2018 Aug;101(8):1439-1451. doi: 10.1016/j.pec.2018.02.013
- Junod Perron N, Klöckner Cronauer C, Hautz SC, Schnabel KP, Breckwoldt J, Monti M, Huwendiek S, Feller S (2018): How do Swiss medical schools prepare their students to become good communicators in their future professional careers: a questionnaire and interview study involving medical graduates, teachers and curriculum coordinators. BMC Med Educ. 2018 Nov 29;18(1):285. doi: 10.1186/s12909-018-1376-y
- Mancinetti M, Guttormsen S, Berendonk C. Cognitive load in internal medicine: What every clinical teacher should know about cognitive load theory. Eur J Intern Med. 2019 Feb;60:4-8. doi: 10.1016/j.ejim.2018.08.013

## Department of Anaesthesiology and Pain Medicine

Inselspital, Bern University Hospital  
3010 Bern



Prof. Frank Stüber  
Director and  
Chair



PD Dr. Lutz Lehmann  
Vice Chair



Prof. Robert Greif  
Head of  
Education



PD Dr. Martin Luginbühl  
Chair Spital  
Tiefenau



Reto Thomann  
Head of  
Nursing



PD Dr. Markus Lüdi  
Head of  
Research

### Research Partners

- Prof. Thierry Carrel, Department of Cardiovascular Surgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Prof. Rivka R. Colen and Dr. Pascal O. Zinn, The University of Texas, MD Anderson Cancer Center, Houston, TX, United States
- Prof. Martin Fiedler and Prof. Carlo Largiadère, Department of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Prof. Stephan M. Jakob and Prof. Joerg C. Schefold, Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Prof. Georg Thalmann and Prof. Fiona Burkhard, Department of Urology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Prof. Stephan Windecker, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

### Research Profile

With anaesthesiology and surgery evolving interdependently, it is important to understand how patients' risk factors and physiological responses affect and are affected by surgical interventions. Our aim in the Department of Anaesthesiology and Pain Medicine is to define the best practices for personalised perioperative patient care, with basic science as a foundation and translational medicine as our vision for the future.

Reflecting the definition of anaesthesiology as a field of collaborative perioperative medicine, our scientific investigations cover a wide range of research topics, including airway management, anaesthetic pharmacology, cardiac anaesthesia, clinical and molecular pain research, emergency medicine, genetics and molecular biology, medical education, pain medicine, perioperative optimisation for major urological surgery, and the respiratory system.

Our goal is to significantly contribute to precision medicine in anaesthesiology and perioperative care, both nationally and internationally. As devoted acute care physicians and scientists, we support the Bern University Hospital's vision of becoming the leading Swiss university hospital.

### Teaching profile

In addition to successfully training more than 60 residents in anaesthesiology and pain medicine each year, we offer several well-established courses and symposia for certified anaesthesiologists. Additionally, many medical master's and doctoral theses are successfully completed under the guidance of our principal investigators. We also train anaesthesia nurses, lab technicians and research assistants.

We aim to teach our staff the fundamentals of anaesthesiology as well as introducing them to cutting-edge innovations. In our faculty development program, we teach colleagues from the Inselspital as well as from other Swiss institutions "the art of lecturing" and offer courses in medical teaching and scientific writing, all open to qualified professionals.

### Highlights 2018

Two of our very successful senior anaesthesiologists – Prof. Lorenz Theiler and Prof. Patrick Wüthrich – were promoted to professor by the University of Bern, acknowledging their many achievements as clinicians, researchers and teachers. As in previous years, we are proud of the many presentations, talks and posters given by our researchers at both national and international conferences. Further, our researchers contributed to more than 70 peer-reviewed and PubMed-listed publications, including both consensus statements and recommendations supported by international societies.

### **Selected Competitive Grants**

- Berner Krebsliga, Bern, Switzerland (Prof. Patrick Wüthrich)
- Gottfried und Julia Bangerter-Rhyner Stiftung, Basel, Switzerland (Dr. Heiko Kaiser)
- Velux Stiftung, Zürich, Switzerland (Prof. Patrick Wüthrich)

### **Selected Publications**

- Erdoes G, Martinez Lopez De Arroyabe B, Bolliger D, Ahmed AB, Koster A, Agarwal S, Boer C, von Heymann C. International consensus statement on the peri-operative management of direct oral anticoagulants in cardiac surgery. *Anaesthesia*. 2018 Dec;73(12):1535-1545. doi: 10.1111/anae.14425
- Girsberger SA, Schneider MP, Löffel LM, Burkhard FC, Wuethrich PY. Effect of thoracic epidural ropivacaine versus bupivacaine on lower urinary tract function: a randomized clinical trial. *Anesthesiology*. 2018 Mar;128(3):511-519. doi: 10.1097/ALN.0000000000001980
- Luedi MM, Singh SK, Mosley JC, Hassan ISA, Hatami M, Gumin J, Anderegg L, Sulman EP, Lang FF, Stueber F, Fuller GN, Colen RR, Zinn PO. Dexamethasone-mediated oncogenicity in vitro and in an animal model of glioblastoma. *J Neurosurg*. 2018 Dec 1;129(6):1446-1455. doi: 10.3171/2017.7.JNS17668
- Riva T, Theiler L, Jaquet Y, Giger R, Nisa L. Early experience with high-flow nasal oxygen therapy (HFNOT) in pediatric endoscopic airway surgery. *Int J Pediatr Otorhinolaryngol*. 2018 May;108:151-154. doi: 10.1016/j.ijporl.2018.02.035
- Zinn PO, Singh SK, Kotrotsou A, Hassan I, Thomas G, Luedi MM, Elakkad A, Elshafeey N, Idris T, Mosley J, Gumin J, Fuller GN, de Groot JF, Baladandayuthapani V, Sulman EP, Kumar AJ, Sawaya R, Lang FF, Piwnica-Worms D, Colen RR. A co-clinical radiogenomic validation study – conserved magnetic resonance radiomic appearance of periostin-expressing glioblastoma in patients and xenograft models. *Clin Cancer Res*. 2018 Dec 15. doi: 10.1158/1078-0432.CCR-17-3420



# Department of Angiology

Inselspital, Bern University Hospital  
Freiburgstrasse, 3010 Bern



Prof. Iris Baumgartner  
Director



Dr. Jörn Dopheide  
Senior Physician



Prof. Heinz Drexel  
Senior Consultant



Dr. Axel Haine  
Senior Physician



Dr. Ulrike Hügel  
Senior Physician



Dr. Mathias Kaspar  
Senior Physician



PD Dr. Marc Schindewolf  
Consultant Physician



PD Dr. Sebastian Sixt  
Consultant Physician, until Oct 2018



Prof. Christoph Thalhammer  
Consultant Physician



Hana Ramadani  
Member of Scientific Staff

## Research Partners

- ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland
- Clinical Trials Unit Bern, Department of Clinical Research, University of Bern, Bern, Switzerland
- Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria
- University Hospital Bern, Department of Visceral Surgery and Medicine, Bern, Switzerland
- University Hospital Bern, Department of Vascular Surgery, Bern, Switzerland
- University Hospital Bern, Department of General Internal Medicine, Bern, Switzerland
- University Hospital Basel, Department of Angiology, Basel, Switzerland
- University Hospital Zürich, Department of Angiology, Zürich, Switzerland
- University Hospital Frankfurt, Department of Hemostaseology, Frankfurt, Germany
- University Hospital Lübeck, Department of Dermatology, Lübeck, Germany
- University Hospital Mainz, Department of Cardiology/Angiology, Mainz, Germany

## Research Profile

The Division of Angiology is dedicated to a multitude of research projects to advance the field of vascular medicine. The spectrum of research ranges from fundamental research to clinical trials that comprise analysis, classification and computational hemodynamic modeling of congenital vascular malformations, stereotactic MRI-based imaging guidance techniques, risk factor analysis and risk factor modulating therapies in peripheral artery disease, endovascular treatment of peripheral artery disease, drug therapy and endovascular management of venous thromboembolism, and contrast-enhanced ultrasound imaging techniques for outcome prediction in atherosclerotic disease.

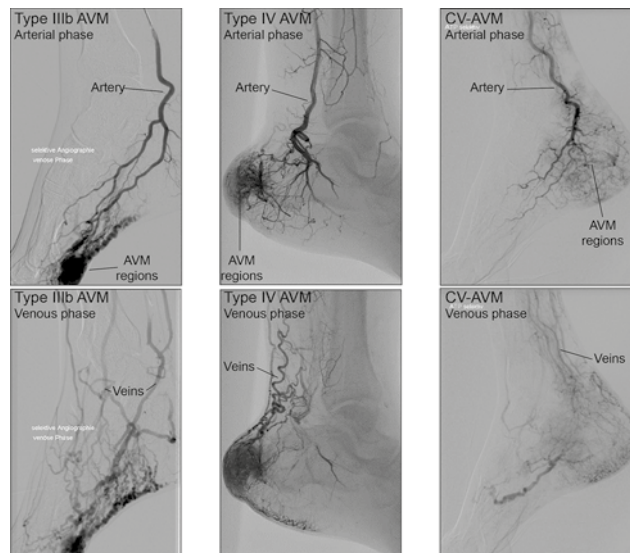
## Teaching Profile

The Division of Angiology participates in University teaching programs for students of medicine and sports-/ physiotherapists. Further activities are regular student lectures and courses (clinical skills), weekly DHGE lectures, and weekly internal education in the field of vascular medicine.

## Highlights 2018

### *Angioarchitecture and hemodynamics of microvascular arterio-venous malformations*

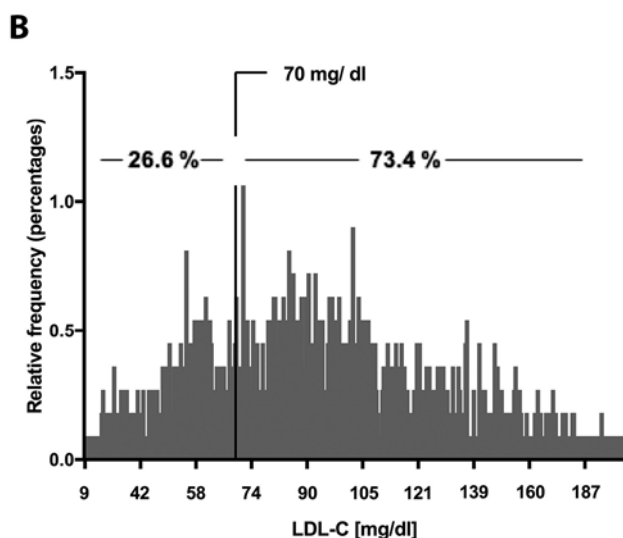
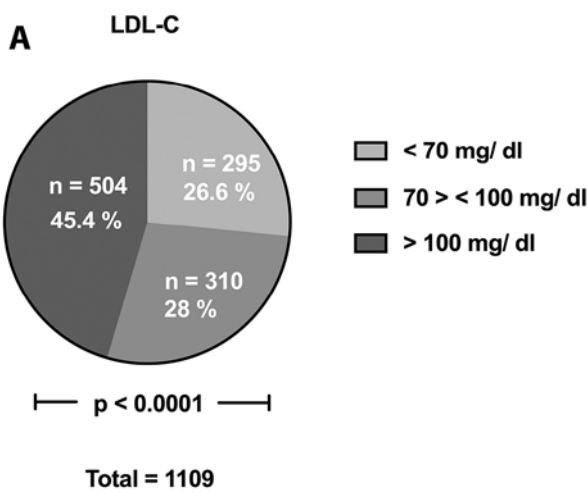
In collaboration with ARTORG Center for Biomedical Engineering Research, University of Bern, Switzerland, we developed a computational model to study the effects of microvascular anomalies on local hemodynamics and their impact on angiographic contrast propagation. Since some microfistular arteriovenous malformations (AVM) do not match the characteristics described in current AVM classification systems, we proposed a new subgroup of microfistular AVMs, composed of enlarged, fistulous paths on the venous half of capillaries and/or dilated draining venules



(hyperdynamic, capillary-venulose malformation [CV-AVM]). The computational model predicts increased arterio-venous contrast agent transit times, highly dispersive transport characteristics and high flow type II and III AVMs for the proposed CV-AVM angioarchitecture. These findings relate to the time-contrast intensity curves sampled from our clinical angiographies.

*Poor attainment of lipid targets in patients with symptomatic peripheral artery disease*

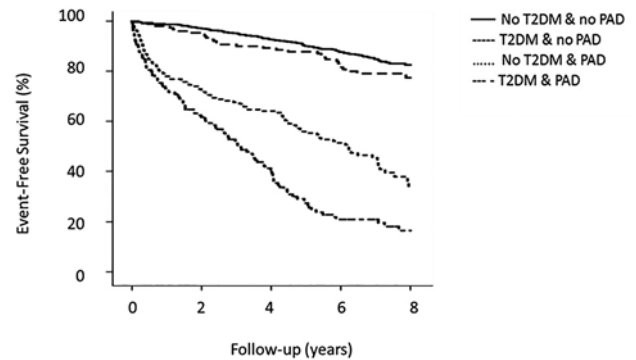
Since patients with peripheral artery disease (PAD) are at very high cardiovascular risk, strict lipid-lowering therapy is recommended. Our single-center observational study aimed at investigating the guideline equitable lipid lowering in 1109 patients with symptomatic PAD. The results show a remarkable undertreatment of LDL-C and non-HDL-C in patients with symptomatic PAD. As statin treatment was associated with a reduced CV mortality rate, our findings call for an increased awareness in clinical lipidology.



*Single and combined effects of peripheral artery disease (PAD) and of type 2 diabetes mellitus (T2DM) on the risk of cardiovascular events*

In collaboration with the Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria, we prospectively recorded cardiovascular events in 1049 subjects (w/o PAD and w/o T2DM) and aimed at investigating the individual and combined effect of T2DM and PAD on future events.

The cardiovascular event rate was lowest in patients with neither PAD nor T2DM (16.7%). Compared to this group the event rate was not significantly increased in T2DM patients without PAD (22.2%, p = 0.077) but higher in non-diabetic patients with PAD (52.6%; p < 0.001) and further increased in patients with both PAD and T2DM (71.2%; p < 0.001) In conclusion, PAD is a stronger risk factor for future cardiovascular events than T2DM, but T2DM in PAD patients strongly increases the incidence of cardiovascular events.



**Awards**

- PD Dr. Marc Schindewolf: Schweizer Preis für Angiologie 2018

**Selected Competitive Grants**

- Dr. Jörn F. Dopheide: Schweizerische Herzstiftung

**Selected Publications**

- Frey S, Cantieni T, Vuillemin N, Haine A, Kammer R, von Tengg-Kobligk H, Obrist D, Baumgartner I. Angioarchitecture and hemodynamics of microvascular arterio-venous malformations. PLoS. One. 2018 Sep 7;13(9):e0203368. doi: 10.1371/journal.pone.0203368. eCollection 2018
- Dopheide JF, Papac L, Schindewolf M, Baumgartner I, Drexel H. Poor attainment of lipid targets in patients with symptomatic peripheral artery disease. Journal of Clinical Lipidology. 2018 May - Jun;12(3):711-717. doi: 10.1016/j.jacl.2018.02.013
- Saely CH, Schindewolf M, Zanolin D, Heinzle CF, Vonbank A, Silbernagel G, Leiberer A, Drexel H, Baumgartner I. Single and combined effects of peripheral artery disease and of type 2 diabetes mellitus on the risk of cardiovascular events: A prospective cohort study. Atherosclerosis. 2018 Oct 6;279:32-37. doi: 10.1016/j.atherosclerosis.2018.09.031
- Baumgartner I, Norgren L, Fowkes FGR, Mulder H, Patel MR, Berger JS, Jones WS, Rockhold FW, Katona BG, Mahaffey K, Hiatt WR. Cardiovascular outcomes after lower extremity endovascular or surgical revascularization: The EUCLID trial. J Am Coll Cardiol. 2018 Oct 2;72(14):1563-1572. doi: 10.1016/j.jacc.2018.07.046
- Schindewolf M, Banik N, Lindhoff-Last E. Reply: Fondaparinux and direct oral anticoagulants: Promising anti-coagulant for management of heparin-induced thrombocytopenia. J Am Coll Cardiol. 2018 Apr 17;71(15):1710-1712. doi: 10.1016/j.jacc.2018.02.026
- Hügel U, Baumgartner I. Implementation of new endovenous treatments of varicosis in the therapy of lateral embryonic veins in Klippel-Trenaunay syndrome. Journal of Vascular Surgery (accepted Dec 2018)

# Department of Cardiology

Inselspital, Bern University Hospital  
Freiburgstrasse, 3010 Bern



Prof. Thomas Pilgrim



Prof. Lorenz Rähler



Prof. Tobias Reichlin



Prof. Marco Valgimigli



Prof. Stephan Windecker

## Research Partners

- Clinical Trial Unit, University of Bern, Bern, Switzerland
- Departments of Cardiology at the University Hospitals Zürich, Basel, Fribourg, Lausanne and Geneva, Switzerland

## Research Profile

The Department of Cardiology at Bern University Hospital has a broad range of clinical research activities. They encompass investigations of devices for percutaneous treatment of coronary artery and valvular heart disease, studies to treat electrophysiological disorders of the heart as well as clinical trials of medicinal products (for example of antithrombotic drugs to prevent thromboembolism and of lipid-modifying drugs for cardiovascular risk reduction). The teams are involved in large scale, multicenter, international, randomized clinical trials as well as in first-in-man human studies using innovative products. The research group has well established national and international partnerships.

## Teaching Profile

The Department of Cardiology participates in University teaching programs for medical students.

## Highlights 2018

Cardiovascular ischemic events commonly arise from atherosclerotic plaque rupture leading to platelet activation, thrombus formation, and reduction of blood flow to the heart or brain. Antithrombotic therapy is central to prevent blood clot formation but it increases bleeding risk. One of the main scientific activities was optimizing the balance between the risk of myocardial ischemia and bleeding prevention in patients with coronary artery disease, undergoing percutaneous coronary intervention (PCI). The final 1-year results of

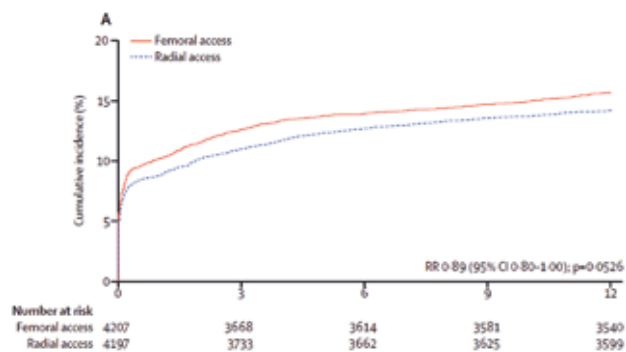
the large-scale, randomized MATRIX trial [1] established the superiority of radial over femoral access site for percutaneous coronary intervention.

The final two-year results of the large-scale randomized GLOBAL LEADERS trial were presented at the 2018 European Society of Cardiology congress in Munich and published in the Lancet [2]. The GLOBAL LEADERS is an open-label, superiority randomized trial designed to challenge the current treatment paradigm of dual antiplatelet therapy (DAPT) for 12 months followed by aspirin monotherapy amongst patients undergoing PCI.

The five years results of the randomised, single-blind, multicentre, non-inferiority BIOSCIENCE trial were published this year [3]. Sirolimus-eluting stents with a biodegradable-polymer coating were compared to everolimus-eluting stents with a non-resorbable polymer coating. The five-year risk of target lesion failure among all-comer patients undergoing percutaneous coronary intervention was similar in both groups.



Catheter Labor at the Bern University Hospital, Inselspital.

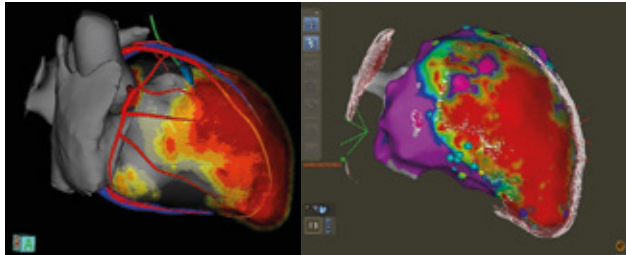


Co-primary composite outcome of all-cause mortality, myocardial infarction, or stroke at 1 year in patients randomised to radial versus femoral access. [1].

Transcatheter Aortic Valve Replacement (TAVR) represents an alternative treatment for patients with severe aortic valve stenosis at increased surgical risk. Refinements in device technology, improved imaging and streamlining of the procedure resulted in a decline in peri-procedural complications, setting the stage for TAVR expansion to intermediate and low risk patients. Our group compares different strategies for the treatment of valvular heart disease, investigate the importance of cardiac comorbidities on clinical outcomes, and investigates newer generation devices for the treatment of aortic stenosis.



In the field of cardiology the interventional treatment of cardiac arrhythmias has had the most spectacular progress over the past decade. In the year 2018, the Inselspital has become the academic center with the largest ablation volume in Switzerland. The interventional treatment of atrial fibrillation and ventricular tachycardias are the most complex procedures and the focus of our research activities. For the ablation of ventricular tachycardias, we are assessing the value of preprocedural imaging by means of cardiac CT or MRI for multimodality substrate assessment. In cardiac pacing, one of the hot topics is leadless pace-



Catheter-Ablation of ventricular Tachycardia using Image Integration of pre-processed cardiac CT's for multimodality substrate assessment.

makers, which has recently become clinically available, but for single chamber pacing only. We studied possibilities for intracardiac communication of multiple leadless pacemakers, which ultimately will be needed for more advanced leadless pacing systems.

#### Selected Competitive Grants

- Swiss National Science Foundation (Grant No 32003B\_163059 "REVEAL in TAVI"; 33IC30\_166855 "SERVE IICT")
- Innosuisse (Grant 31010.1 IP-LS "Translational development of a medical device to treat microvascular obstruction in heart attack patients")

#### Selected Publications

- Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet*. 2018 Sep 8;392(10150):835-848. doi: 10.1016/S0140-6736(18)31714-8
- Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised

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- Pilgrim T, Piccolo R, Heg D, Roffi M, Tüller D, Müller O, Moarof I, Siontis GCM, Cook S, Weilenmann D, Kaiser C, Cuculi F, Hunziker L, Eberli FR, Jüni P, Windecker S. Ultrathin-strut, biodegradable-polymer, sirolimus-eluting stents versus thin-strut, durable-polymer, everolimus-eluting stents for percutaneous coronary revascularisation: 5-year outcomes of the BIOSCIENCE randomised trial. *Lancet*. 2018 Sep 1;392(10149):737-746. doi: 10.1016/S0140-6736(18)31715-X
- Asami, Windecker S, Praz F, Lanz J, Hunziker L, Rothenbühler M, Räber L, Roost E, Stortecky S, Pilgrim T. Transcatheter aortic valve replacement in patients with concomitant mitral stenosis. *Eur Heart J*. 2018 Dec 28. doi: 10.1093/eurheartj/ehy834. [Epub ahead of print]
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## Department of Cardiovascular Surgery

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Head of Cardiovascular Engineering



Prof. Alexander Kadner  
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PD Dr. Sarah Longnus  
Research Group Leader



PD Dr. Florian Schönhoff  
Consultant Physician

### Research Partners

- Cardiac Surgery, University of Alberta, Edmonton, Canada
- Department of Biomedicine, University of Basel and University Hospital Basel, Basel, Switzerland
- Department of Transplantation, Royal Papworth Hospital, Papworth Everard, Cambridge, UK
- Integrated Actuators Laboratory - Zentrum für künstliche Muskeln, EPFL Lausanne, Microcity Neuchâtel, Switzerland
- Laboratoire de Signalisation et Physiopathologie Cardiovasculaire, INSERM, Université Paris-Sud, Université Paris-Saclay, Châtenay-Malabry, France
- St Vincent's Hospital, University of New South Wales, Victor Chang Cardiac Research Institute, Sydney, Australia
- Department of Vascular Surgery and Neurophysiology, Maastricht University Medical Center, Maastricht, The Netherlands
- German Aortic Center Hamburg, University Medical Center, Hamburg, Germany

### Research Profile

The Department of Cardiovascular Surgery is active in multiple areas of both clinical and preclinical research. Interactions among clinicians, researchers and engineers are encouraged to promote high-quality and innovative translational research. This dynamic and productive environment provides ideal conditions for the training of junior clinicians, research scientists and biomedical engineers.

### Teaching Profile

Members of the Department of Cardiovascular Surgery participate in University teaching at several levels. We provide clinical training and course lectures for both undergraduate and graduate students. In addition, we supervise and mentor students completing their Master's degrees, MD Dissertations, or PhD degrees.

### Highlights 2018

#### Clinical research

Thoracic aortic pathologies involving the aortic arch are now approached through a combination of cardiac, vascular, and endovascular surgery. Multiple treatment options have become available in the past years. To understand the complexity of these pathologies, it is important to know the natural history of the disease, indications for treatment, and all available treatment options. The common aim of the

European Association for Cardio-Thoracic Surgery and the European Society for Vascular Surgery to cover all aspects of aortic arch disease has led to the generation of an expert consensus document. Our department co-chaired this project and, with four members in the writing committee, substantially contributed to its simultaneous publication in the respective journals of the above-mentioned European societies.

Over the past year, we continued leading research efforts in large multicenter registries such as the ARCH Project. The ARCH project sources data from 37 large, aortic centers in 12 countries on 5 continents. We assessed the rate of permanent neurological deficit, mortality and other neurological events after total arch replacement using branched and non-branched hybrid devices in patients enrolled in the ARCH registry. We demonstrated that the choice of device affects neither stroke rate, nor mortality, but does influence the rate of spinal cord ischemia.

Stroke is a major drawback of open and endovascular thoracic aortic surgery. We developed a novel, glass model of thoracic-aortic-flow that allows assessment of air embolization during endovascular, thoracic aneurysm repair. This model simulates the real-life surgical setting with implantation of thoracic endografts in a closed-loop pressure system under digital camera visualization. Considerable release of air bubbles from the endograft, and subsequent embolization to the supraaortic branches, were confirmed. How these experimental results translate to clinical settings and their impact on patient outcome remains to be determined.

#### Experimental research

##### Center for Artificial Muscles

Reconstruction medicine still has great difficulty in finding a suitable replacement for damaged or destroyed muscle tissue. With the new Center for Artificial Muscles at Microcity in Neuchâtel, and in collaboration with the EPFL, we are developing universal electromechanical multifunctional actuators for the heart and the aorta. The support of the Werner Siemens Foundation has enabled this new Center for Artificial Muscles to establish itself as one of the leading international centers for regenerative heart, urology, and facial surgery.

### *Donation after circulatory death (DCD)*

Donation after circulatory death (DCD) holds great promise for improving cardiac graft availability, one of the major limitations in heart transplantation today. Although recent clinical reports attest to the feasibility of heart transplantation with DCD, concerns persist regarding the period of warm ischemia to which DCD organs are exposed between circulatory arrest and procurement. Although severe tissue injury can occur rapidly with warm ischemia, the heart is able to tolerate limited durations. Because pre-ischemic treatments are limited for ethical reasons in DCD, protective strategies applied at graft procurement (reperfusion) are of particular importance in optimizing graft quality. We have previously reported that three controlled reperfusion approaches, mild hypothermia, mechanical post-conditioning and hypoxia, effectively improve cardiac recovery. Given the key role of mitochondria in cardiac ischemia reperfusion injury, we hypothesize that these three reperfusion strategies provoke mitochondrial changes that underlie their cardioprotective effects. In an experimental model of DCD, we have recently demonstrated that all three strategies improve the coupling between oxygen-consumption and cardiac-work, and increase tissue ATP content, in parallel with increased functional recovery. However, these reperfusion strategies differentially affect mitochondrial function, integrity and dynamics. Characterization of the role of mitochondria in cardioprotective reperfusion strategies should aid in the identification of new, mitochondrial-based therapeutic targets and in the development of effective reperfusion strategies that could ultimately facilitate DCD heart transplantation.

### *Biogenic Polymer-Based Heart Valves for Congenital Cardiac Surgery*

A promising novel concept for valve prostheses are polymeric tri-leaflet valves. Various polymers can offer improved hemodynamics and durability, while avoiding complicated fabrication processes required with animal tissue. Current technological advances in fabrication make polymeric valves an interesting and viable option. Polymeric materials can easily be moulded into a desired shape, making it possible to closely mimic native heart-valve architecture. Currently, the principal objective is to identify a polymeric material with appropriate durability and low thrombogenicity. Considering these requirements, biogenic polymers (BP) are highly interesting candidates for the development of heart valves. The attributes of BP include high tensile strength, biocompatibility, haemocompatibility, micro-porosity, and biodegradability that make it ideal for a broad range of biomedical



Printed valve holder with a biogenic polymer patch sutured inside (left), 3D-printed valve holder design (22mm) (right).

applications, including artificial skin. The research project aims to evaluate the applicability of BP material for prosthetic heart valves. The mechanical properties of BP sheets will be characterized, along with morphological characteristics. Leaflets from these sheets will be used to design and manufacture a BP-based heart valve for cardiac and congenital cardiac surgery.

### **Selected Competitive Grants**

- A collaborative platform for artificial muscles (collaboration with EPFL & Nanocity), Siemens Stiftung
- Prevention of paraplegia in thoraco-abdominal aneurysms PAPA-ARTiS, EU Horizon 2020
- Mycotic aortic aneurysms and aortic graft infections, INSEL Gruppe grant 2016-2018
- A publicly available collection of virtual and physical 3D models of congenital heart defects for surgical planning and training, Schweizerische Herzstiftung

### **Selected Publications**

- Czerny M, Schmidli J, Adler S, van den Berg JC, Bertoglio L, Carrel T, Chiesa R, Clough RE, Eberle B, Etz C, Grabenwöger M, Haulon S, Jakob H, Kari FA, Mestres CA, Pacini D, Resch T, Rylski B, Schoenhoff F, Shrestha M, von Tengg-Kobligk H, Tsagakis K, Wyss TR; EACTS/ESVS scientific document group. Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch: an expert consensus document of the European Association for Cardio-Thoracic surgery (EACTS) and the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2018 Oct 11. pii: S1078-5884(18)30692-0. doi: 10.1016/j.ejvs.2018.09.016. [Epub ahead of print]
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- Sanz MN, Farine E, Niederberger P, Méndez-Carmona N, Wyss RK, Arnold M, Gulac P, Fiedler GM, Gressette M, Garnier A, Carrel TP, Tevaearai Stahel HT, Longnus SL. Cardioprotective reperfusion strategies differentially affect mitochondria: Studies in an isolated rat heart model of donation after circulatory death (DCD). *Am J Transplant.* 2018 Jul 18. doi: 10.1111/ajt.15024
- Schoenhoff FS, Tian DH, Misfeld M, Perreas KG, Spielvogel D, Mohr FW, Beyersdorf F, Yan TD, Carrel TP. Impact of reimplantation technique of supra-aortic branches in total arch replacement on stroke rate and survival: results from the ARCH registry. *Eur J Cardiothorac Surg.* 2018 Dec 1;54(6):1045-1051. doi: 10.1093/ejcts/ezy194
- Wyss RK, Méndez-Carmona N, Sanz MN, Arnold M, Segiser A, Fiedler GM, Carrel TP, Djafarzadeh S, Tevaearai Stahel HT, Longnus SL. Mitochondrial integrity during early reperfusion in an isolated rat heart model of donation after circulatory death-consequences of ischemic duration. *J Heart Lung Transplant.* 2018 Dec 21. pii: S1053-2498(18)31790-X. doi: 10.1016/j.healun.2018.12.013. [Epub ahead of print]



## Department of Clinical Chemistry

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Director



Prof. Carlo Largiadè  
Deputy Director



PD Dr. Ursula Amstutz



PD Dr. Michaela Fux



PD Dr. Alexander Leichtle



PD Dr. Jean-Marc Nuoffer

### Research Partners

- Institute of Pharmacology, University of Bern, Bern, Switzerland
- Canadian Pharmacogenomics Network for Drug Safety, University of British Columbia, Vancouver, Canada
- Laboratory of Biometry, University of Thessaly, Greece
- Department of Statistics and OR, Complutense University of Madrid, Madrid, Spain
- Department of Nephrology, University of Bern, Bern, Switzerland
- Mayo Clinic Cancer Center, Mayo Clinic, Rochester, Minnesota, USA
- Institute of Pathology, University of Bern, Bern, Switzerland
- Department of Medical Oncology and Hematology, Cantonal Hospital, St. Gallen, Switzerland
- Department of Rheumatology, Immunology and Allergology, Bern University Hospital, Bern, Switzerland
- mitoNet (DACH-research Network for mitochondrial medicine)

### Research Profile

The research focus of the Institute of Clinical Chemistry is on translational research and precision medicine. Specific research topics encompass pharmacogenomics and drug metabolism, liquid biopsy, inherited metabolic diseases, clinical cytomics, and computational medicine. Two of our research groups focus on metabolomics and genomics in the context of drug response. Their ultimate aim is to translate scientific knowledge into clinically useful markers for individualized drug prescription or dosing. This focus has recently been extended to cell-free DNA in the context of drug resistance, residual disease monitoring and organ transplant rejection. The clinical cytomics group investigates the cellular and molecular basis of immune dysfunctions. In addition, they study the relationship between cellular and humoral immunity in common variable immunodeficiency (CVID). The fourth group focuses on the characterization of genetic and secondary metabolic diseases. The research encompasses the field of mitochondrial medicine and ammonia detoxification and the development of pathway analysis, using combined metabolomic and bioenergetic analysis of living cells. The computational medicine group focuses on predictive modeling of clinically relevant outcomes from laboratory data, on deep evaluation of “-omics” data, especially metabolomics, and on the development and application of bioinformatics tools for laboratory medicine.

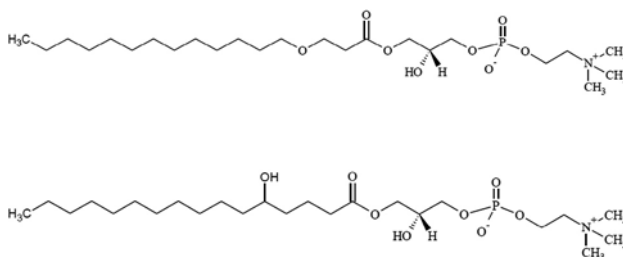
### Teaching Profile

The institute participates in University teaching programs for students of medicine and biomedicine (including students of the University of Fribourg), and of molecular life sciences.

### Highlights 2018

#### *Metabolic profiling for the identification of distinct metabolic signatures in serum/plasma*

With the help of ultra high-performance liquid chromatography coupled to high-resolution mass spectrometry (UHPLC-HRMS), we successfully isolated a novel metabolic signature associated with idiopathic pulmonary fibrosis. By using the additional ion mobility spectrometry capability of our HRMS instrument, we putatively identified 3-hydroxydecanoyl carnitine and a LysoPC (Scheme 1). In another study, our global metabolic profiling approach facilitated the discovery of new metabolites associated with everolimus dose requirement in heart transplant patients. The clinical meaning of the detected metabolites and their significance need to be evaluated in future studies. Our works demonstrate that global metabolic profiling by UHPLC-HRMS helps characterizing disease-associated metabolites and new metabolic signatures useful to guide drug therapy.

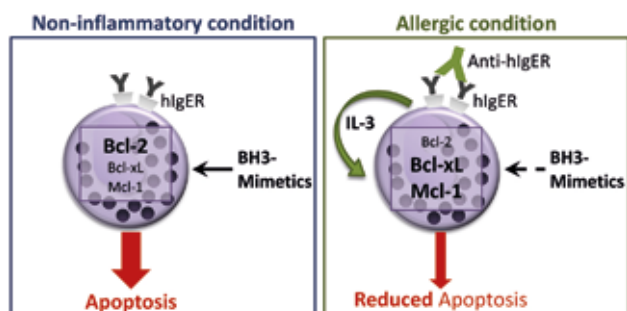


Scheme 1. Potential structures of the LysoPC, which was elevated in serum of IPF patients compared to controls. Adapted from Rindlisbacher et al.

#### *Allergic conditions positively affect the survival of human basophils*

Basophils function as effector and immunoregulatory cells of allergic inflammation during which anti-apoptotic conditions seem to prevail. However, the underlying mechanism regulating survival in human basophils under non-inflammatory and allergic conditions remains elusive. To evaluate the importance of anti-apoptotic Bcl-2 family members Bcl-2, Bcl-xL and Mcl-1, we made use of BH3-mimetics which inhibit Bcl-2, Bcl-xL and Mcl-1. We mimicked allergic inflammation by treating human basophils with IL-3 or by cross-linking the

high affinity IgE receptor (hlgER). We reported that under non-inflammatory condition basophil survival depends on constitutive Bcl-2 expression. In contrast, under allergic conditions, Bcl-xL and Mcl-1 are upregulated. Importantly, cross-linking of hlgER and the concomitant autocrine effect of IL-3 provide a survival advantage as evidenced by less susceptibility to BH3-mimetic-mediated apoptosis. In essence, under allergic conditions, human basophils not only acquire a pro-inflammatory phenotype as reported previously, but also benefit from a survival advantage that potentially allows them to perpetrate and maintain allergic inflammation.



We show that IL-3 and hlgER-activated basophils have a survival advantage compared to resting basophils, which manifests itself by upregulation of Bcl-xL and Mcl-1, enabling human basophils to resist pro-apoptotic stimuli, such as BH3-mimetics.

#### Pharmacogenomics of adverse drug reactions

For many drugs, the factors that render some patients more susceptible to severe adverse drug reactions (ADRs) are still largely unknown. Two such adverse drug reactions include metamizole-induced agranulocytosis, a severe and potentially life-threatening loss of granulocytes secondary to metamizole use, and vincristine-induced peripheral neuropathy, a debilitating adverse effect from chemotherapy. To gain novel insights into the mechanisms underlying these ADRs, we are conducting genetic association studies using array-based genotyping of common single nucleotide polymorphisms (SNPs). In the context of vincristine-induced peripheral neuropathy, we were able to replicate an association previously identified in a genome-wide association study (GWAS) and identify additional candidate genes, which have previously been related to inherited diseases with neuropathy phenotypes. Similarly, for metamizole-induced agranulocytosis, we are conducting the first GWAS related to this ADR to identify genetic susceptibility factors.

#### Selected Competitive Grants

- Swiss National Science Foundation (grant No.310030-163205; 31003A-160206)
- Swiss Personalized Health Network: Project «L4CHLAB» (co-applicant)

#### Selected Publications

- Lesche, D., Sigurdardottir, V., Leichtle, A.B., Nakas, C.T., Christians, U., Englberger, L., Fiedler, M., Largiadèr, C.R., Mohacsi, P., and Sistonen, J., 2018. Targeted and global pharmacometabolomics in everolimus-based immunosuppression: association of co-medication and lysophosphatidylcholines with dose requirement. *Metabolomics* 14, 3. <https://doi.org/10.1007/s11306-017-1294-8>
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- Wright GEB, Amstutz U, Drögemöller BI, Shih J, Rassekh S, Hayden MR, Carleton BC, Ross CJD, Canadian Pharmacogenomics Network for Drug Safety Consortium. Pharmacogenomics of Vincristine-Induced Peripheral Neuropathy Implicates Pharmacokinetic and Inherited Neuropathy Genes. *Clin Pharmacol Ther.* 2018 Jul 12
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## Department of Cranio-Maxillofacial Surgery

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Inga Grigaitiene  
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Biology



Prof. Niklaus Lang  
Senior Scientific  
Consultant

### Research Partners

- Metal Physics and Technology, Department of Materials, ETH Zurich, Zurich, Switzerland
- Advanced Research Center, School of Life Dentistry at Niigata, Nippon Dental University, Niigata, Japan
- National Dental Centre Singapore, SingHealth, Duke-National University of Singapore, Singapore
- Department of Periodontology, College of Dental Medicine, Nova Southeastern University, Florida, USA
- Department of Veterinary Clinical Sciences, Faculty of Veterinary, University of Santiago de Compostela, Lugo, Spain
- Bone Biology & Orthopaedic Research, Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland
- International Bone Research Association (IBRA), Basel, Switzerland
- Geistlich Pharma, Wolhusen, Switzerland

### Research Profile

Our Department is made up of an international team who perform a wide range of oral and maxillofacial surgeries. Facial fractures, bony deficits due to atrophy and growth disturbances, and facial bone defects are the main focus of our work.

Our department is investigating the biological process of bone regeneration in connection with the use of various bone substitutes and bone grafts for different indications. In light of the steady development in surgical techniques, we have broadened our focus and are now exploring how implants – such as osteosynthesis devices made of titanium and biodegradable materials – influence bone regeneration. Following the principle of translational research, the hypotheses of our studies are closely linked to clinical practice.

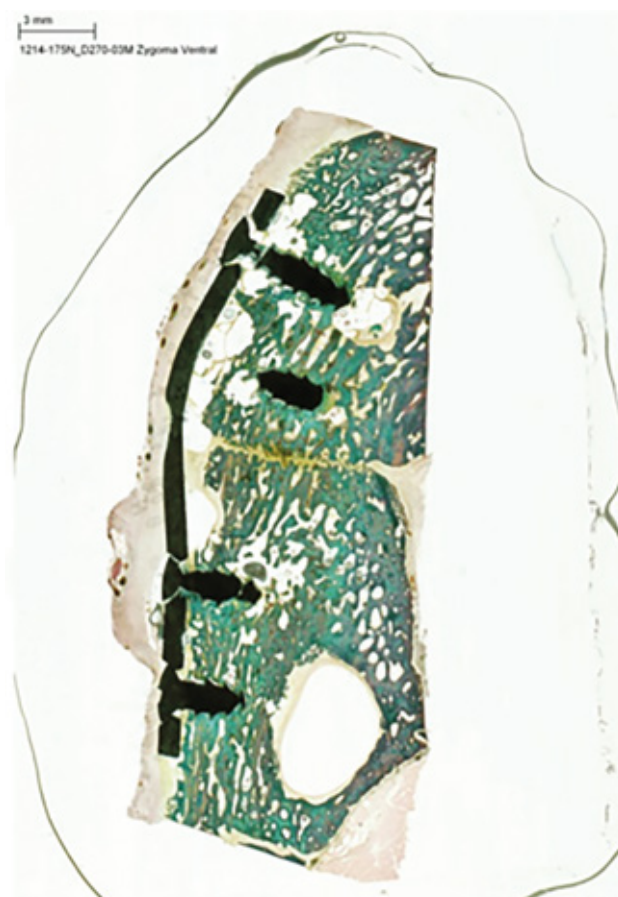
### Teaching Profile

Our department is involved in a range of undergraduate teaching programs in both medicine and dentistry at the University of Bern. We also offer complete postgraduate clinical training and specialization curriculums for Oral and Maxillofacial Surgery. These meet official Swiss and European standards and are based on so-called double full qualification for degrees in both medicine (MD) and dentistry (DDS/DMD). In addition, we provide clinical and scientific fellowship programs which are designed for international candidates who are pursuing professional careers, particularly in academics. In 2018, a new fellowship program

has been established for residents in training for Oral and Maxillofacial Surgery at the National University of Singapore, in which each candidate performs an elective course for 6 weeks in Bern.

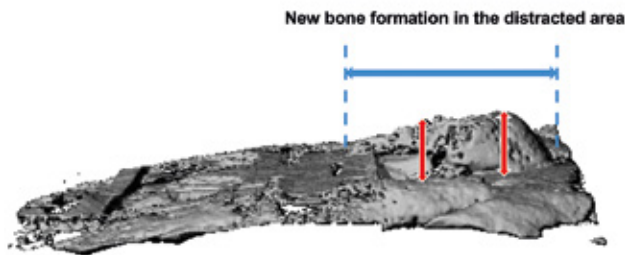
### Highlights 2018

We have continued our research on biodegradable magnesium implants for fracture fixation. A new research project emerged from the cooperation with the group of Prof. Löffler (ETH Zürich) and Prof. Steffen (University of Zürich). This project titled “Design of biomedically adjusted magnesium alloys and implants to generate a paradigm shift in craniomaxillofacial surgery” has been awarded a Swiss National Science Foundation grant (Sinergia) of 2.2 million Swiss Francs.



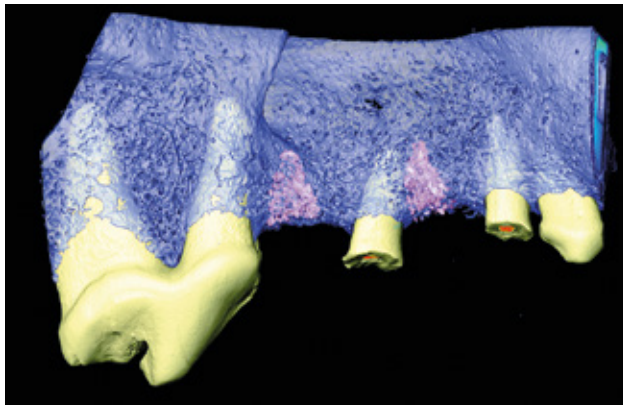
Bone histology 1 month after zygomatic osteotomy fixed by a biodegradable magnesium plate.

In the field of biomaterials, we have finally found in a long-term evaluation that conventional artificial block bone substitutes such as  $\alpha$ -TCP/HA,  $\beta$ -TCP and DBBM have only minor effect on new bone formation. Autogenous block bone grafts are superior for vertical bone augmentation, even without barrier membrane. Our research on interaction between the periosteum and bone has been driven forward. A new research project to understand the molecular signals that control periosteum-dependent bone repair and regeneration has also been awarded a Swiss National Science Foundation grant this year.



Micro-CT image of new bone formed on the calvaria of rat following gradual elevation of periosteum at 14-day healing period. (Blue arrow: bone length; Red arrows: bone height).

For bone regeneration, we pay special attention to recombinant human bone morphogenetic protein (rhBMP)-9, which is considered one of the most osteogenic growth factors among BMP-family. In this project, it was for the first time revealed that rhBMP9 is capable of inducing ectopic new bone formation in vivo. Furthermore, a series of in vivo bone defect models proved that up to four times lower doses of rhBMP9 may be utilized to regenerate same-size bone defects when compared to rhBMP2.



The 3D-reconstructed microCT image of the implantation of bone grafting materials combined with rhBMP9 in the bone defect after tooth extraction.

The bone-biological laboratory of our research division is now known for the high image quality of histology. It was a great pleasure that the laboratory has received three honorable mentions from renowned scientific journals so far.

### Selected Competitive Grants

- Swiss National Science Foundation (Synergia grant nr. CRSII5\_180367 / 1) – Design of biomedically adjusted magnesium alloys and implants to generate a paradigm shift in cranio-maxillofacial surgery (B. Schaller)
- Swiss National Science Foundation (grant nr. 31003A\_182350/1): Pumping the periosteum: an experimental study in a rat calvarium model (N. Saulacic)
- ITI Research Grant (nr. 1287\_2018): Foreign body reaction induced by differently shaped bone substitutes (M. Fujioka-Kobayashi)
- AO Foundation Research Fund: Effects of BMP9 on new bone formation (N. Saulacic)
- International Bone Research Association/IBRA: Efficacy of monocortical screw fixation using anatomically shaped 3D-plates for bridging of mandibular fractures and continuity defects (B. Schaller)

### Selected Publications

- Schaller B, Matthias Burkhard JP, Chagnon M, Beck S, Imwinkelried T, Assad M. Fracture Healing and Bone Remodeling With Human Standard-Sized Magnesium Versus Poly(lactide-Co-Glycolide) Plate and Screw Systems Using a Mini-Swine Craniomaxillofacial Osteotomy Fixation Model. *J Oral Maxillofac Surg.* 2018 Oct;76(10):2138-2150. doi: 10.1016/j.joms.2018.03.039
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## Department of Dermatology

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Prof. Eliane Müller  
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Researcher



Prof. Robert Hunger  
Consultant  
Physician



Prof. Dagmar Simon  
Consultant  
Physician



PD Dr. Helmut Beltraminelli  
Consultant  
Physician

### Research Partners

- Prof. J. McGrath, Genetic Skin Disease Group, King's College London, London, UK
- Prof. A. Lanzavecchia, Institute for Research in Biomedicine, Bellinzona, Switzerland
- Dr. KX. Yan, Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China
- Prof. L. Bruckner-Tudermann, Dept. of Dermatology, University of Freiburg, Germany
- Prof. J. Masenga, The Regional Dermatology Training Centre, Tanzania
- Prof. N. Ortonne, Department of Pathology, C.H. U. Henri Mondor, Paris, France
- Prof. B. Homey, Department of Dermatology, University Hospital Düsseldorf, Düsseldorf, Germany
- Prof. M. Hertl, Hautklinik, Universitätsklinikum Marburg, Germany
- Prof. B. Snijder, Institute of Molecular Systems Biology, ETH, Zürich, Switzerland

### Research Profile

Our Department performs basic and translational research focused on the mechanisms of inflammatory and autoimmune skin diseases as well as on the regulation of cell-cell adhesion and of cytoarchitecture. Specifically, our objectives are:

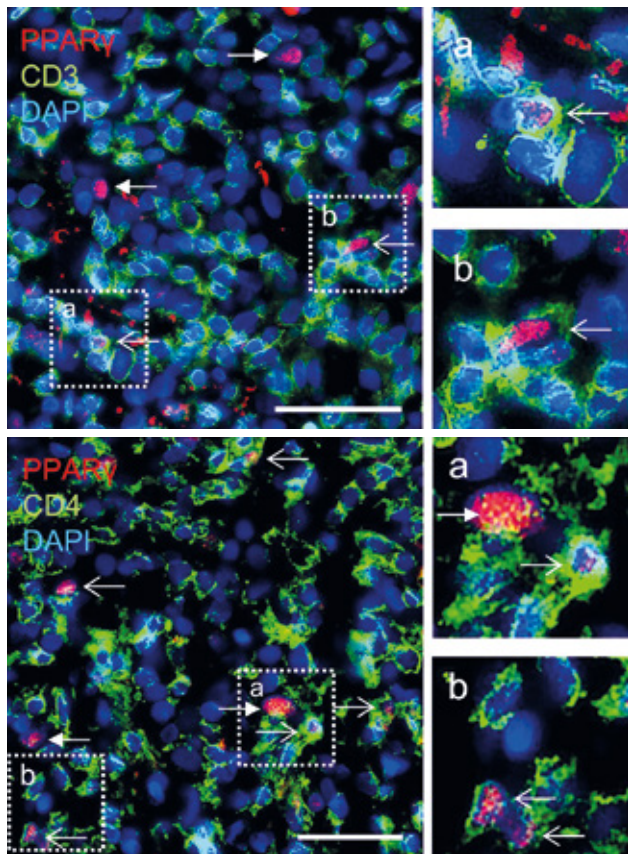
- To characterise the nature of T-helper 9 cells and their role in various diseases: atopic eczema, psoriasis, hidradenitis suppurativa and drug reactions
- To study the autoimmune response and the molecular events leading to skin blistering in pemphigus
- To assess the mechanisms of the interaction of plakin family members with various intermediate filaments in epithelia and striated muscle cells
- To understand how stem cells contribute to homeostasis of the skin
- To carry out clinical trials with different targeted therapies for atopic dermatitis, psoriasis and melanoma

### Teaching Profile

Our Department participates in various pre-graduate teaching programs in both the Medical Faculty and the Faculty of Science. Furthermore, the Department has a close exchange with the Regional Dermatology Training Centre in Tanzania. The objective of the Centre is to promote the care of skin disease in sub-Saharan Africa. We regularly host one to three African specialists for training in dermatopathology.

### Highlights 2018

*Human "T<sub>H</sub>9" cells are a subpopulation of PPAR $\gamma$ <sup>+</sup> T<sub>H</sub>2 cells*  
While T<sub>H</sub>1, T<sub>H</sub>2, and T<sub>H</sub>17 cells are well-defined T<sub>H</sub> cell lineages in humans, it remains debated whether IL-9-producing T<sub>H</sub> cells represent a bona fide "T<sub>H</sub>9" lineage. In mice, "T<sub>H</sub>9" cells have been shown to have superior capacity to mediate anti-tumor immunity and to cause allergic tissue inflammation. In humans our understanding of the characteristics and function of IL-9-producing T<sub>H</sub> cells is still poor. Our work has provided evidence that human IL-9-producing T<sub>H</sub> cells are better described as a subpopulation of skin-homing and skin-resident T<sub>H</sub>2 cells: IL-9-producing T<sub>H</sub> cells express the chemokine receptors CCR4 and CCR8, produce high levels of IL-5 and IL-13, and express T<sub>H</sub>2-lineage-associated transcription factors. The "T<sub>H</sub>9" phenotype in these cells is the result of activation-dependent and transient IL-9 production which is accompanied by downregulation of T<sub>H</sub>2 cytokines. These IL-9<sup>+</sup> T<sub>H</sub>2 cells differ from "conventional" T<sub>H</sub>2 cells in that they express the ligand-activated transcription factor PPAR $\gamma$ , a known master regulator of cellular metabolism. Just as IL-9 itself, PPAR $\gamma$  is induced in naive T<sub>H</sub> cells by priming with IL-4 and TGF- $\beta$  ("T<sub>H</sub>9"-priming). Functionally, PPAR $\gamma$  is required for full IL-9 production in human T<sub>H</sub> cells. IL-9<sup>+</sup> T<sub>H</sub>2 cells infiltrate acute allergic skin inflammation in humans in high numbers, which supports our hypothesis that "T<sub>H</sub>9" cells are in fact early activated T<sub>H</sub>2 cells. Our studies have hence identified IL-9-producing T<sub>H</sub> cells as a phenotypically and functionally distinct subpopulation of T<sub>H</sub>2 cells that depend on PPAR $\gamma$  for full effector functions.



Detection of PPAR $\gamma$ <sup>+</sup> T helper cells in human allergic contact dermatitis: (A+B) Representative pictures of immunofluorescence for PPAR- $\gamma$  and CD3 (A) or CD4 (B) in lesional skin of acute allergic contact dermatitis. Scale bars: 50 $\mu$ m. Open arrows: PPAR- $\gamma$ <sup>+</sup>/CD3<sup>+</sup> cells (A) or PPAR- $\gamma$ <sup>+</sup>/CD4<sup>+</sup> cells (B). Closed arrows: PPAR- $\gamma$ <sup>+</sup>/CD3<sup>-</sup> cells (A) or PPAR- $\gamma$ <sup>+</sup>/CD4<sup>-</sup> cells (B).

#### Identification and characterization of pathogenic variants of desmoplakin

Desmoplakin, a member of the plakin family of cytolinkers, is an essential component of the desmosomes, cell-cell adhesion complexes. Genetic alterations of the desmoplakin gene are variably associated with skin, hair and or heart pathologies. The genotype-phenotype relationship of desmoplakin gene variants is still unclear. We have developed a sensitive biochemical method, which enables to identify deleterious versus silent variants in the carboxyl terminal domain of desmoplakin. The tail of desmoplakin tail is for its interaction with intermediate filaments. Our results indicate that binding of desmoplakin to epidermal keratins and the muscle-specific desmin relies on the same recognition sites. Therefore, deleterious desmoplakin C-terminal variants, in a homozygous or compound heterozygous state, that are associated with an early skin phenotype are most likely to be also pathogenic in the heart and lead to cardiomyopathy.

#### Selected Competitive Grants

- SNF Pemphigus-from pathogenesis to therapeutics (Pegasus): Epitope spreading in pemphigus (CHF 212'463; L. Borradori)
- SNF Sinergia: A One health approach to unravel novel genes and molecular pathways in dermatology (CHF: 2'493'769; E. J Müller, co-applicant)
- Swiss Personalised Health Network (SPHN) Board: Identification of biomarkers and therapeutic targets in inflammatory disease immunotherapy by high-dimensional single cell analysis and cluster proteomics (total: CHF 1'283'000, Ch. Schlapbach, co-applicant)
- Peter Hans Hofschneider Stiftungsprofessur für molekulare Medizin (Prof. Ch. Schlapbach)

#### Selected Publications

- Simon D, Page B, Vogel M, Bussmann C, Blanchard C, Straumann A, Simon HU. Evidence of an abnormal epithelial barrier in active, untreated and corticosteroid-treated eosinophilic esophagitis. *Allergy*. 2018 Jan;73(1):239-247. doi: 10.1111/all.13244
- Cazzaniga S, Apfelbacher C, Diepgen T, Ofenloch RF, Weisshaar E, Molin S, Bauer A, Mahler V, Elsner P, Schmitt J, Ballmer-Weber BK, Spring P, Naldi L, Borradori L, Simon D; CARPE study groups of Germany and Switzerland. Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data. *Br J Dermatol*. 2018 Jan;178(1):229-237. doi: 10.1111/bjd.15660
- Thomi R, Cazzaniga S, Seyed Jafari SM, Schlapbach C, Hunger RE. Association of Hidradenitis Suppurativa with T Helper 1/T Helper 17 Phenotypes: A Semantic Map Analysis. *JAMA Dermatol*. 2018 May 1;154(5):592-595. doi: 10.1001/jamadermatol.2018.0141
- Seyed Jafari SM, Wiedmer C, Cazzaniga S, Frangež Ž, Shafiqi M, Beltraminelli H, Weber B, Simon HU, Hunger RE. Correlation of Vascular Endothelial Growth Factor subtypes and their receptors with melanoma progression: A next-generation Tissue Microarray (ngTMA) automated analysis. *PLoS One*. 2018 Nov 8;13(11):e0207019. doi: 10.1371/journal.pone.0207019. eCollection 2018
- Meier-Schiesser B, Feldmeyer L, Jankovic D, Mellett M, Satoh TK, Yerly D, Navarini A, Abe R, Yawalkar N, Chung WH, French LE, Contassot E. Culprit drugs induce specific IL-36 overexpression in Acute Generalized Exanthematous Pustulosis. *J Invest Dermatol*. 2018 Nov 2. pii: S0022-202X(18)32779-9. doi: 10.1016/j.jid.2018.10.023. [Epub ahead of print]
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- Favre B, Bégré N, Bouameur JE, Lingasamy P, Conover GM, Fontao L, Borradori L. Desmoplakin interacts with the coil 1 of different types of intermediate filament proteins and displays high affinity for assembled intermediate filaments. *PLoS One*. 2018 Oct 4;13(10):e0205038. doi: 10.1371/journal.pone.0205038. eCollection 2018

# Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UEM)

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Prof. Zeno Stanga



PD Dr. Markus Laimer



Prof. Stavroula Mouggiakakou



Dr. Roman Trepp



Prof. Regula Everts



Prof. Lia Bally

## Research Partners

- Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, UK
- Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, UK
- Department of Internal Medicine, Medical University of Graz, Austria
- Department of Management, Technology, and Economics, ETH Zürich, Switzerland
- Department of Biology, Institute of Molecular Systems Biology, ETH Zürich, Switzerland
- Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zürich, Switzerland
- Center of Laboratory Medicine, Inselspital Bern, Switzerland
- Department for Nephrology and Hypertension, Inselspital Bern, Switzerland
- ARTORG Center for Biomedical Engineering Research, Diabetes Technology, University of Bern, Switzerland
- Support Center for Advanced Neuroimaging (SCAN), University Institute of Diagnostic and Interventional Neuroradiology, Inselspital Bern, Bern University Hospital, Switzerland
- Clinical Trials Unit (CTU), University of Bern, Switzerland

## Research Profile

Our research groups cover the field of diabetes, endocrinology, nutrition, and metabolism. Within the framework of the Diabetes Center Bern, an important scope is the development, investigation and implication of novel technological approaches in the field together with international collaborators and industrial partners. Novel technologies are also utilized for the development of enhanced image-based nutritional analysis combining computer vision with artificial intelligence. Such personalized nutrition approaches are embedded in a platform for deep metabolic phenotyping, using mass spectrometric, stable isotope and imaging technologies that will leverage the discovery of mechanistic information and deliver novel health care solutions to improve clinical pathway management. Our nutritional research encompasses malnutrition and nutrient supplements and a novel group led by a tenured track professor will aim at combining technological developments and novel -omics technologies in this area. Endocrine research focuses on neuroendocrine tumors, thyroid, parathyroid, and pituitary disease. Finally, metabolic research encompasses the investigation of various disease models, covering the range from type 1 diabetes to

inborn errors of metabolism. The neuroendocrinology and neurometabolism research group investigates the impact of endocrine and metabolic diseases on cognitive performance and cerebral and neurometabolic mechanisms.

## Teaching Profile

Our University clinic participates in University teaching programs for students of medicine, dental medicine, and biomedicine, additionally, we teach Master-students in Biomedical Engineering.

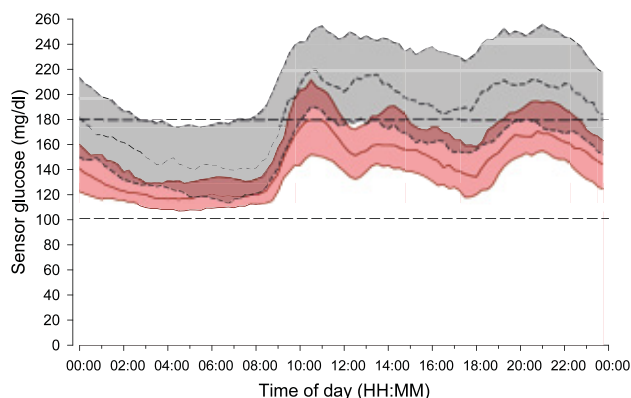
## Highlights 2018

### Operative Start of the Diabetes Center Bern (DCB)

The year 2018 marked the operative start of the DCB, embedded within the Swiss Institute for Translational and Entrepreneurial Medicine (sitem-insel) aiming at the investigation of modern diabetes-related treatment strategies, and translation into applicable medical products. First projects have been successfully conducted (e.g. closed-loop insulin delivery studies, computer-vision based meal assessment, etc).

### Closed-Loop Insulin Delivery (Artificial Pancreas)

Closed-loop insulin delivery (also known as the artificial pancreas) is an emerging approach for the treatment of diabetes. Closed-loop systems combine real-time sensor glucose measurements from a continuous glucose monitor with a control algorithm that directs insulin delivery via an insulin pump, offering a more physiological way of insulin therapy. An area in great need of improvement is diabetes care in hospital where only a minority of patients achieve recommended therapeutic targets. In a randomized controlled two-country clinical trial we compared the safety



and efficacy of closed-loop insulin delivery with conventional insulin therapy in hospitalized patients receiving non-critical care. Closed-loop insulin delivery resulted in significantly better glycemic control than usual care (5.5 hours per day more in target) without increasing the risk of hypoglycaemia. Incremental benefits of closed-loop insulin therapy were also seen in follow-up studies focusing on challenging patient populations such as patients receiving dialysis or nutrition support whilst in hospital. This landmark study was presented at the American Diabetes Association's 78th Scientific Sessions in Orlando, Florida, USA and was simultaneously published in the *New England Journal of Medicine*.

#### *Metabolic Research in Type 1 Diabetes*

SGLT-2 inhibitors currently represent the most intensely investigated drugs in the field of diabetes, yet data on hormonal regulation of glucose homeostasis and related safety are not available for type 1 diabetes (T1D). Recent and ongoing studies of our research group are investigating the influence of the SGLT2 inhibitor dapagliflozin on hormonal glucose regulation and ketogenesis in T1D under different metabolic conditions. Another research group investigates exercise-associated fuel metabolism in T1D, aiming at novel approaches to improve glucose control in T1D. A current focus lies on alternative carbohydrate supplementation and the associated metabolic changes (FruDeg study).

#### *Individualized nutritional support in medical inpatients improve important clinical outcomes including survival*

The EFFORT trial, published in *The Lancet*, demonstrates that providing patients who are found to be at nutritional risk treated with individualised nutritional support results in a better outcome than in those given the standard hospital diet. The intervention led to a significantly better outcome when the primary composite end point was assessed (adverse clinical outcome defined as all-cause mortality, intensive care unit admission, non-elective hospital readmission, major complications and decline in functional status at 30 days). In addition, mortality (7.2% vs. 9.9%) and functional decline at 30 days were significantly lower, and quality of life and improvement in activities of daily living significantly better in the intervention group. This study shows that a simple intervention in patients at nutritional risk admitted to medical wards can result in significant improvements in outcome, with a need to treat 25 patients to prevent one adverse clinical outcome and 37 to prevent one death.

#### **Selected Competitive Grants**

- JDRF, National Institute for Health Research Cambridge Biomedical Research Centre, Wellcome Strategic Award (100574/Z/12/Z)
- Swiss National Science Foundation (P1BEP3\_165297); European Union Seventh Framework Program (FP7-PEOPLE-2011-IAPP) grant agreement no. 286408
- MyTreat - 18172.1 PFLS-LS, Investigator Initiated Clinical Trial (Novo Nordisk Fonds) for TabDeg Study and FruDeg Study
- Young Independent Investigator Grant Award of the Swiss Society of Endocrinology and Diabetology

#### **Selected Publications**

- Bally L, Thabit H, Hartnell S, et al. Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care. *N Engl J Med*. 2018 Aug 9;379(6):547-556. doi: 10.1056/NEJMoa1805233. Epub 2018 Jun 25.
- Melmer A, Kempf P, Lunger L, et al. Short-term effects of dapagliflozin on insulin sensitivity, postprandial glucose excursion and ketogenesis in type 1 diabetes mellitus. *Diabetes Obes Metab*. 2018 Nov;20(11):2685-2689. doi: 10.1111/dom.13439. Epub 2018 Jul 12.
- Schuetz P, Fehr R, Baechli V, et al. Individualized nutritional support in medical inpatients at nutritional risk: a randomized clinical trial. *Lancet* 2018 (In press).
- Ruan Y, Bally L, Thabit H, et al. Hypoglycaemia Incidence and Recovery During Home Use of Hybrid Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes. *Diabetes Obes Metab*. 2018 Aug;20(8):2004-2008. doi: 10.1111/dom.13304. Epub 2018 Apr 16.
- Tauschmann M, Thabit H, Bally L et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet*. 2018 Oct 13;392(10155):1321-1329. doi: 10.1016/S0140-6736(18)31947-0. Epub 2018 Oct 3.



## Department of Diagnostic and Interventional Neuroradiology

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Prof. Roland  
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PD Dr. Christoph  
Ozdoba Physician  
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Michela  
Mordasini  
Head of Medical  
Technical  
Neuroradiology



Prof. Marwan  
El-Koussy  
Consultant



PD Dr. Pasquale  
Mordasini  
Consultant

### Research Partners

- Department of Neurology, University Hospital Bern and University of Bern, Bern, Switzerland
- Department of Neurosurgery, University Hospital Bern and University of Bern, Bern, Switzerland
- University Hospital of Psychiatry, Bern, Switzerland
- Division of Child Neurology, Department of Pediatrics, University Hospital Bern and University of Bern, Bern, Switzerland
- Institute for Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
- Department of Psychology, University of Bern, Bern, Switzerland
- Division of Neuroradiology, Toronto Western Hospital, Toronto, Canada
- Department of Clinical Neurology, University of California Los Angeles (UCLA), USA
- Department of Informatics, Technical University Munich, Munich, Germany
- Excellence Center for Ultra-High-Field MRI, Medical University Vienna, Vienna, Austria

### Research Profile

#### Neurovascular research

The research group focuses on treatment strategies for neurovascular diseases (aneurysms, AVM etc.) and especially the evaluation and treatment of acute ischemic stroke. The researchers combine preclinical development of techniques in bench-top and animal models and evaluate their application in large-scale international clinical studies.

#### Advanced Neuroimaging and Digitalisation

The research of the Support Center of Advanced Neuroimaging (SCAN) focuses on the translation of quantitative imaging methods, artificial intelligence technology and automated image analysis into clinical practice, sequence development and methodological counselling for neuroimaging studies. In this domain, the researchers of the SCAN have participated in international neuroimaging trials (e.g. ENINGMA Epilepsy and Parkinson's disease), neuroimaging challenges and data analysis networks in cerebrovascular research, neuro-oncology, neuro-immunology, sleep-related disorders, epilepsy and neurodegenerative disorders.

#### CSF Hypo- und Hypertension Syndromes

The multidisciplinary group of the Neurocenter develops new imaging modalities and interventional/surgical treatment options for patients with CSF leakage syndromes and idiopathic intracranial hypertension.

### Teaching Profile

The Department has been involved in various teaching and activities of the University and Neurocenter. We have co-organized the 2018 Clinical Neuroscience Bern (CNB) Meeting and CNB Science Slam with a special focus on artificial intelligence and machine learning. The Departments of Neuroradiology and Neurology have organized the ESMINT/ESO/ESNR European Stroke Winter School for stroke physicians in training. We actively participate in the teaching activities of the European academy of neurology in the domain of neuroimaging, the Organization of Human Brain Mapping (OHBM) and the European stroke organization as well as in various educational programs of the University of Bern.

### Highlights 2018

- Swiss Epilepsy Research Prize 2018 to Prof. Wiest, Dr. Kiefer and Prof. Schindler for the Development of a new MR technology to detect effects of epileptic activity by MRI
- Peter-Huber Prize (researcher award of the Swiss Society of Neuroradiology) for Dr. Eike Immo Piechowiak
- Top 3 position at the international Brain Tumor Segmentation Challenge (BRATS) of the Society for Medical Image Computing & Computer Assisted Intervention in Granada/Spain

### Selected Competitive Grants

*SNF grants, accepted 2018*

- SINERGIA Project "Predict and Monitor Epilepsy After a First Seizure: The Swiss-First Study (PI Prof. Wiest) CHF 2.666.000 CHF)
- SINERGIA Project "Hydrogel" (PI Dr. Mosimann, 1.138.000 CHF)
- SNF Project "Introduction of High Field Optimized Fast 3D MR Spectroscopic Imaging for IDH Typing of Gliomas and Assisted Surgical Neuro Navigation" (PI Dr. Slotboom) 364.000 CHF
- HORIZON 2020 INSPIRE MED (CI Dr. Slotboom) 281.000 CHF
- Novartis Innovation Grant (PI Dr. McKinley) 180.000 CHF

### Selected Publications

- Dobrocky T, Mosimann PJ, Zibold F, Mordasini P, Raabe A, Ulrich CT, Gralla J, Beck J, Piechowiak EI. Cryptogenic Cerebrospinal Fluid Leaks in Spontaneous Intracranial Hypotension: Role of Dynamic CT Myelography. *Radiology*. 2018 Dec;289(3):766-772. doi: 10.1148/radiol.2018180732
- Mosimann PJ, Kaesmacher J, Gautschi D, Bellwald S, Panos L, Piechowiak E, Dobrocky T, Zibold F, Mordasini P, El-Koussy M, Wiest R, Bervini D, Wagner F, Arnold M, Jung S, Galimanis A, Gralla J, Fischer U. Predictors of Unexpected Early Reocclusion After Successful Mechanical Thrombectomy in Acute Ischemic Stroke Patients. *Stroke* 2018; 49 (11) :2643-2651. doi: 10.1161/STROKEAHA.118.021685
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- Kellner-Weldon F, El-Koussy M, Jung M, Jossen M, Klinger-Gratz PP, Wiest R. Cerebellar hypoperfusion in migraine attack: incidence and significance. *AJNR Am J Neuroradiol*. 2018 Jan 11. doi: 10.3174/ajnr.A5508. [Epub ahead of print]
- Commowick O, Istace A, Kain M, Laurent B, Leray F, Simon M, Pop SC, Girard P, Améli R, Ferré JC, Kerbrat A, Tourdias T, Cervenansky F, Glatard T, Beaumont J, Doyle

S, Forbes F, Knight J, Khademi A, Mahbod A, Wang C, McKinley R, Wagner F, Muschelli J, Sweeney E, Roura E, Liadó X, Santos MM, Santos WP, Silva-Filho AG, Tomas-Fernandez X, Urien H, Bloch I, Valverde S, Cabezas M, Vera-Olmos FJ, Malpica N, Guttmann C, Vukusic S, Edan G, Dojat M, Styner M, Warfield SK, Cotton F, Barillot C. Objective Evaluation of Multiple Sclerosis Lesion Segmentation using a Data Management and Processing Infrastructure. *Sci Rep*. 2018; 8(1):13650. doi: 10.1038/s41598-018-31911-7

## Department of Diagnostic, Interventional and Pediatric Radiology (DIPR)

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Deputy Director



PD Dr. Ingrid Böhm  
Project Leader



Prof. Andreas Christe  
Head of Depart. SLS



Dr. Dominik Günsch  
Attending



PD Dr. Adrian Huber  
Attending



PD Dr. Michael Ith  
Medical Physicist



PD Dr. Bernd Jung  
Medical Physicist



Prof. Christoph Meinrad Kempf  
Project Leader



PD Dr. Martin Maurer  
Senior Attending



Dr. Sylvia Meryl Nyilas  
PhD, Resident



Dr. Verena Carola Obmann  
Attending



PD Dr. Alexander Pöllinger  
Senior Attending



Prof. Val Murray Runge  
Senior Attending



Dr. Nico Olivier Ruprecht  
PhD, PostDoc

### Research Partners

- ARTORG, Biomedical Engineering Center and Department of Biomedical Research (DBMR), Bern, Switzerland
- Radiological Physics, Radiology and Nuclear Medicine, University of Basel, Basel, Switzerland
- German Cancer Research Center (dkfz), Heidelberg, Germany
- Switzerland Innovation Park, Biel/Bienne, Switzerland
- ETH Zürich and EPFL / CHUV Lausanne, Switzerland
- Clinical Departments, Insel Group, Switzerland
- Ohio State University (OSU), Columbus, OH, USA
- Departments of Radiology and Biomedical Engineering at Case Western Reserve University, Cleveland, OH, USA
- University of Duke, NC, USA
- Swiss Working Group for Clinical Cancer Research (SAKK), Bern, Switzerland

### Research Profile

DIPR maintains an innovative research culture in order to provide high standard performance and for the purpose of the well-being of all patients. Various measures have improved the cooperation with other research partners. At present we are involved in 20 cooperation-studies as well as 10 DIPR-IIT projects; in addition we are delivering support to 50 ongoing clinical studies.

Three permanent staff positions in Medical Physics and Computer Vision Engineering support the development of new MR sequences and an imaging processing platform, this platform is being established in the imaging laboratory. In close collaboration with many clinical sites including pediatric partners, multiparametric imaging and advanced image analysis are in the process of being translated into clinical routine to further improve diagnosis, treatment planning and navigation during intervention. Our productive collaboration with e.g. the ARTORG center in Bern allows us to work with biomedical engineers of various clinical fields that help us to test and apply innovative imaging methods and image processing.

Since 2014 DIPR is building up an experimental radiology laboratory at the Department for BioMedical Research, University of Bern to perform tumor cell ex vivo experiments as well as studies with focus on contrast media.

### Teaching Profile

DIPR teaches medical students of the University of Bern in years 2 to 5 of the study of medicine. It provides lectures and practical courses from basic imaging anatomy to radiological pathological correlations. DIPR is an active member of the SIWF/ISFM (Schweizerische Institut für ärztliche Weiter- und Fortbildung). Radiology hosts residents of the European School of Radiology (ESOR). Our teaching program is also engaged with medical students and Biomedical Engineering students. Our Department is the largest training site in German speaking part of Switzerland for the Registered Radiographer Advanced Federal Diploma of Higher Education. DIPR is also a member of the training program for commercial employees and Healthcare Assistants.

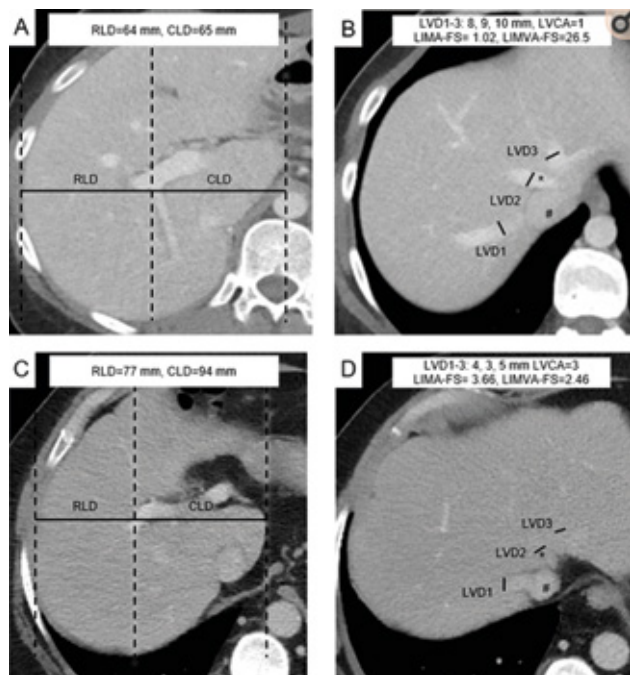
### Highlights 2018

#### MR elastography

Chronic liver disease and consequent liver fibrosis, is an important healthcare issue but still remains under recognized, leading to significant morbidity and mortality. Detection and quantification of diffuse liver disease remains challenging but is desirable to avoid invasive and expensive biopsies. The goal of our research is to develop quantitative biomarkers for diffuse liver disease in CT and MRI.

In CT imaging we compared four different fibroses scores: CRL-R = caudate-right-lobe ratio, LIMV-, LIMA- and LIMVA-fibrosis score, with "LIM" for liver imaging morphology, "V" for liver vein diameter and "A" for attenuation and we could demonstrate that CT fibrosis scores, notably LIMA and LIMVA were able to predict significant liver fibrosis. Further ongoing analysis explores the use of volumetry and surface nodularity scores.

Our multiparametric MRI protocol included besides MR elastography, proton density fat fraction (PDFF), T1, T2\* mapping and SWI imaging. While most clinical liver MR protocols are based on a series of weighted images, quantitative liver imaging is of utmost interest in the research environment. In our prospective study, we could show that T1 relaxation times decrease with increasing grade of liver fibrosis. While SWI performed better than T2\* to separate patients with and without liver fibrosis, T2\* performed slightly better in a multiparametric combination with MR elastography, PDFF, and T1. Further interesting findings were the dependency of T1 and T2\* relaxation parameters of the location of measurements since we could prove alteration of results by susceptibility artefacts in lung adjacent liver segments. SWI and T2\*-mapping are highly dependent on liver steatosis grades. Nevertheless, both parameters are useful predictors for liver fibrosis when using a multiparametric approach.



Liver imaging morphology and attenuation fibrosis score (LIMA-FS) and liver imaging morphology, vein diameter and attenuation fibrosis score (LIMVA-FS) in two patients.

### Selected Competitive Grants

- Prof. Andreas Christe – Stiftung Lindenhof support INTACT – lung project 17-08-F
- PD Dr. Adrian Thomas Huber – Stiftung zur Krebsbekämpfung – for MR Elastography equipment, application 414

### Selected Publications

- Fischer K, Yamaji K, Luescher S, Ueki Y, Jung B, von Tengg-Kobligk H, Windecker S, Friedrich MG, Eberle B, Guensch DP. Feasibility of cardiovascular magnetic resonance to detect oxygenation deficits in patients with multi-vessel coronary artery disease triggered by breathing maneuvers. *J Cardiovasc Magn Reson.* 2018 May 7;20(1):31. doi: 10.1186/s12968-018-0446-y
- Boehm I, Heverhagen JT. Delayed reaction following gadolinium-based contrast agent application. *Magn Reson Imaging.* 2018 Jul;50:10-11. doi: 10.1016/j.mri.2018.03.007
- Anthimopoulos MM, Christodoulidis S, Ebner L, Geiser T, Christe A, Mouggiakakou SG. Semantic Segmentation of Pathological Lung Tissue with Dilated Fully Convolutional Networks. *IEEE J Biomed Health Inform.* 2018 Mar 26. doi: 10.1109/JBHI.2018.2818620
- Nyilas S, Schreder T, Singer F, Poellinger A, Geiser TK, Latzin P, Funke M. Multiple breath washout: A new and promising lung function test for patients with idiopathic pulmonary fibrosis. *Respirology.* 2018 Aug;23(8):764-770. doi: 10.1111/resp.13294
- Kim SY, Maurer MH, Richter JK, Heverhagen JT, Boehm IB. Gadolinium depositions after the application of the hepatospecific gadolinium-based contrast agent gadoxetate disodium. *Eur J Intern Med.* 2018 Jan;47:e9-e11. doi: 10.1016/j.ejim.2017.09.033
- Runge VM, Heverhagen JT. Advocating the Development of Next-Generation High-Relaxivity Gadolinium Chelates for Clinical Magnetic Resonance. *Invest Radiol.* 2018 Jul;53(7):381-389. doi: 10.1097/RLI.0000000000000454



## Department of Emergency Medicine

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FRCEM MSc  
Director and  
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Dr. Monika  
Brodman  
Maeder  
MME  
International  
Emergency  
Medicine



Dr. Martin  
Müller  
Ressource & Risk  
Management



PD Dr. Wolf  
Hautz  
MME  
Diagnostic Error  
and Patient Safety



Dr. Thomas  
Sauter  
Simulation and  
Teaching



Dr. David  
Srivastava  
Refugee Health

### Research Partners

- Prof. Stavroula Mouggiakakou University of Bern, ARTORG Center for Biomedical Engineering Research, Diabetes Technology, Bern, Switzerland
- Institut für Gebirgsnotfallmedizin EURAC, Bozen, Italy
- CHUV Lausanne, Lausanne, Switzerland
- HUG Genève, Genève, Switzerland
- Max Planck Institute for Human Development Berlin, Germany
- Institute of Educational Measurement, University of Oslo, Oslo, Norway
- Sarah Lawrence College, New York University School of Medicine, NY, USA
- Charité, Berlin, Germany
- Erasmus Medical Center Rotterdam, The Netherlands

### Research Profile

The Department of Emergency Medicine focuses its research on questions of clinical relevance and applicability - under the lead of Prof. Exadaktylos - in an attempt to improve emergency care. Six working groups currently investigate different aspects of emergency care, including diagnostic error and patient safety (PD Dr. Hautz), direct new oral anticoagulants (Dr. Sauter), refugee health (Dr. Srivastava), resource and risk management (Dr. Müller), Infection (PD Dr. Ricklin & Dr. Ehrhard) and wilderness medicine (Dr. Brodmann Maeder). We heavily invest in the scientific training of medical students and young graduates and supervise around 10 master thesis and 10 dissertation projects annually.

### Teaching Profile

The Department of Emergency Medicine is actively involved in undergraduate and postgraduate medical education and hosts a continuous education curriculum for emergency physicians. In undergraduate education, we both lead and participate in numerous interdisciplinary teachings and offer a maximum of 12 concurrent two-month internship positions to final year students. We train medical graduates in emergency medicine and emergency ultrasound and host a variety of interprofessional education activities. The Department received two national awards for its interprofessional training programs and a national award from the Swiss Institute for Research and Education in Medicine (SIWF) for exceptional postgraduate teaching (Dr. Sauter). We further received a competitive grant from Bern University to fund a teaching improvement project in undergraduate education.

Currently, the educational activities of the department are coordinated by three consultants with a formal qualification in education (Master in medical education) and we biannually fund a juniors colleague in the participation in that program as part of our capacity building efforts. One of our consultants was appointed associate editor in two international medical educational journals.

### Highlights 2018

In 2017, the department celebrated its 20th birthday. During the year, we hosted the 2nd European Conference on Diagnostic Error, which was attended by 160 participants from 28 different countries. Several renowned keynote speakers presented their work, including Sir Liam Donaldson, WHO Envoy for Patient Safety, Professor Gerd Gigerenzer, Director of the Max Planck Institute for Human Development Berlin, and Sue Sheridan, Director of Patient Engagement of the Society to Improve Diagnosis in Medicine, USA. The two-day conference resulted in several practice improvement initiatives and three international research initiatives. The conference was funded by numerous industry sponsors and received funding from the Swiss National Science Foundation.

To experimentally investigate diagnostic processes in experienced physicians, we obtained funding for a guest Professorship awarded to Prof. Silvia Mamede from the Erasmus Medical Center Rotterdam and conducted the first of a total of three planned studies under that program.

The university department of emergency medicines continued in 2018 its successful cooperation with the Prof Mouggiakakou's research group in the field of applied machine learning and artificial intelligence. The future goal is to strengthen the translational aspect of AI and ML in emergency medicine, especially in outcome orientated fields and systems for computer-aided diagnosis. Several publications have been accepted in high ranked journals under both affiliations.

We further implemented the first prospective European registry of emergency patients treated with direct new oral anticoagulants and concluded the world's first prospective study on diagnostic error in emergency care. In November 2018, we included the first patient into a highly challenging multidisciplinary study of the occlusion of the aorta in

patients under refractory cardiac arrest – the first study of its kind worldwide.

We also established a new research group investigating medical aspects of ED resource usage under the lead of Dr. Müller, which receives funding from the Swiss Academy of Medical Sciences (SAMW) and obtained a CTU grant from the Department of Research at Inselspital.

Dres. Ricklin and Ehrhard further established a multidisciplinary research group at the interface between emergency medicine and infectious diseases. Together with colleagues from the Institute for infectious diseases and the corresponding clinic, the group works on the antibiotic stewardship program in emergency medicine.

#### **Selected Competitive Grants**

- Project Partner on the SNF Project “DETECT - Dizziness Evaluation Tool for Emergent Clinical Triage”
- Bangarter-Rhyner Stiftung for the BerNOAC Registry
- SNF funding for the 2nd European Conference on Diagnostic Error in Medicine
- SAMW funding for the investigation of resource usage in emergency medicine
- CTU-Grant of the Department of Research at Inselspital for the investigation resource usage in emergency care
- Guest professorship from the Department of Research at Inselspital for Prof. Silvia Mamede

#### **Selected Publications**

- Sauter TC, Capaldo G, Hoffmann M, Birrenbach T, Hautz SC, Kämmer JE, Exadaktylos AK, Hautz WE. Non-specific complaints at emergency department presentation result in unclear diagnoses and lengthened hospitalization: a prospective observational study. *Scand J Trauma Resusc Emerg Med.* 2018 Jul 16;26(1):60. doi: 10.1186/s13049-018-0526-x
- Müller M, Seidenberg R, Schuh SK, Exadaktylos AK, Schechter CB, Leichtle AB, Hautz WE. The development and validation of different decision-making tools to predict urine culture growth out of urine flow cytometry parameter. *PLoS One.* 2018 Feb 23;13(2):e0193255. doi: 10.1371/journal.pone.0193255. eCollection 2018
- Sauter TC, Hegazy K, Hautz WE, Krummrey G, Ricklin ME, Nagler M, Borner U, Exadaktylos AK. Epistaxis in anticoagulated patients: Fewer hospital admissions and shorter hospital stays on rivaroxaban compared to phenprocoumon. *Clin Otolaryngol.* 2018 Feb;43(1):103-108. doi: 10.1111/coa.12904
- Hautz WE, Sauter TC, Lehmann B, Exadaktylos AK. Professionalisation rather than monopolisation is the future of emergency medicine in Europe. *Eur J Anaesthesiol.* 2018 Mar;35(3):234-235. doi: 10.1097/EJA.0000000000000744



2nd European Conference on Diagnostic Error in Medicine, August 2018.

## Department of ENT, Head and Neck Surgery

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Prof. Marco Caversaccio  
Chairman



Prof. Martin Kompis  
Head of Audiology



Prof. Eberhard Seifert  
Head of Phoniatriy



Prof. Dominique Vibert  
Head of Neurootology



PD Dr. Roland Giger  
Deputy Director



Prof. Georgios Mantokoudis  
Head of Cochlea-Implants



Dr. Wilhelm Wimmer  
Head of Hearing Research Laboratory

### Research Partners

- ARTORG Center, ISTB, University of Bern, Switzerland
- Department for BioMedical Research (DBMR), University of Bern, Switzerland
- Institute for Medical Education, Institute of Psychology, University of Bern, Switzerland
- Department of Neuroradiology, Nephrology, Radiology, Vascular surgery, University Hospital of Bern, Switzerland
- Department of Neurology, Ophthalmology, Physiotherapy, University Hospital of Bern, Switzerland
- Department of Otorhinolaryngology, University Hospital of Zürich, Switzerland
- INRIA Research Center, Sophia Antipolis, France
- ORL University Hospital Modena, Italy
- Nottingham Hearing Biomedical Research Unit, University of Nottingham, UK
- Johns Hopkins University, Department of Neurology, USA

### Research Profile

The Department of ENT, Head and Neck Surgery is developing and integrating new technologies that aim to improve patient care. Projects at our center encompass areas such as oncology in ENT or vestibular loss, but major emphasis lies in projects centered around the ear, hearing and the treatment of hearing loss. In a collaborative effort with the Hearing Research Laboratory at the ARTORG Center, our research activities aim to provide innovative technology to help hearing impaired patients and to assist clinicians in the diagnosis and treatment of hearing pathologies. The range of projects includes cochlear implantation, tinnitus, spatial hearing and hearing through bone conduction and involves preclinical studies, anatomical studies, and the conduction of clinical trials with patients.

### Teaching Profile

Besides training of young ENT surgeons on a daily basis and in internal courses, a number of university courses are taught by the members of our department:

- Courses (lectures) in ENT for medical students
- Course (lectures) in biomedical acoustics
- Clinical skills in ENT for medical students
- Course (lectures) on ENT for dentists
- Course (lectures) on Phoniatics for speech therapists (University of Fribourg)
- Course (lectures) on speech fluency disorders for speech therapists (University of Fribourg)
- Course (lectures) on audiology for speech therapists (University of Fribourg)

### Highlights 2018

*An Additional Dimension in Endoscopic Ear Surgery: A Randomized Comparison between Two- and Three-Dimensional Endoscopy*

Endoscopic Ear Surgery (EES) is an emerging technique allowing minimal-invasive treatment of middle ear pathologies through the external auditory canal. Until recently, the available camera systems allowed only two-dimensional (2D) visualization of the middle ear. With the introduction of three-dimensional (3D) endoscopes, the surgeon is provided with additional information. In cooperation with the Institute of psychology, we compared the impact of 3D-endoscopy on surgical performance in a randomized study under laboratory conditions. We found that especially novices benefit from the additional information provided and that even senior surgeons require a decent learning curve regarding the 3D technique.



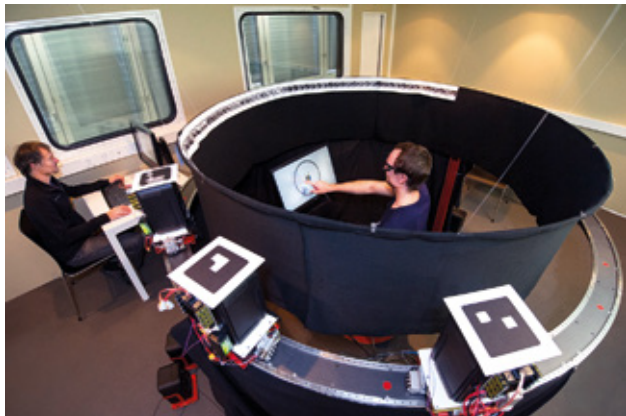
Cognitive evaluation in an OP-setup of 3D endoscopy.

*Improved Diagnostics for Inner Ear Diseases (Hearing Research Laboratory)*

Our multidisciplinary research group primarily focuses on the development of new diagnostic methods for inner ear diseases. Currently available audiological equipment has not changed considerably over the years. By introducing computer-assisted tools, robotic technology and e-health approaches, we aim to improve the specificity and sensitivity of currently available diagnostic solutions. In addition, new measurement paradigms can help to improve our understanding of auditory mechanisms in healthy subjects and patients. Other ongoing projects focus on novel objective assessment methods for tinnitus diagnosis using neural



activity monitoring and acoustic mechanisms for temporary tinnitus suppression.



Prototype for dynamic sound field audiometry and localization tests.

#### *Dizziness Center Bern*

Dizziness is defined by a disturbed spatial perception and the causes are manifold. The correct diagnosis is often difficult and false diagnoses can cause serious damage. In the vertigo centre, various specialists cooperate to treat patients and to perform research on vertigo. Only recently positional vertigo can now be diagnosed and treated with a 3D therapy chair. Patients are treated in a seated posture and the load on the shoulders, pelvis and spine is low. In parallel, virtual reality glasses are used to measure the eye movements of vertigo patients for diagnostic purposes.

A national funded grant study is investigating the improvement of diagnosis in patients with acute vertigo and the early detection of patients with stroke. The aim is to use a novel, non-invasive video-oculography device to evaluate the diagnostic value of conventional tests for the identification of stroke patients.



3D Therapy Chair.

#### **Selected Competitive Grants**

- Eurostars-2, EU Horizon 2020 and Eureka (E! 11597 RCI)
- SNF PostDoc.Mobility Fellowship (Nr. 180822)
- SNF Grant, DETECT Study (320030\_173081)
- CTU-Forschungs-Grant 2018 (2017-01)

#### **Selected Publications**

- Roccio M, Perny M, Ealy M, Widmer HR, Heller S, Senn P. Molecular characterization and prospective isolation of human fetal cochlear hair cell progenitors. *Nat Commun.* 2018 Oct 2;9(1):4027. doi: 10.1038/s41467-018-06334-7
- Anschuetz L, Huwendiek S, Stricker D, Yacoub A, Wimmer W, Caversaccio M. Assessment of middle ear anatomy teaching methodologies using microscopy versus endoscopy: A randomized comparative study. *Anat Sci Educ.* 2018 Nov 14. doi: 10.1002/ase.1837
- Gawliczek T, Wimmer W, Munzinger F, Caversaccio M, Kompis M. Speech understanding and sound localization with a new nonimplantable wearing option for Baha. *Biomed Res Int.* 2018 Sep 25;2018:5264124. doi: 10.1155/2018/5264124. eCollection 2018
- Yacoub A, Anschuetz L, Schneider D, Wimmer W, Caversaccio M. Minimally invasive lateral endoscopic multiport approach to the infratemporal fossa: a cadaveric study. *World Neurosurg.* 2018 Apr;112:e489-e496. doi: 10.1016/j.wneu.2018.01.065
- Nisa L, Barras D, Medova M, Aebersold DM, Medo M, Poliakova M, Koch J, Bojaxhiu B, Elicin O, Dettmer MS, Angelino P, Giger R, Borner U, Caversaccio MD, Carey TE, Ho L, McKee TA, Delorenzi M, Zimmer Y. Comprehensive genomic profiling of patient-matched head and neck cancer cells: A preclinical pipeline for metastatic and recurrent disease. *Mol Cancer Res.* 2018 Dec;16(12):1912-1926. doi: 10.1158/1541-7786.MCR-18-0056



## Department of General Internal Medicine

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Prof. Jacques Donzé  
Leitender Arzt  
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PD Dr. Maria Wertli  
Leitende Ärztin  
und Stv. Leiterin  
Poliklinik



Prof. Manuel Haschke  
Chefarzt und  
Leiter Klinische  
Pharmakologie

### Research Partners

- Department of medicine, University of Pittsburgh, Pennsylvania, USA
- Institute of Primary Health Care (BIHAM)
- Geriatric Medicine, Cliniques universitaires Saint-Luc, Brussels, Université catholique de Louvain, Belgium
- Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons (EPHOR), University Medical Centre Utrecht, The Netherlands
- Department of Medicine (Geriatrics), University College Cork, Cork, Ireland
- Clinical Trials Unit, University of Bern, Bern, Switzerland.
- Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA
- Division of Angiology and Haemostasis, Geneva University Hospital, Geneva, Switzerland
- Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland
- European Drug Emergencies Network (Euro-DEN), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal

### Research Profile

The research conducted at the Department of General Internal Medicine includes a variety of patient-oriented clinical research projects. The main research expertise are:

- Venous thromboembolism
- Patient multimorbidity, polypharmacy, and complexity
- Subclinical hypothyroidism
- Hospital readmission
- Overdiagnosis
- Pain therapy
- Personalized drug therapy and drug safety

### Teaching Profile

The department is very engaged in teaching of medical and dental medicine students and covers both bedside and ex cathedra teaching, from the bachelor to the master level. Clinical Skills Training and OSCE exams are also part of the teaching activity. We also offer internships for Swiss and foreign medical students.

### Highlights 2018

*Thyroid hormone therapy provided no benefits in adults with subclinical hypothyroidism*

The benefit of thyroid hormone therapy in subclinical hypothyroidism is uncertain. We conducted a systematic review and meta-analysis of 19 randomized-controlled trials with 2061 adults with subclinical hypothyroidism. Thyroid hormone therapy lowered mean TSH into reference range, but was not associated with benefit regarding general quality of life (n=739, SMD -0.15, 95%CI -0.29 to 0.00, I<sup>2</sup> 65.9%) and thyroid-related symptoms (n=801, SMD 0.03, 95%CI -0.11 to 0.16, I<sup>2</sup> 0.0%). Among non-pregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms.

*A novel, validated diagnostic algorithm for pregnant women with suspected pulmonary embolism*

Data on the optimal diagnostic management of pregnant women with suspected pulmonary embolism (PE) are limited. We conducted a multicenter prospective diagnostic management study at 11 hospitals in Switzerland and France between 2008 and 2016. Overall, 395 pregnant women with suspected PE underwent a standardized diagnostic strategy involving pretest clinical probability assessment, high-sensitivity D-dimer testing, bilateral lower limb compression ultrasonography (CUS), and computed tomography pulmonary angiography (CTPA). Among these, PE was diagnosed in 7.1%. The rate of symptomatic venous thromboembolic events at 3 months was 0.0% (95% CI, 0.0% to 1.0%) among untreated women after exclusion of PE on the basis of negative results on the diagnostic work-up. A diagnostic strategy based on assessment of clinical probability, D-dimer measurement, CUS, and CTPA can safely rule out PE in pregnant women.

*Using dried blood spots to monitor antiretroviral drug treatment*

Therapeutic drug monitoring (TDM) is an important tool to guide dose-adaptations and to monitor treatment adherence in critical diseases. Dried blood spot (DBS) samples

do not require uninterrupted cold-chains, which often are not available in resource-poor regions. We conducted a field study to evaluate whether DBS are suitable to monitor antiretroviral treatment in rural Tanzania. DBS and matching plasma samples were collected from 299 patients treated with efavirenz, nevirapine or ritonavir-boosted lopinavir and analyzed in Switzerland using a fully automated LC-MS/MS method. After adjusting DBS concentrations by hematocrit and drug fraction bound to plasma proteins, bias compared to plasma concentrations was acceptable for nevirapine and efavirenz (mean bias -2.9% and -9.6%, respectively), but not for lopinavir (-32.8%). Thus, DBS is a suitable technique for TDM in resource-poor regions, but sample stability under field conditions needs to be assessed for every analyte.

### **Selected Competitive Grants**

- HORIZON 2020
- Swiss National Science Foundation (Grant no. 320030\_172676; 31003A\_160206; 407440\_167339/1; 32003B\_179346/1)
- Swiss National Science Foundation Professorship (PP00P3\_170656)
- SGAIM Foundation

### **Selected Publications**

- Feller M, Snel M, Moutzouri E, Ford I, Gussekloo J, Kearney PM, Mooijaart S, Quinn T, Aujesky D, Stott D, Westendorp R, Rodondi N, Dekkers OM. Thyroid hormone therapy for subclinical hypothyroidism in adults: a systematic review and meta-analysis of randomized-controlled trials. *Journal of the American Medical Association (JAMA)* 2018;320:1349-59
- Tritschler T, Kraaijpoel N, Le Gal G, Wells PS. Venous thromboembolism: advances in diagnosis and treatment. *Journal of the American Medical Association (JAMA)* 2018;320:1583-94
- Duthaler U, Berger B, Erb S, Battegay M, Letang E, Gaugler S, Natamatungiro A, Mnzava D, Donzelli M, Krähenbühl S, Haschke M. Using dried blood spots to facilitate therapeutic drug monitoring of antiretroviral drugs in resource-poor regions. *Journal of Antimicrobial Chemotherapy* 2018 73:2729-37
- Righini M, Robert-Ebadi H, Elias A, Sanchez O, Le Moigne E, Schmidt J, Le Gall C, Cornuz J, Aujesky D, Roy PM, Chaleur C, Rutschmann O, Poletti PA, and Le Gal G, for the CT-PE-Pregnancy group. The diagnosis of pulmonary embolism during pregnancy. A multicenter prospective management outcome study. *Annals of Internal Medicine* 2018;169:766-73
- MR Blum, B Gencer, L Adam, M Feller, T-H Collet, BR da Costa, M Feller, J Dopheide, M Depairon, G Sykiotis, P Kearney, J Gussekloo, R Westendorp, DJ Stott, DC Bauer, N Rodondi. Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly with Subclinical Hypothyroidism, A Randomized Trial. *J Clin Endocrinol Metab* 2018;8:2988-97

## Department of Geriatrics

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Stuck  
Department  
Director



Prof. Andreas  
Schönenberger  
Clinical  
Director

### Research Partners

- Institute of Social and Preventive Medicine, University of Bern, Switzerland
- Department of Cardiology, University of Bern, University Hospital Bern, Switzerland
- Department of Orthopedics and Traumatology, University of Bern, Switzerland
- Department of ENT, Head and Neck Surgery, University of Bern, Switzerland
- Department of Geriatrics, University of Basel, University Hospital Basel, Switzerland
- Geriatrics, University of Geneva, University Hospital Geneva, Switzerland
- Department of Geriatrics, University of Lausanne, University Hospital Lausanne, Switzerland
- Department of Geriatrics, University of Zurich, University Hospital Zurich, Switzerland
- Department of Internal Medicine, Hospital San Giovanni, Bellinzona, Switzerland
- National Institute of Gerontology and Geriatrics, Ana Aslan, Bucharest, Romania
- Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
- Department of Geriatrics and Medicine, University of Florence, Florence, Italy
- Rehabilitation Center Kliniken Valens, Valens, Switzerland

### Research Profile

The research is closely related to the clinical activities of the Geriatrics Department, with inpatient units for acute geriatrics (Spital Tiefenau), for inpatient rehabilitation (Spital Belp) and for ambulatory and co-management geriatric services (Inselspital). The main research domains involve:

- geriatric assessment in ambulatory and in hospitalized older patients
- mobility assessment in older patients
- hearing assessment in older patients
- health risk assessment in healthy older people
- frailty and risk assessment in older patients
- rehabilitation in older patients
- geriatric management in patients with orthopedic and traumatology disorders

For this purpose, the Department of Geriatrics of the University of Bern collaborates closely with the Institute of Social and Preventive Medicine at the University of Bern, and conducts research projects in collaboration with clinical partners in other clinical disciplines and geriatric departments nationally and internationally.

### Teaching Profile

Teaching geriatrics is one of the key missions of the Department of Geriatrics of the University of Bern. The main focus is teaching of medical students, students in medical dentistry, and postgraduate teaching of residents in internal and geriatric medicine. Main focus of teaching include

- geriatric assessment, including use of technology for functional assessment
- decision-making capacity in older persons, including ethical aspects
- geriatric syndromes (e.g., dementia, falls, incontinence)
- polypharmacy in older persons, including use of decision aids and checklists
- hospital discharge planning in older patients

### Highlights 2018

#### *Geriatric assessment in patients undergoing transcatheter aortic valve implantation*

This prospective cohort comprised 330 consecutive TAVI patients  $\geq 70$  years who had a pre-intervention multidimensional geriatric assessment. Based on an analysis of one-year survival data, the following conclusion could be drawn: This is the first study showing that the assessment of frailty significantly enhances prediction of 1-year mortality after TAVR in combined risk models with conventional risk scores and relevantly contributes to this improvement. Further predictive analyses are under way, based on 3-year outcomes including measures of survival, mortality, and quality of life.

#### *Regional variation of cost of care in the last 12 months of life in Switzerland*

Based on insurance data on 113'277 persons of all age groups living in Switzerland we analyzed indicators of quality of care at the end of life, and specifically evaluated how age is associated with quality of care. We found demographic, health, and socioeconomic differentials in the lack of health insurance claims, and possibly costs, in the last year of life. Several groups of patients identified by sex, age, civil status, and cause of death had a higher probability of not having health insurance claims

#### *Swiss Frailty Network and Repository (SFN+R)*

The Department of Geriatrics Bern, in collaboration with the four other University Geriatric Departments in Switzerland is participating in one of the seven initial driver projects of the Swiss Personalized Health Network. The plan is to find a consensus on how to measure frailty, not only for patients hospitalized in the geriatric departments, but also

for all older patients admitted to University hospitals in Switzerland. With this approach, it will be possible to add measures of frailty to personalized databases. The ultimate goals of this project include: (1) to establish acute care treatment guidelines for senior patients with possible or established frailty and (2) to prevent negative frailty-related outcomes.

As an interim achievement, the expert group defined a consensus on how to measure frailty with the same approach at the five University hospitals. Combined with information for electronic health records, the purpose is to develop a tool which can be used for hospital-wide identification of frail persons, both for clinical and research purpose.

#### *Accelerometer-based measurement of physical activity*

We conducted a validation study for measuring physical activity of patients in a geriatric rehabilitation setting using a body-worn accelerometer. Our results indicated previously underestimated limitations of a tool, which has been broadly used in older community-dwelling samples. A new validation study with a next-generation tool is under way, with the expectation that slow movements of geriatric rehabilitation patients can be reliably measured with this new approach. The master thesis contributing to these results received the master thesis award of the University of Third Age, University of Bern 2018.

#### **Selected Competitive Grants**

- Swiss Personalized Health Network: Swiss Frailty Network and Repository 2018 to 2020 (Co-Investigator: CHF 1.785 Mio)

#### **Selected Publications**

- Chamberlain JD, Gmünder HP, Hug K, Jordan X, Moser A, Schubert M, Brinkhof MWG. Differential survival after traumatic spinal cord injury: evidence from a multi-center longitudinal cohort study in Switzerland. *Spinal Cord*. 2018 Oct;56(10):920-930. doi: 10.1038/s41393-018-0163-2. Epub 2018 Jun 12
- DuMontier C, Clough-Gorr KM, Silliman RA, Stuck AE, Moser A. Health-related quality of life in a predictive model for mortality in older breast cancer survivors. *J Am Geriatr Soc*. 2018 Jul;66(6):1115-1122. doi: 10.1111/jgs.15340. Epub 2018 Mar 13
- Moser A, Bopp M, Zwahlen M, Swiss National Cohort study group. Calibration adjustments to address bias in mortality analyses due to informative sampling – a census-linked survey analysis in Switzerland. *PeerJ*. 2018 Feb 13;6:e4376. doi: 10.7717/peerj.4376. eCollection 2018
- Oesch P, Kool J, Fernandez-Luque L, Brox E, Evertsen G, Civit A, Hilfiker R, Bachmann S. Exergames versus self-regulated exercises with instruction leaflets to improve adherence during geriatric rehabilitation: a randomized controlled trial. *BMC Geriatr* 2017;17:77. doi: 10.1186/s12877-017-0467-7
- Panczak R, von Wyl V, Reich O, Luta X, Maessen M, Stuck AE, Berlin C, Schmidlin K, Goodman DC, Egger M, Clough-Gorr K, Zwahlen M. Death at no cost? Persons with no health insurance claims in the last year of life in Switzerland. *BMC Health Serv Res* 2018;178. doi: 10.1186/s12913-018-2984-2
- Schoenenberger AW, Moser A, Bertschi D, Wenaweser P, Windecker S, Carrel T, Stuck AE, Stortecky S. Improvement of risk prediction after transcatheter aortic valve replacement by combining frailty with conventional risk scores. *JACC-Cardiovasc Inte* 2018;11:395-403. doi: 10.1016/j.jcin.2017.11.012



## Department of Hematology and Central Hematology Laboratory

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Department for BioMedical Research, University of Bern, Murtenstrasse 40, 3010 Bern



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Prof. Sacha  
Zeerleder  
Head Transfusion  
Medicine, Apheresis and  
Hematopoietic Stem  
Cell Transplantation  
Programm

### Partners

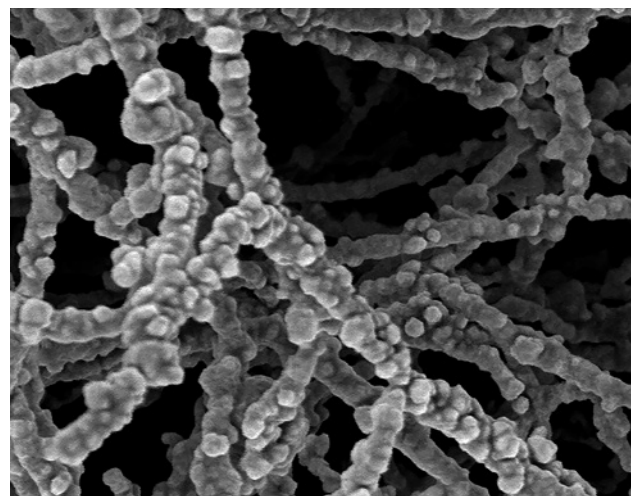
- Departments of General Internal Medicine, Pediatrics, Medical Oncology, Inselspital, Bern, Switzerland
- Institute of Chemical Sciences and Engineering, EPFL, Lausanne, Switzerland
- Transplant Complications Working Party and Severe Aplastic Anemia Working Party of the European Society for Blood and Bone Marrow Transplantation
- Departments of Epidemiology & Biostatistics, Medicine and Biochemistry & Molecular Biology and Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, USA
- Department of Internal Medicine-Infectious Diseases and Center of Molecular Medicine, University Medical Center Amsterdam, Amsterdam, The Netherlands
- Institute of Research in Immunology and Cancer, University of Montreal, Montreal, Canada
- Division of Hematology/Oncology, Boston Children's Hospital and Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA

### Research Profile

The Department of Hematology and Central Hematology Laboratory was founded in 1965. Nine research groups are involved in the investigation of epidemiological and pathophysiological processes as well as diagnosis, prognosis and therapeutic approaches of blood-related disorders. The research spectrum comprises fundamental, translational and clinical research. Current areas of laboratory research programs include inflammation and hematopoiesis (R. Allam), mouse models of hematophysiology & hematopathology with their translation to human hematological disorders (A. Angelillo-Scherrer), hematopoiesis & molecular genetics (G.M. Baerlocher & E. Oppliger Leibundgut), Personalized treatment for patients with myeloid malignancies (N. Bonadies), hemostasis (J.A. Kremer Hovinga Stebel) and

innate immunity in hematological diseases (S. Zeerleder). Additional research topics are telomere biology, telomere biology in bone marrow failure syndromes and telomerase inhibition in myeloproliferative neoplasms (G.M. Baerlocher), targeted diagnostics in hematological malignancies (V.U. Bacher), late effects after hematopoietic stem cell transplantation and cancer treatments and bone marrow failure (A. Rovó), thrombotic microangiopathies and Von Willebrand disease (J.A. Kremer Hovinga Strebel) and diagnosis, prognosis, monitoring and treatment in patients with hemostatic disorders (M. Nagler).

Part of the research requires access to patients registries, biobanks or cohorts to collect epidemiological data, improve and standardize diagnosis and treatment and monitor outcomes. Examples are the International hereditary thrombotic



Scanning electron microscopy image from the fibrin network of a hemophilia B mouse. Fibrin fibers from this mouse have a larger diameter and are more porous than those from a wild-type mouse; thus, the hemophilia B mouse's fibrin fibers might be less resistant to fibrinolysis. Cover of Blood, March 22, 2018, 131(12).

thrombocytopenic (TTP) registry and the Swiss myelodysplastic syndrome (MDS) registry/biobank. Finally, part of the research occurs in the context of national and international working groups.

### Teaching Profile

The department participates in University teaching programs for students of medicine, dental medicine and biomedical sciences.

### Highlights 2018

#### *Treatment of acquired thrombotic thrombocytopenic purpura (TTP) with caplacizumab*

TTP is a rare thrombotic microangiopathy. Autoantibodies inhibit ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). ADAMTS13 is a protease cleaving Von Willebrand factor (VWF) and thereby restraining VWF-platelet adhesion. Therefore, inhibition of ADAMTS13 allows unrestrained VWF-platelet adhesion and microthrombosis. Caplacizumab is an anti-VWF humanized, single-variable-domain immunoglobulin that inhibits VWF-platelet interaction. The phase 3 HERCULES study confirmed that treatment with caplacizumab reduces time to platelet count normalization, incidence of a composite of TTP-related death, recurrence, or thromboembolic event during study drug treatment, and recurrences during the study.

#### *High Gas6 in plasma predicts venous thromboembolism (VTE) recurrence, major bleeding and mortality in the elderly*

Growth arrest-specific gene 6 (Gas6) is a pro-hemostatic protein with an unknown predictive ability for recurrent VTE. The performance of Gas6 to predict VTE recurrence, major bleeding and mortality in the elderly was prospectively investigated. Gas6 was measured in 864 patients at the time of the index VTE and in 70% of them, also 12 months later. High Gas6 at diagnosis was associated with VTE recurrence, major bleeding and mortality. Gas6 levels measured 12 months after the index VTE are discriminatory for VTE recurrence. These findings support further studies to assess the performance of Gas6 for adjusting anticoagulation length.

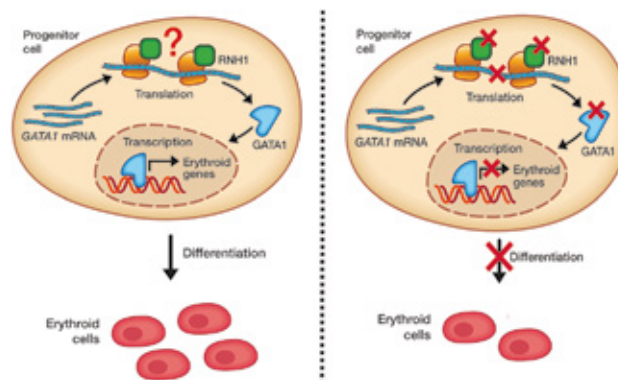
#### *Trends of incidence, mortality, and survival of multiple myeloma in Switzerland between 1994 and 2013*

A retrospective registry study performed with data from the National Institute for Cancer Epidemiology and Registration database in Switzerland (1994-2013), allowed the identification of 5770 patients with multiple myeloma. An increase in incidence was found and attributed to demographic changes. There was also a trend to longer relative survival with substantial increase in patients aged less than 75 years and only minimal changes in older persons.

#### *Ribonuclease inhibitor 1 (RNH1) regulates erythropoiesis by controlling GATA1 translation*

Ribosomal proteins (RP) regulate specific gene expression by selectively translating subsets of messenger RNAs (mRNAs). RNH1 binds to ribosomes and regulates erythropoiesis by controlling translation of the erythroid transcription factor GATA1. RNH1 deficient mice die due to impaired production of mature erythroid cells from progenitor cells. In murine embryos lacking RNH1, mRNA levels of Gata1 are normal, but GATA1 protein levels are reduced. RNH1 binds to the 40S subunit of ribosomes and facilitates polysome formation on Gata1 mRNA to confer transcript-specific translation. In

addition, RNH1 knockdown in human CD34+ progenitor cells decreased erythroid differentiation. These data established a role for RNH1 in erythropoiesis and allowed to add RNH1 to the list of ribosomal-associated factors that regulate specific mRNA translation.



Ribonuclease inhibitor 1 (RNH1) binds to ribosome and regulates GATA1 mRNA translation. RNH1 deficiency leads to defect in GATA1 translation and erythropoiesis.

### Selected Competitive Grants

- Swiss National Science Foundation (No. PP00P3\_157486, 314730\_173127, 310030\_160269, 32003B\_179334)
- Swiss Cancer Research (Health Services Research grant, HSR-4085-11-2016)

### Selected Publications

- Andres M, Feller A, Arndt V, the NICER Working Group. Trends of incidence, mortality, and survival of multiple myeloma in Switzerland between 1994 and 2013. *Cancer Epidemiol.* 2018 Apr;53:105-110. doi: 10.1016/j.canep.2018.01.015
- Chennupati V, Veiga DF, Maslowski KM, Andina N, Tardivel A, Yu EC, Stilinovic M, Simillion C, Duchosal MA, Quadroni M, Roberts I, Sankaran VG, MacDonald HR, Fasel N, Angelillo-Scherrer A, Schneider P, Hoang T, Allam R. Ribonuclease inhibitor 1 regulates erythropoiesis by controlling GATA1 translation. *J Clin Invest.* 2018 Apr 2;128(4):1597-1614. doi: 10.1172/JCI94956
- Scully M, Cataland S, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, Metjian A, de la Rubia J, Pavenski K, Callewaert F, Biswas D, De winter H, Zeldin RK for the HERCULES Investigators. Treatment of acquired thrombotic thrombocytopenic purpura with Caplacizumab. *N Engl J Med.* 2019 Jan 24;380(4):335-346. doi: 10.1056/NEJMoa1806311
- Schnegg-Kaufmann A, Calzavarini S, Limacher A, Mean M, Righini M, Staub D, Beer JH, Frauchiger B, Osterwalder J, Kucher N, Matter CM, Husmann M, Banyai M, Aschwanden M, Mazzolai L, Hugli O, Nagler M, Daskalakis M, Rodondi N, Aujesky D, Angelillo-Scherrer A. High Gas6 in plasma predicts venous thromboembolism recurrence, major bleeding and mortality in the elderly. A prospective multicenter cohort study. *J Thromb Haemost.* 2018 Dec 20. doi: 10.1111/jth.14365 [Epub ahead of print]
- Tichelli A, Beohou E, Labopin M, Socié G, Rovó A, Badoglio M, van Biezen A, Bader P, Duarte RF, Basak G, Salooja N for the Transplant Complications Working Party of the EBMT. Evaluation of second solid cancers after hematopoietic stem cell transplantation in European patients. *JAMA Oncol.* 2018 Nov 21. doi: 10.1001/jamaoncol.2018.4934 [Epub ahead of print]

## Department of Infectious Diseases

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Rauch  
Deputy Head of  
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### Research Partners

- Institute for Infectious Diseases, University of Bern, Bern, Switzerland, [www.ifik.unibe.ch](http://www.ifik.unibe.ch), including Swiss Centre for Antibiotic resistance, Anresis, [www.anresis.ch](http://www.anresis.ch)
- Swiss HIV Cohort Study, [www.shcs.ch](http://www.shcs.ch)
- Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland
- leDEA, International Epidemiology Databases to Evaluate AIDS, National Institute of Health, Bethesda, USA
- Swissnoso, Nationales Zentrum für Infektionsprävention, [www.swissnoso.ch](http://www.swissnoso.ch)
- Swiss Transplant Cohort Study, [www.stcs.ch](http://www.stcs.ch)
- Funginos, Fungal Infections Network of Switzerland
- EUROSIDA [www.chip.dk/Studies/EuroSIDA](http://www.chip.dk/Studies/EuroSIDA)
- Swiss Tropical and Public Health Institute, Basel, Switzerland
- Liver Center, Department of Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland
- Kirby Institute, Sydney, Australia, <https://kirby.unsw.edu.au/>

### Research Profile

Being part of the Bern University Hospital our research focuses on clinical aspects and epidemiology of infectious diseases. Lab facilities are in the partner Institute for Infectious Diseases (IFIK). We conduct collaborative research involving the entire spectrum of infectious diseases with our clinical partners within the Insel Group.

HIV infection is one area of research. We lead many research projects within the framework of the Swiss HIV Cohort Study and international collaborations. Main research focuses are HIV/ Hepatitis co-infections, both in the European and the African context, opportunistic infections, migration and HIV, and epidemiology of HIV and sexually transmitted infections.

Locally and in international collaborations, we investigate incidence, course and treatment of infectious diseases in people who inject drugs.

The infection prevention unit has a focus on healthcare-associated infections and conducts research partnering with a number of clinical specialties of the Insel Group and

collaborates with IFIK and the external surveillance systems Anresis and Swissnoso. Study designs range from qualitative research to clinical trials on to large data analyses.

Together with IFIK we are active in clinical and microbiological research on bacterial resistance.

The publication list is available here <https://boris.unibe.ch/view/divisions/DCD5A442BB13E17DE0405C82790C4DE2.html>.

### Teaching Profile

The department is in charge of the teaching program Infectious Diseases for students in medicine, mainly in the master study part, but also in the bachelor part. We are actively involved in clinical skills training and problem based learning modules. Medical students can spend practical months in our department. We are involved in teaching programs of Dental Medicine and Biomedicine and Biology. Our department is accredited for postgraduate education in Infectious Diseases and Tropical Medicine.

### Highlights 2018

#### *HIV, viral hepatitis and sexually transmitted infections*

We expanded and strengthened our research agenda in HIV, viral hepatitis and sexually transmitted infections. This research focus was awarded in 2018 by a new SNF professorship, an SNF project grant and an ESTHER grant to support collaborative research with Subsaharan Africa. Together with the established networks of the Swiss HIV Cohort Study and international collaborations, these grants will allow to establish in-depth investigations of epidemiology and clinical course of HIV, viral hepatitis and sexually transmitted infections.

#### *Infections after solid organ transplantation*

Several ongoing projects investigate infections after solid organ transplantation within the Swiss Transplant Cohort Study. We demonstrated recently that clostridial infections are associated with graft loss in solid organ recipients [Béguelin et al, referenced below].

### *Infection prevention and hospital epidemiology*

As one of the largest hospitals to contribute to the Swiss national surveillance system (Swissnoso), we secured independent funding for analysing the database of >300'000 surgeries. In the SNF project listed below we will enhance this dataset with additional information and create a statistical model of surgical site infection development.

Due to an outbreak of vancomycin-resistant enterococci we shifted our attention to characteristics of intrahospital transmission (Wassilew et al, referenced below), among which a data science projects to elicit yet undetected transmission pathways stands out.

Further, our team participated in a well-published estimation of global *Mycobacterium chimaera* numbers, an emergent pathogen in patients exposed to *M. chimaera* contaminated heater cooler units of heart lung machines (Sommerstein et al, referenced below).

### **Selected Competitive Grants**

- SNF Professorship PP00P3\_176944: Towards the functional cure of hepatitis B virus infection: longitudinal studies to assess long-term outcomes in Switzerland and sub-Saharan Africa. G. Wandeler
- SNF Project grant 32003B\_179500: Understanding the drivers of surgical site infection: Investigating and modeling the Swissnoso surveillance data. PI J. Marschall
- SNF Project grant 324730\_179567: The role of sexual behaviour dynamics and treatment-as-prevention in the spread of HIV, Hepatitis C and syphilis: Predicting the conditions for control and elimination. PI A. Rauch
- SNF Marie Heim Vögtlin PMPDP3\_171259: Clinical Impact and Evolution of AmpC Producers under Selective Pressure of Different Antimicrobials: a Molecular Analysis to Predict Risk Factors for Cephalosporin Resistance and to Evaluate the Best Antibiotic Treatment Strategy, B. Babouee Flury
- SNF Project grant 33CS30\_177499 : Swiss HIV Cohort Study. A. Rauch und H. Furrer co-applicants

### **Selected Publications**

- Veit O, Domingo C, Niedrig M, Staehelin C, Sonderegger B, Delphine H, Stoeckle M, Calmy A, Schiffer V, Bernasconi E, Flury D, Hatz C, Zwahlen M, Furrer H; Swiss HIV Cohort Study. Long-term immune response to yellow fever vaccination in HIV-infected individuals depends on HIV-RNA suppression status: Implications for vaccination schedule. *Clin Infect Dis*. 2018 Mar 19;66(7):1099-1108. doi: 10.1093/cid/cix960
- Béguelin C, Suter A, Bernasconi E, Fehr J, Kovari H, Bucher HC, Stoeckle M, Cavassini M, Rougemont M, Schmid P, Wandeler G, Rauch A; Swiss HIV Cohort Study. Trends in HCV treatment uptake, efficacy and impact on liver fibrosis in the Swiss HIV Cohort Study. *Liver Int*. 2018 Mar;38(3):424-431. doi: 10.1111/liv.13528
- Cusini A; Béguelin C; Stampf, S; Boggian, K; Garzoni, C; Koller, M; Manuel, O; Meylan, P; Mueller, N J; Hirsch, H; Weisser, M; Berger, C; van Delden, C (2018). Clostridium difficile Infection is Associated with Graft Loss in Solid Organ Transplant Recipients. *Am J Transplant*. 2018 Jul;18(7):1745-1754. doi: 10.1111/ajt.14640
- Sommerstein R, Hasse B, Marschall J, Sax H, Genoni M, Schlegel M, Widmer AF; Swiss Chimaera Taskforce. Global Health Estimate of Invasive *Mycobacterium chimaera*

Infections Associated with Heater-Cooler Devices in Cardiac Surgery. *Emerg Infect Dis*. 2018 Mar;24(3):576-578. doi: 10.3201/eid2403.171554

- Wassilew N, Seth-Smith HM, Rolli E, Fietze Y, Casanova C, Führer U, Egli A, Marschall J, Buetti N. Outbreak of vancomycin-resistant *Enterococcus faecium* clone ST796, Switzerland, December 2017 to April 2018. *Euro Surveill*. 2018 Jul;23(29). doi: 10.2807/1560-7917.ES.2018.23.29.1800351



## Department of Intensive Care Medicine

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Director  
Chief Physician

Brigitte Hämmerli  
Head of IIMC  
Nursing  
Deputy Nursing Manager

Felix Zürcher  
Head of Logistics

Prof. Jörg C. Schefold  
Chief Physician  
Head of Research

### Research partners

- Prof. M. Moller, Prof. A. Perner, Center for Research in Intensive Care (CRIC), Copenhagen, Denmark
- ANZIC Clinical Trials Group, Australia and New Zealand
- Prof. V. Pettilä, Helsinki University Hospital, Helsinki, Finland
- PD Dr. M. Siegemund, Universitätsspital Basel, Basel, Switzerland
- ETH Zürich, EPFL Lausanne, Switzerland
- Prof. K. Amrein, Medical University of Graz, Vienna, Austria
- Prof. W. Doehner and Prof. von Haehling, Cachexia Research Groups, Charité University Medicine Berlin and Goettingen University, Germany
- Prof C. Storm, Charité Center of Excellence for Cardiac Arrest, Berlin, Germany

### Research Profile

Key objective of the research group is to advance the pathophysiological understanding of critical illness and associated (multiple) organ failure. Clinical trials (including international multicenter trials) with external partners are performed that focus on organ failure, metabolism/immune responses and severe infections. Experimental research projects include animal models particularly on the pathophysiology of circulatory, cerebral and gastrointestinal function. Experimental research is e.g. performed in cooperation with the ARTORG center.

### Teaching Profile

The department provides the full spectrum of training in Intensive Care Medicine. This includes training to qualify as an ICU specialist, training for medical students, advanced training for specialist nurses to qualify as certified experts in intensive nursing (NDS HF) and training for individuals to become professional healthcare assistants. A broad spectrum of educational methods including simulator-based training is performed. Echocardiography, Sonography and ECMO training is provided for Intensive Care Medicine professionals.

### Selected Competitive Grants

SNF, "Prophylaxis and Treatment of Staphylococcus spp. Intravascular and extravascular infections using phages" (700'000 CHF, Prof. Y.-A. Que).

### Selected Publications

Link: <http://www.intensivmedizin.insel.ch/de/forschung/publikationen/>

- Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, Keus F, Guttormsen AB, Bendel S, Borthwick M, Lange T, Rasmussen BS, Siegemund M, Bundgaard H, Elkmann T, Jensen JV, Nielsen RD, Liborius L, Bestle MH, Elkjær JM, Palmqvist DF, Bäcklund M, Laake JH, Bådstøløkken PM, Grönlund J, Breum O, Walli A, Winding R, Iversen S, Jarnvig IL, White JO, Brand B, Madsen MB, Quist L, Thornberg KJ, Møller A, Wiis J, Granholm A, Anthon CT, Meyhoff TS, Hjortrup PB, Aagaard SR, Andreasen JB,

Sørensen CA, Haure P, Hauge J, Hollinger A, Scheuzger J, Tuchscherer D, Vuilliamenet T, Takala J, Jakob SM, Vang ML, Pælestik KB, Andersen KLD, van der Horst ICC, Dieperink W, Fjølner J, Kjer CKW, Sølling C, Sølling CG, Karttunen J, Morgan MPG, Sjøbø B, Engstrøm J, Agerholm-Larsen B, Møller MH; SUP-ICU trial group. Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU. *N Engl J Med*. 2018 Dec 6;379(23):2199-2208. doi: 10.1056/NEJMoa1714919.

- Moller PW, Hana A, Heinisch PP, Liu S, Djafarzadeh S, Haenggi M, Bloch A, Takala J, Jakob SM, Berger D. The Effects of Vasoconstriction and Volume Expansion on Venous Arterial ECMO Flow. *Shock*. 2018 Jun 5. doi: 10.1097/SHK.0000000000001197. [Epub ahead of print]

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- Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA, Resch G, Rousseau AF, Ravat F, Carsin H, Le Floch R, Schaal JV, Soler C, Fevre C, Arnaud I, Bretaudeau L, Gabard J. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis*. 2019 Jan;19(1):35-45. doi: 10.1016/S1473-3099(18)30482-1

- Collet MO, Caballero J, Sonnevill R, Bozza FA, Nydahl P, Schandl A, Wøien H, Citerio G, van den Boogaard M, Hästbacka J, Haenggi M, Colpaert K, Rose L, Barbateskovic M, Lange T, Jensen A, Krog MB, Egerod I, Nibro HL, Wetterslev J, Perner A; AID-ICU cohort study co-authors. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. *Intensive Care Med*. 2018 Jul;44(7):1081-1089. doi: 10.1007/s00134-018-5204-y

# Department of Magnetic Resonance Spectroscopy and Methodology (AMSM)

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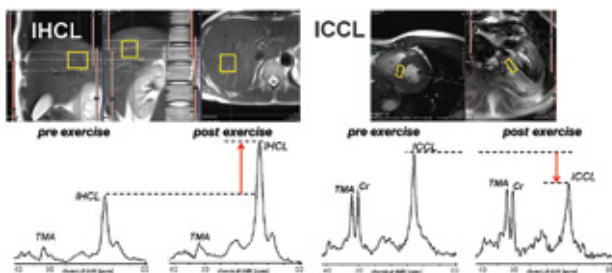
Damian Hertig

## Research Partners

- Department of Endocrinology, Diabetes and Clinical Nutrition, Bern University Hospital, Bern, Switzerland
- University Clinic for Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland
- Department of Neurology, Bern University Hospital, Bern, Switzerland
- Department of Nephrology and Hypertension, Bern University Hospital, Bern, Switzerland
- Institute for Biomedical Engineering, University and ETH Zürich, Zürich, Switzerland
- Institute of Diagnostic and Interventional Neuroradiology, Bern University Hospital, Bern, Switzerland
- Center of Laboratory Medicine, Bern University Hospital, Bern, Switzerland
- Max Planck Institute for Biological Cybernetics, Tuebingen, Germany
- University Children's Hospital and Children's Research Center, Zürich, Switzerland
- Department of Physiology, University of Lausanne, Lausanne, Switzerland
- Department of Biochemistry and Molecular Biology Universitat Autònoma de Barcelona, Barcelona, Spain

## Research Profile

Magnetic resonance imaging (MRI) and spectroscopy (MRS) are powerful and extremely versatile methods for non-invasive studies and diagnostic examinations in humans. Our group is using these MRI and MRS methods in close collaboration with clinical partners primarily in prospective studies of different organs. We also develop novel methods to suit pertinent needs to study physiology and pathology, together



with the underlying mechanisms, in situ. Currently most MRI and MRS studies are performed in brain, kidney, muscle, liver, and heart (see Figure for effect of short term exercise on ectopic lipid reservoirs in liver and muscle). In addition, high resolution NMR studies are performed on biopsies, cell cultures and body fluids.

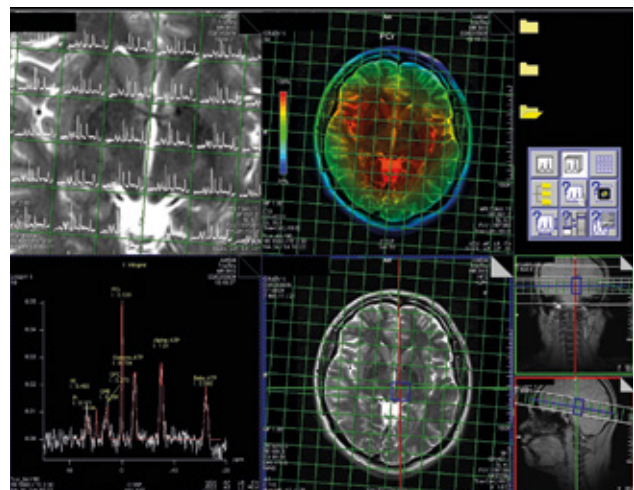
## Teaching Profile

The AMSM participates in University teaching programs for students of medicine, chemistry, biochemistry, and biomedical sciences.

## Highlights 2018

### Brain Physiology

A newly started SNF grant aims at the development of MR methods and synergistic postprocessing methods that are tailored to the observation of brain metabolism, yet are also transferable to other organs. In collaboration with the ETH and University of Zurich, as well as the MPI in Tübingen, exchange processes between amide protons and water are studied in human brain at the highest field strengths available for investigation of human subjects. MRS is optimized for evaluation of systemic brain diseases and for optimal reproducibility in longitudinal studies. Diffusion properties of brain metabolites are investigated with dedicated



methodology in collaboration with the Clinic for Neurology. A similar MRS sequence was also developed for the study of microstructure in brain and muscle.

#### European Innovative Training networks (ITNs)

TRANSACT (TRANSforming Magnetic Resonance Spectroscopy into A Clinical Tool) was an EU-funded Marie Curie Initial Training Network (<http://www.transact-itn.eu/>), which aimed at improving and automating MRS methods and postprocessing tools such that the clinical use of MRS becomes more robust and widespread. The specific aim of our subproject was the definition and automatic recognition of spectral quality and clinical usability such that radiologists without specific methodological knowledge should be better able to use MRS in their routine. Machine learning networks were shown to yield similar accuracy as human experts for quality assessment in spectra acquired for brain tumor assessments and deep learning was used for artifact detection. A follow-up ITN (Inspire-Med) was submitted and granted to focus on multi-parametric and multi-modal MRI/MRS and PET techniques in a European multicenter research and training network.

#### Renal Function

Renal Function in native and transplanted kidneys has been investigated by multi-modal MRI and MRS in preparation of a Sinergia Grant. Renal function deteriorates after kidney transplantation for multiple reasons. The functional MR modalities differ in terms of sensitivity for cortical or medullary renal tissue and in their assessed determinants. We aim at a better perception of the physiologic basis behind functional MR-parameters and why they may be changed in renal disease. Reproducibility and comparability studies have been performed employing several functional MR methods, such as diffusion weighted imaging, arterial spin labelling, and oxygen dependent MRI. In clinical studies renal ectopic lipids were investigated by MRS and MRI, fMRI measurements were performed for the Bernese renal biopsy registry, or the impact of functional kinking of iliac arteries on perfusion and oxygenation was investigated.

#### High-Resolution Magic Angle Spinning NMR

Since MR spectra in vivo have a limited spectral resolution, high-resolution magic angle spinning (HR-MAS) NMR techniques were applied to correlate spectra of tissue and body fluids in vivo and vitro. HR-MAS makes NMR spectroscopy applicable also to semi-solid materials including biological tissues or cell cultures, which under static conditions yield only poorly resolved NMR spectra providing only little information. HR-MAS allows to metabolically characterize tissue types like brain, muscle, prostate, breast, liver, or kidney. Several HR-MAS studies have been performed on biopsies like muscle or sheep brain as well as on cell cultures and analyzed by statistical "metabonomical" methods. Most

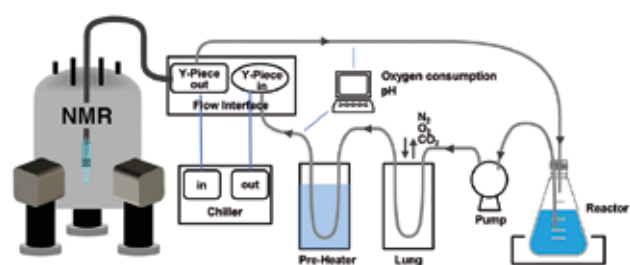
recently, a Bioreactor was established for investigating metabolic responses of living cells inside the NMR upon challenges in real-time (see Fig).

#### Selected Competitive Grants

- Swiss National Science Foundation, grant No. 320030\_175984; 320030\_170062
- Marie-Curie Initial Training Networks, PITN-GA-2012-316679, H2020-MSCA-ITN-2018-813120

#### Selected Publications

- Precht C, Diserens G, Vermathen M, Oevermann A, Lauper J, Vermathen P. Metabolic profiling of listeria rhombencephalitis in small ruminants by 1 H high-resolution magic angle spinning NMR spectroscopy. *NMR Biomed.* 2018 Dec;31(12):e4023. doi: 10.1002/nbm.4023. Epub 2018 Oct 17
- Döring A, Adalid V, Boesch C, Kreis R. Diffusion-weighted magnetic resonance spectroscopy boosted by simultaneously acquired water reference signals. *Magn Reson Med.* 2018 Apr 24. doi: 10.1002/mrm.27222. [Epub ahead of print]
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## Department of Medical Oncology

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PD Dr. Carsten Riether



Dr. Martin Berger



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### Research Partners

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- Department of Biomedicine, University of Basel, Basel, Switzerland
- Institute of Pathology, University of Basel, Basel, Switzerland
- Institute of Pathology, University of Bern, Bern, Switzerland
- Institute of Oncology Research, Bellinzona, Switzerland
- GENCODE project, Hinxton, United Kingdom
- International Cancer Genome Consortium (ICGC)

### Research Profile

The Department of Medical Oncology comprises research groups involved in basic and translational research as well as a clinical trial unit in which more than 160 patients are treated every year in interventional phase I-III studies. The aim of the work of Prof. Rory Johnson' group (GOLD Lab) is to understand the role of long non-coding RNAs (lncRNAs) in human diseases, using a combination of computational and experimental methods. The research group is part of the National Centers for Competence in Research (NCCR) "RNA & Disease". Immuno-Oncology is another focus of the department. This includes preclinical studies in mouse models, translational studies and clinical phase I-III trials. A main goal of the preclinical studies is to understand the interaction of immune cells, especially cytotoxic T cells with leukemia and cancer stem cells. The molecular mechanisms that protect the disease-initiating stem cells from elimination will be employed to design novel therapeutic strategies.

Investigator-initiated clinical studies are performed in different tumor entities but a major field of study is in the field of haemato-oncology. The goal is to improve treatment protocols for autologous stem cell transplantation. Several studies assessing the outcome of patients after autologous stem cell transplantation, the mobilization procedure and

the high-dose chemotherapy schemes are ongoing. In addition, a clinical phase I/II study in patients with acute myeloid leukemia testing a therapeutic strategy developed in our research lab is currently recruiting.

In March 2018 Jörg Beyer joined the Department as Chief-Physician. With a broad clinical background in hematology and medical oncology, he has a strong focus in urogenital tumors and survivorship care. He coordinates the Global Germ-Cell Cancer Collaborative Group and is currently involved in the steering committee of the International Germ Cell Cancer Collaborative Group efforts.

### Teaching Profile

The Department of Medical Oncology participates in the lectures for students of medicine (4<sup>th</sup> to 6<sup>th</sup> year), biomedicine and biology. We also teach students of biomedicine of the University of Fribourg. In addition, we train students in clinical skills and in the field of oncology (4<sup>th</sup> to 6<sup>th</sup> year).

### Highlights 2018

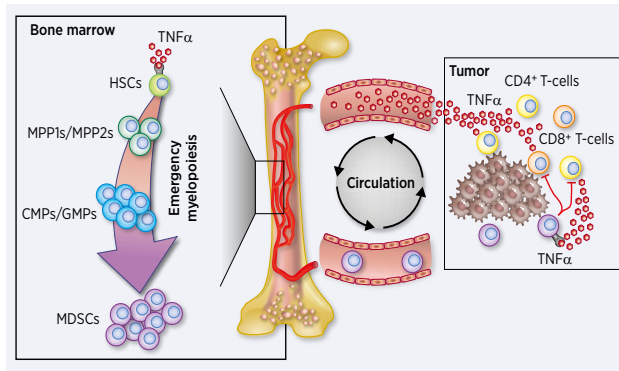
#### *Identification of biomarkers in colon cancer*

The interaction between the tumor and its stromal environment plays an important role in the development of tumors. Just recently, we demonstrated that stromal, but not epithelial PD-L1 expression correlated with less aggressive tumor features in colon cancer patients, which translated into improved outcome. This beneficial effect could be observed independent of the microsatellite status. Similar to PD-L1, stromal PD-1 expression was also associated with favorable tumor characteristics, resulting in improved outcome. Therefore, stromal PD-1/PD-L1 might serve as a prognostic marker in colon cancer patients.

#### *A novel immune-regulatory circuit that dampens anti-tumoral immune responses*

It is now very well established that various tumors are highly immunogenic and induce a specific CD8 T cell response. However, immunosuppressive mechanisms render these tumor-specific T cells ineffective. The definition of such

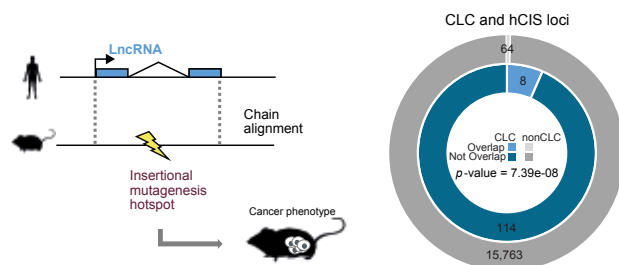
immunosuppressive mechanisms led to novel and very efficacious therapeutic approaches, e.g. the blockade of the PD-1/PD-L1 interaction. In addition, immunosuppressive myeloid cells such as myeloid-derived suppressor cells (MDSCs) reduce anti-tumoral immune responses. However, so far, MDSCs are difficult to target. We now documented that tumor-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells produce TNF-alpha that activates hematopoietic stem cells (HSCs) in the bone marrow resulting in a myeloid skewing with an increased production of myeloid progenitors and MDSCs.



TNF-alpha secreted by CD4<sup>+</sup> (and partially CD8<sup>+</sup>) T cells induces myelopoiesis resulting in the increased production of MDSCs, which inhibit the CD8<sup>+</sup> T cell immune response in the tumor.

#### Mapping and drugging the lncRNAs that promote tumorigenesis

The human genome contains tens of thousands of newly-discovered “long noncoding RNA” genes (lncRNAs), with potential as therapeutic targets in cancer. However, the vast majority of lncRNAs are completely uncharacterised and methods to identify cancer lncRNAs are painstaking. We have curated a resource of the already-known cancer-causing lncRNAs, called “Cancer Long noncoding RNA Census” (CLC). CLC enables us for the first time to investigate the unique properties of cancer lncRNAs. More importantly, we have combined CLC with tumorigenesis screens from mouse, to demonstrate for the first time that some lncRNAs’ cancer-causing functions have been conserved over tens of millions of years of evolution. Together this research brings us closer to comprehensively mapping and drugging the lncRNAs that promote tumorigenesis. This work was performed as part of our collaboration with the International Cancer Genome Consortium (ICGC) (Uszyczynska-Ratajczak et al., Nat Rev Genet, 2018).



Evolutionarily-ancient cancer-causing lncRNAs can be identified by mapping cancer driver mutations from mouse mutagenesis screens to the human genome (left). These mutations are statistically enriched amongst previously-reported cancer lncRNAs (right).

#### Inherited lymphoma

Most malignant lymphomas arise sporadically, yet familial clustering is known, suggesting a genetic contribution to disease risk. Familial lymphoma cases are a valuable tool to investigate risk genes. We studied a Swiss/Japanese family with two sisters affected by an aggressive lymphoma in the mediastinum. The somatic landscape of both lymphomas was marked by alterations affecting multiple components of the JAK-STAT pathway. Consequently, this pathway was constitutively activated. Potential lymphoma risk variants were identified by whole-exome sequencing of the germline DNA derived from siblings and unaffected family members. This analysis revealed a pathogenic variant in TIRAP, an upstream regulator of NF-κB, in both affected siblings and their mother. The TIRAP p.R81C variant increased B-cell proliferation and enhanced NF-κB pathway activity. The identification of an inherited TIRAP variant provides evidence for a novel link between genetic alterations affecting the NF-κB pathway and lymphomagenesis.co.

#### Selected Competitive Grants

- SNF (Group Ochsenbein, Group Riether, Group Johnson)
- KFS (Group Ochsenbein, Group Riether, Group Johnson, Group Beyer, Group Pabst)
- Helmut Horten Stiftung (Group Johnson)

#### Selected Publications

- Al Sayed MF, Amrein MA, Bührer ED, Huguenin AL, Radpour R, Riether C, Ochsenbein AF. T-cell-secreted TNF-alpha induces emergency myelopoiesis and myeloid-derived suppressor cell-differentiation in cancer. *Cancer Res.* 2018 Nov 2. pii: canres.3026.2018. doi: 10.1158/0008-5472.CAN-17-3026
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- Burkhard R, Keller I, Arambasic M, Juskevicius D, Tzankov A, Lundberg P, Bruggmann R, Dirnhöfer S, Radpour R, Novak U. TIRAP p.R81C is a novel lymphoma risk variant which enhances cell proliferation via NF-κB mediated signaling in B-cells. *Haematologica.* 2018 Oct 31. pii: haematol.2018.201590. doi: 10.3324/haematol.2018.201590. [Epub ahead of print]

## Department of Nephrology and Hypertension

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Prof. Daniel Fuster  
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Lab Head

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- Prof. Murielle Bochud, IUMSP, Lausanne, Switzerland
- Prof. Alain Doucet, Collège de France, Paris, France
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- Prof. Claudio Ponticelli, Istituto Clinico Humanitas IRCCS, Rozzano, Italy
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- Dr Ali Gharavi, Columbia University Medical Center, New York, NY, USA
- Prof. Orson Moe, UT Southwestern, Dallas, TX, USA

### Research Profile

The department of Nephrology and Hypertension is the centre for patients with kidney diseases and hypertension in the canton Bern. Six different research groups are involved in the investigation of pathophysiological mechanisms contributing to renal function loss upon hypoxia, chronic allograft failure after kidney transplantation, formation of kidney stones and development of renal fibrosis. Our interdisciplinary approach includes different cell culture models, molecular biology, gas chromatography and mass spectrometry, magnetic resonance imaging and animal experimentation with several transgenic mice and rat models. Patients are recruited for a biobank, which includes renal biopsies, plasma, 24h urine, genomic DNA and peripheral blood mononuclear cells. Renal imaging and blood pressure measurements add to the patient characterisation. Recruitment is also ongoing for the NOSTONE study, a multicenter, randomized, placebo-controlled, double-blind trial to assess the efficacy of standard and low dose of hydrochlorothiazide on the recurrence of kidney stones. Local expertise is also increasing with the bone anchored port, a novel vascular access for renal replacement therapy that has been developed by researchers of our department together with Otorhinolaryngology, Cardiovascular Surgery and ARTORG, and in collaboration with Cendres+Métaux, Bienne. Diagnostic's improvement and implement of novel therapeutic approaches should enhance the patients' well-being.

### Teaching Profile

Our department participates in University teaching programs for students in medicine, biomedical sciences and membrane biochemistry in Bern. It also supervises bachelor and master students for their elective modules, master thesis and PhD.

Our staff is additionally responsible for the CAS/DAS in Translational Nephrology at the University of Bern.

### Highlights 2018

#### *Improvement of bioanalytical methods for steroidomics*

We developed and validated a high-resolution platform for the measurement of steroids using two-dimensional gas chromatography coupled to time-of-flight mass spectrometry. Whereas common analysis methods only provide a very limited view of the steroid network, this novel approach provides a comprehensive snapshot of the urinary steroid metabolome. In addition to improved coverage of the steroid metabolome, this method shows higher sensitivity and specificity compared to traditional techniques and therefore greatly reduces the risk of misassignments. This approach also works for notoriously difficult samples such as newborns and rodents urine.

Additionally, we could show how comprehensive urinary steroid profiling can be used as tool for the diagnostic of polycystic ovarian syndrome. Whereas single steroids are not suitable as markers due to low specificity and sensitivity, disease detection based on a panel of steroids is highly encouraging. The use of machine-learning algorithms for data analysis was also evaluated in this respect.

#### *Role of Zinc transport in blood pressure regulation and glucose homeostasis*

Genome-wide association studies (GWAS) have identified ZIP8 variant rs13107325 (SNP) (A391T) as a pleiotropic SNP variants of the human genome associated with a wide variety of diseases affecting blood pressure, body mass index and HDL cholesterol. Consequently, our group has initiated the analyse of Zip8 knock-in mice bearing the ZIP8 rs13107325-T SNP to investigate the functional changes generated by this single-point mutation A391T. We investigated their renal phenotype, using metabolic cages to collect 24h urine and calculate balances. Blood pressure was measured by telemetry. Glucose metabolism was assessed by intraperitoneal glucose and insulin tolerance tests in animals fed with control diet or western diet. These experiments demonstrated a role for ZIP8 in urinary pH, electrolyte handling, blood pressure and glucose homeostasis. Targeting ZIP8 by pharmaceutical approach could be an attractive strategy for the treatment of hypertension and diabetes.

#### *Fetal hypoxia to premature renal aging*

Our lab is interested at studying mechanisms leading to renal fibrosis and progression to chronic kidney diseases (CKD). Intrauterine growth retardation (IUGR), resulting in

low birth weight (LBW), increases the risk of adulthood diseases (hypertension, diabetes mellitus and/or CKD). An often underestimated risk factor for the development of IUGR is high altitude (>2400m above sea level) and the concomitant exposure to chronic hypoxic conditions, which affects more than 140 million people. Kidneys of LBW patients are characterized by nephron under-endowment. We mimicked fetal oxygen deprivation by exposing gravid mice to chronic hypoxic conditions (10% O<sub>2</sub>). Freshly isolated embryonic kidneys were submitted to bottom-up proteome profiling. We showed that chronic hypoxia during kidney development leads to local inflammation in the proximity of newly forming nephrons and modulation of proteins associated with aging, which could provide an explanation for the nephron under-endowment found in LBW kidney patients.

### **Selected Competitive Grants**

- Mechanisms of thiazide-induced glucose intolerance (SNF, Prof. Daniel Fuster)
- Role of vitamin D and vitamin D metabolizing enzymes in the prevention of atherosclerosis (SNF, PD Dr. G. Escher)
- Thiazides in the recurrence prevention of calcareous nephrolithiasis (SNF, Prof. Daniel Fuster)
- NCCR Kidney.CH (SNF, Prof. Huynh Do Uyen)
- NCCR TransCure (SNF, Prof. Daniel Fuster)

### **Selected Publications**

- Claus M, Herro R, Wolf D, Buscher K, Rudloff S, Huynh-Do U, Burkly L, Croft M, Sidler D. The TWEAK/Fn14 pathway is required for calcineurin inhibitor toxicity of the kidneys. *Am J Transplant.* 2018 Jul;18(7):1636-1645. doi: 10.1111/ajt.14632
- Pathare G, Dhayat NA, Mohebbi N, Wagner CA, Bobulescu IA, Moe OW, Fuster DG. Changes in V-ATPase subunits of human urinary exosomes reflect the renal response to acute acid/alkali loading and the defects in distal renal tubular acidosis. *Kidney Int.* 2018 Apr;93(4):871-880. doi: 10.1016/j.kint.2017.10.018
- Dhayat NA, Lüthi D, Schneider L, Mattmann C, Vogt B, Fuster DG. Distinct phenotype of kidney stone formers with renal phosphate leak. *Nephrol Dial Transplant.* 2019 Jan 1;34(1):129-137. doi: 10.1093/ndt/gfy170
- Bileck A, Verouti SN, Escher G, Vogt B, Groessl M. A comprehensive urinary steroid analysis strategy using two-dimensional gas chromatography - time of flight mass spectrometry. *Analyst.* 2018 Sep 10;143(18):4484-4494. doi: 10.1039/c7an01990d
- Dhayat NA, Marti N, Kollmann Z, Troendle A, Bally L, Escher G, Grössl M, Ackermann D, Ponte B, Pruijm M, Müller M, Vogt B, Birkhäuser MH, Bochud M, Flück CE. Urinary steroid profiling in women hints at a diagnostic signature of the polycystic ovary syndrome: A pilot study considering neglected steroid metabolites *PLoS One.* 2018 Oct 11;13(10):e0203903



# Department of Neurology

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Prof. Andrew Chan  
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Prof. Antoine Adamantidis  
Extraordinarius



Prof. Urs Fischer  
Extraordinarius



Prof. Marcel Arnold



Prof. Selma Aybek



Prof. Klemens Gutbrod



Prof. Paul Krack



Prof. Johannes Mathis



Prof. René Müri



Prof. Kai Rösler



Prof. Smita Saxena



Prof. Kaspar Schindler



Prof. Werner Z'Graggen

## Research Partners

- Department of Diagnostic and Interventional Neuro-radiology, Bern University Hospital, Bern, Switzerland
- Department of Neurosurgery, Bern University Hospital, Bern, Switzerland
- Gerontechnology and Rehabilitation Group, ARTORG Center, University of Bern, Bern, Switzerland
- CRPP Sleep Health, University of Zürich, Zürich, Switzerland
- Institute for Research in Biomedicine, Università della Svizzera italiana, Bellinzona, Switzerland
- Department of Neurology, McGill University, Montreal, Canada
- Institute of Biotechnology, University of Helsinki, Finland
- Department of Neurology, University of Leyden, Leyden, the Netherlands

## Research Profile

The department of Neurology of Bern is the largest neurological department in Switzerland. The Department is committed to clinical, translational and basic research as the basis for innovation and future development of medicine, and we aim to combine clinical practice with basic research in a multidisciplinary fashion. We currently are supported by 22 SNSF grants, an interfaculty research cooperation (IRC) grant and through other foundations and organizations. In 2018, we published 144 research articles and reviews.

Research topics relevant for the department of Neurology include the investigation of sleep and its disorders, stroke, epilepsy, neuroimmunology, neurorehabilitation, movement disorders, neurological functional disorders and neurodegeneration.

Research is coordinated in three poles:

- Center of experimental neurology (ZEN), with animal models of stroke, narcolepsy, neurodegenerative diseases and neuroimmunology
- The Neuro Clinical Trial Unit (NCTU), for the coordination of large randomized clinical trials
- Human neurophysiological laboratories

## Teaching Profile

Undergraduate teaching as well as supervision of bachelor and master theses are provided for students.

## Highlights 2018

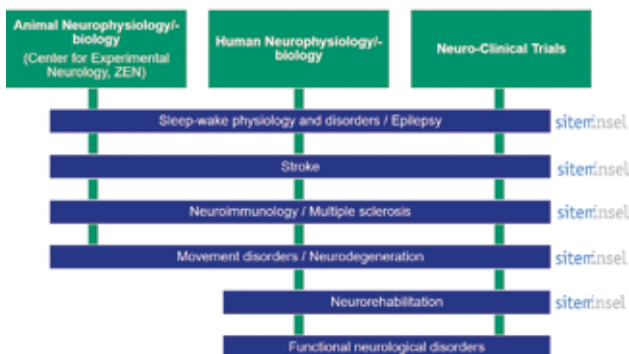
### Staff achievements

The University of Bern granted 6 Mio CHF for an IRC project supervised by Prof. Claudio Bassetti. Prof. Selma Aybek was awarded a SNSF Professorship and Dr. med. Maxime Baud received a SNSF Ambizione Grant. Prof. Paul Krack, joined us as head physician and was awarded the "Parkinson Schweiz" Professorship.

### Three large randomized clinical trials were launched

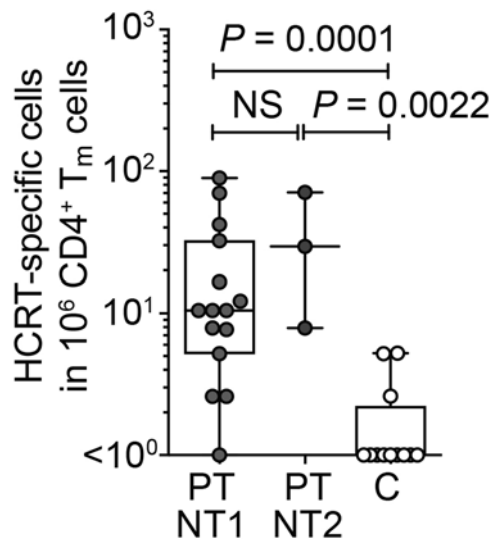
Three international, multicenter, randomized-controlled trials are conducted in close collaboration with the NCTU and CTU. The ELAN trial (PI: Prof. Urs Fischer) aims to determine the benefit of early versus late initiation of oral anticoagulants in stroke patients. The SWIFT DIRECT trial (Co-PI: Prof. Urs Fischer and Prof. Jan Gralla) aims to assess whether direct mechanical thrombectomy with stent retrievers is non-inferior to pretreatment with intravenous thrombolysis followed by mechanical thrombectomy. The eSATIS trial (PI: Prof. Claudio Bassetti) assesses the effect of sleep apnea treatment on the acute outcome of stroke.

## Research Organigram Neurology



*The importance of autoimmune responses in patients with narcolepsy (see selected publication 1 below)*

Narcolepsy is a chronic sleep disorder caused by the loss of neurons that produce hypocretin (HCRT) in the lateral hypothalamus. A study published in Nature with Prof. F. Sallusto and Prof. C. Bassetti as senior co-authors (see "selected publications" below) reported the existence of HCRT-targeting CD4+ T cells in patients with narcolepsy. This discovery gives a strong support to the hypothesis of an autoimmune origin of narcolepsy and opens new diagnostic and treatment opportunities.



Frequencies of HCRT-targeting cells per million memory CD4+ T cells in patients with narcolepsy (with, NT1, and without, NT2, cataplexy) and controls (C).

*Thalamic dual control of sleep and wakefulness (see selected publication 2 below)*

Slow-waves (0.5 - 4 Hz) predominate in the cortical electroencephalogram during non-rapid eye movement (NREM) sleep in mammals. They reflect the synchronisation of large neuronal ensembles alternating between active (UP) and quiescent (DOWN) states and propagating along the neocortex. The thalamic contribution to cortical UP-states and sleep modulation remains unclear. Here we show that spontaneous firing of centromedial thalamus (CMT) neurons in mice is phase advanced to global cortical UP-states and NREM-wake transitions. Tonic optogenetic activation of CMT neurones induces NREM-wake transitions, whereas burst activation mimics UP-states in the cingulate cortex (CING) and enhances brain-wide synchrony of cortical slow-waves during sleep, through a relay in the antero-dorsal thalamus (AD). Finally, we demonstrate that CMT and AD relay neurones promote sleep recovery. These findings suggest that tuning of CMT neuronal firing can modulate brain-wide cortical activity during sleep and provides dual control of sleep-wake states.

### Selected Competitive Grants

- Decoding Sleep: From Neurons to Health & Mind (IRC-Grant; Prof. Claudio Bassetti; 6.2 Mio CHF)
- Sense of Agency and Stress in Functional Neurological Disorders (SNSF; Dr. med. Selma Aybek; 1'583'722 CHF)
- Chronobiology of seizure risk in epilepsy (SNSF; Dr. Maxime Baud; 963'000 CHF)
- Synaptic dysfunction in motoneuron disease (SNSF; Prof. Smita Saxena; 700'000 CHF)
- The Bern heart and brain interaction study (BEHABIS) - Interaction between brain and heart in acute ischemic stroke (SNSF; PD Dr. med. Simon Jung; 362'250 CHF)
- Annemarie Oppenheim Parkinson Award 2018 (Prof. Paul Krack; 100'000 CHF)

### Selected Publications

- Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, Jovic S, Jarrossay D, Mathis J, Zellini F, Becher B, Lanzavecchia A, Khatami R, Manconi M, Tafti M, Bassetti CL\*, Sallusto F\*. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*. 2018 Oct;562(7725):63-68. doi: 10.1038/s41586-018-0540-1
  - Gent TC, Bandarabadi M, Herrera CG, Adamantidis AR. Thalamic dual control of sleep and wakefulness. *Nat Neurosci*. 2018 Jul;21(7):974-984. doi: 10.1038/s41593-018-0164-7
  - Seiffge DJ, Werring DJ, Paciaroni M, Dawson J, Warach S, Milling TJ, Engelter ST, Fischer U\*, Norrving B\*. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol*. 2019 Jan;18(1):117-126. doi: 10.1016/S1474-4422(18)30356-9
  - Evangelopoulos ME, Miclea A, Schrewe L, Briner M, Salmen A, Engelhardt B, Huwiler A, Chan A, Hoepner R. Frequency and clinical characteristics of multiple sclerosis rebounds after withdrawal of fingolimod. *CNS Neurosci Ther*. 2018 Oct;24(10):984-986. doi: 10.1111/cns.12992
  - Preisig BC, Eggenberger N, Cazzoli D, Nyffeler T, Gutbrod K, Annoni JM, Meichtry JR1, Nef T, Müri RM. Multimodal communication in aphasia: perception and production of co-speech gestures during face-to-face conversation. *Front Hum Neurosci*. 2018 Jun 14;12:200. doi: 10.3389/fnhum.2018.00200. eCollection 2018
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## Department of Neurosurgery

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- University Department of Neurology, Bern University Hospital, Bern, Switzerland
- Department of Diagnostic and Interventional Neuro-radiology, Bern University Hospital, Bern, Switzerland
- Swiss Center for Electronics and Microtechnology, Neuchâtel, Switzerland
- Department of Neurobiology Research, University of Southern Denmark, Odense C, Denmark
- Division of Pharmacology and Toxicology, Vetsuisse Faculty, University of Bern, Bern, Switzerland
- Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, UK
- Institute for Exact Sciences, University of Bern, Bern, Switzerland
- Mathematical Oncology Laboratory, Universidad de Castilla-La Mancha, Ciudad Real, Spain
- Swiss Federal Institute of Technology Lausanne (EPFL), Lausanne, Switzerland

### Research Profile

Our department has both clinical and experimental research areas. Our clinical research commitment is driven by the need to improve and refine neurosurgical operations. Focusing on this area, we examine and test how to translate increasingly frequent emerging new technologies into neurosurgical practice. Development of new and innovative technologies or modification of procedures to improve safety and success of neurosurgical operations include intraoperative imaging, neuromonitoring, augmented reality, navigation associated developments, targeted procedures and 3D printing, robotics and simulation techniques. Another focus in collaboration with the neurocenter clinical trial unit are clinical studies or trials to investigate different managements or treatments. We also investigate in several projects topics of diagnosis and treatment of cerebral ischemia and hemorrhage. In our laboratory of regenerative experimental medicine we aim at the development and improvement of therapeutic strategies for neurodegenerative diseases, including Parkinson's disease. Specifically, we investigate the regenerative and neuroprotective potential of soluble factors secreted by circulating endothelial precursor-stem cells termed Endothelial Progenitor Cells.

### Teaching Profile

The Department of Neurosurgery participates in University teaching programs for students of medicine. We organize workshops for medical students and have 3 dozen medical students on in-house rotations per year. We organize a series of both national and international courses on specialized topics of neurosurgery. The research laboratory is co-organizer of the lecture series "Disease and Repair in the CNS" (27340-FS2018-0) for master students of the gcb Bern. Hans Rudolf Widmer serves as mentor and co-advisor for PhD students of the gcb Bern. We supervise master and doctoral students of the medical faculty.

### Highlights 2018

Our spinal robotics group received 2 Mio Swiss Francs funding for bridging the gap to clinical application of robotics the common surgical problem of avoiding misplacement of pedicle screws on the spine. Navigation has already proven to improve accuracy compared to fluoroscopy, but robotics may provide tactile information that is superior to human perception.

Our neuromonitoring group has continued to investigate the use of continuous mapping in motor eloquent brain tumors, and examined the benefit of using this technique in vestibular schwannoma and spinal cord surgery.

Intracerebral hemorrhage remains a major unresolved problem. Our SNF founded SWITCH trial investigates a new form of surgical treatment that does, for the first time, not harm the brain. The Inselspital leads and coordinates this trial and has succeeded to recruit now 97 patients in 7 European countries.

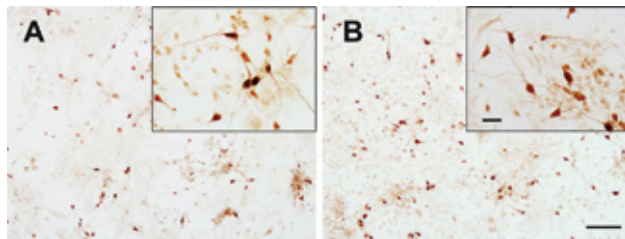
Spontaneous intracranial hypotension (SIH) is a disabling form of headache in otherwise healthy young patients. Since years we focus on this disease, we have established an interdisciplinary SIH-board and our research on the spinal causes continues, having the largest patient series in Europe.

Technological improvement and innovation in DBS implantable segmented leads and brain recording device, analysis of cerebral electrophysiological signals and new image modalities improve our understanding on the physiopathology of movement disorders, epilepsy, psychiatric disease and chronic pain

Neurocritical Care: The group focused on methods for detection of hypoperfused brain areas during the vasospasm phase after subarachnoid hemorrhage using ultrasound and CT perfusion imaging, monitoring of ventricular width and changes of intracranial pressure with ultrasound and others.

Neurooncology: Over 10 000 people showed tremendous interest in the HORA0 project, with more than 270 researchers and 18 teams from over 30 countries across every continent participating in the competition. Ultimately, a total of 45 projects from 23 different countries were submitted on the crowdsourcing platform herox.com. The finalists will present their proposed solutions to the public on March 14, 2019, at the HORA0 Conference, held in conjunction with Brainweek Bern.

We found that paracrine factors from endothelial progenitor cells support the survival and differentiation of cultured striatal progenitor cells and that these effects involve both proteinaceous and lipidic factors. This may represent a novel cell-free approach for the treatment of neurodegenerative diseases. The microphotographs show striatal progenitor cell cultures treated without (A) or with Endothelial Progenitor Cell-derived paracrine factors (B) and stained for GABA. Scale bars: 100  $\mu$ m, 25 $\mu$ m (inserts).



#### Selected Competitive Grants

- BRIDGE Project 20B2-1\_176498 / 1: Towards intelligent sensor enhanced robotic neurosurgery
- Novartis Foundation, Basel (grant No. 16C195)
- "RESURGE – Randomized controlled comparative phase II trial on surgery for glioblastoma recurrence", Schweizerischer Nationalfonds
- Implantable Autonomous Wireless Bio-Electronics for High-Resolution Monitoring and Detection of Epilepsy in-vivo, Schweizerischer Nationalfonds
- Electrophysiological recordings to optimize deep brain stimulation for Parkinson's disease: Parkinson Schweiz

#### Selected Publications

- Di Santo S, Meyer M, Ducray AD, Anderegg L and Widmer HR (2018). A combination of NT-4/5 and GDNF is favorable for cultured human nigral neural progenitor cells. *Cell Transplant.* 2018 Apr;27(4):648-653. doi: 10.1177/0963689717753188
- Liu H, He Z, April S, Trefny P, Rougier JS, Abriel H, Salemi S, Olariu R, Widmer HR and Simon HU (2018). Biochemical re-programming of human dermal stem cells to neurons by increasing mitochondrial membrane potential. *Cell Death Differ.* 2018 Aug 28. doi: 10.1038/s41418-018-0182-8. [Epub ahead of print]

- Roccio M, Perny M, Ealy M, Widmer HR, Heller S and Senn P (2018). Molecular characterization and prospective isolation of human fetal cochlear hair cell progenitors. *Nat Commun.* 2018 Oct 2;9(1):4027. doi: 10.1038/s41467-018-06334-7
- Deletis V, Seidel K, Sala F, Raabe A, Chudy D, Beck J, Kothbauer KF. Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. *J Neurol Neurosurg Psychiatry.* 2018 Jul;89(7):754-761. doi: 10.1136/jnnp-2017-317172
- Raabe C, Fichtner J, Beck J, Gralla J, Raabe A. Revisiting the rules for freehand ventriculostomy: a virtual reality analysis. *J Neurosurg.* 2017 May 19:1-8. doi: 10.3171/2016.11.JNS161765



## Department of Nuclear Medicine

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Prof. Axel  
Rominger  
Director/Head of  
Clinical Research



PD Dr. Ali  
Afshar-Oromieh  
Deputy Director



PD Dr. Kuangyu  
Shi  
Scientific Head of  
Artificial Intelligence and  
Translational Theranostics

### Research Partners

- Departments of Neurology, Otolaryngology, Head and Neck Surgery, Radiation Oncology, Radiology, Urology, Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland
- University Hospital of Psychiatry, Bern, Switzerland
- Department for Biomedical Research (DBMR), University of Bern, Bern, Switzerland
- Department of Chemistry and Biochemistry, University of Bern, Bern, Switzerland
- Department of Nuclear Medicine, Heidelberg, Germany
- Technical University Munich, Munich, Germany
- Ludwig-Maximilian-University Munich, Munich, Germany
- UCSF, San Francisco, USA
- Fudan University, Shanghai, China
- Kindai University, Osaka, Japan

### Research Profile

Our department is focusing on oncological and neurological research through molecular imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT).

We are establishing a translational research environment to support development of novel radiotracers for diagnostics and therapy (theranostic approach). This entails radiochemistry, initial preclinical characterization including in vivo investigations in rodents, with ultimate translation to use in humans. Our primary emphasis on urooncological studies with PSMA ligands shall broaden to other tumor targets. This includes dosimetric aspects in light of novel peptide receptor-mediated radionuclide therapies. In the neurological field, we are principally interested in molecular imaging PET studies of neurodegenerative diseases in conjunction with advanced image analysis techniques.

We have established the Artificial Intelligence and Translational Theranostics (AITT) Lab, which is dedicated to developing novel deep learning algorithms for image analysis targeting early detection, differential diagnosis, and treatment planning in oncological and neurological settings.

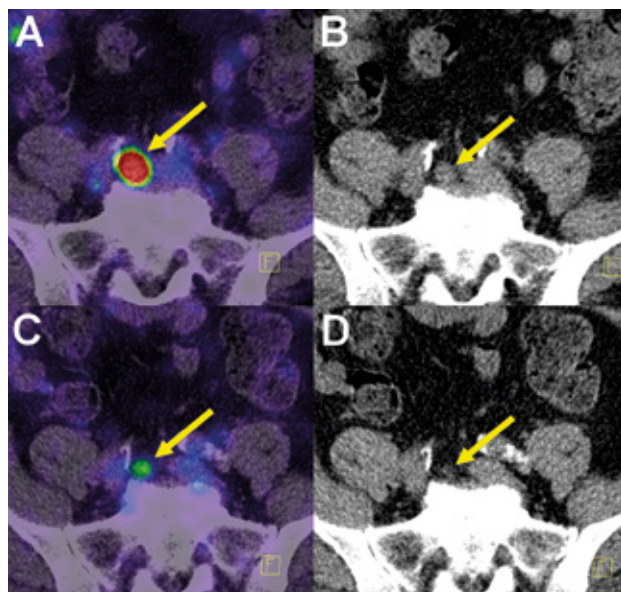
### Teaching Profile

The Department offers lectures within the curricula for students of of Medical and Biomedical Sciences at the University of Bern. Further, we are involved in the education of medical technical radiology assistants.

### Highlights 2018

Contrary to conventional wisdom, we have shown that long-term androgen deprivation therapy (ADT) significantly

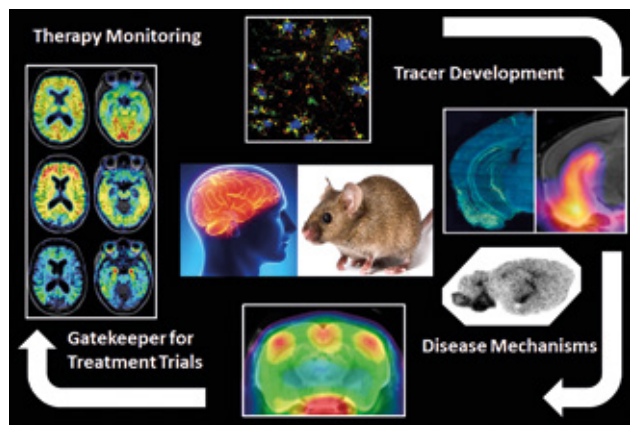
interferes with tumor visibility to PSMA imaging of prostate cancer. This new finding calls for a revision of current guidelines, such that PET/CT examinations with PSMA-ligands should properly be conducted before commencement of ADT. Furthermore, we saw that inflammatory lymph nodes also take up PSMA-ligands, which presents an important pitfall in image interpretation. In cooperation with other clinics, our department expended considerable effort in 2018 towards establishing regulatory approval of PSMA-ligand endoradiotherapies. We shall introduce this novel and highly promising method for the amelioration of metastatic prostate cancer in Switzerland during 2019.



Lymph node metastasis of a patient (yellow arrows) are clearly visible to PSMA-ligand PET/CT without prior to ADT (A, B), but became significantly less conspicuous with a complete PSA response to ADT (C,D).

PET enables non-invasive investigation of molecular alterations in living brain. PET methods can be applied translationally, proceeding from transgenic animal models of neurodegenerative disease to studies in human patients. With the advent of novel molecular imaging markers targeting pathological hallmarks of neurodegenerative diseases, new options have arisen for monitoring disease progression. The repertoire of available tracers serves for mapping activation of microglia, the resident macrophages of brain, along with primary pathologies such as  $\beta$ -amyloid and tau depositions. In clinical trials of disease-modifying agents for Alzheimer's disease, molecular imaging confirms the baseline state and

progression of pathology markers, and thus increasingly serves as a gatekeeper for including patients into clinical trials.



Translational research from bench to bedside.

In the AITT lab we have developed a deep learning method, the so-called deep supervised residual U-Net, to detect and segment prostate cancer lesions on PSMA imaging. This enables the characterization of numerous lesions of heterogeneous size and tracer uptake, which distribute in a variety of anatomical contexts with different tissue background, which makes possible further optimization of therapeutic response, while maximizing the theranostic benefit for PSMA-targeted radionuclide therapy.

In contrast to traditional deep learning on segmented lesions using convolutional neural networks, the AITT has developed densely-connected convolutional neural network for the differential diagnosis of various pancreatic lesions, all with minimal manual input. This network procedure facilitates deep learning with limited training datasets. We also created a saliency map to assist physicians in interpreting the deep learning recommendations.

Other activities of the AITT aim to differentiate automatically Parkinson's disease from atypical parkinsonian syndromes, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These diseases have broadly similar symptoms, making difficult their differential diagnosis at

early stages. Therefore, we have developed a deep projection neural network (DPNN) to extract directly representative image patterns during the machine learning procedure.

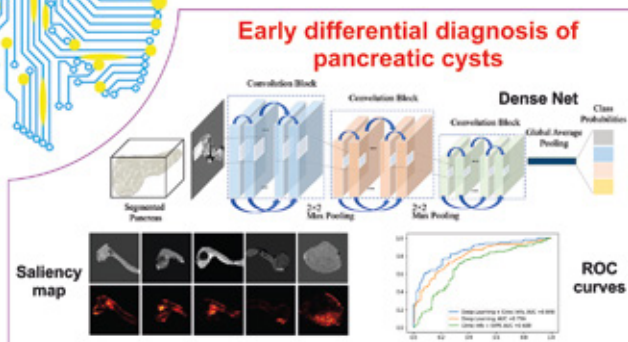
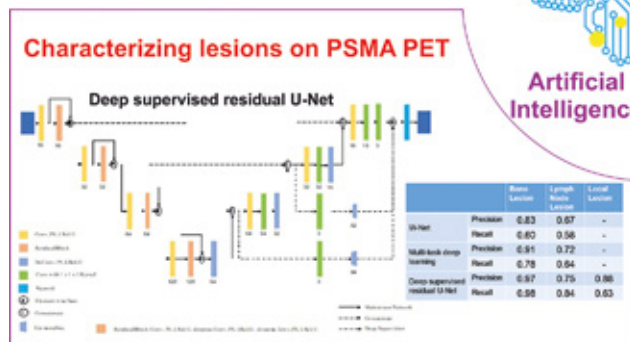
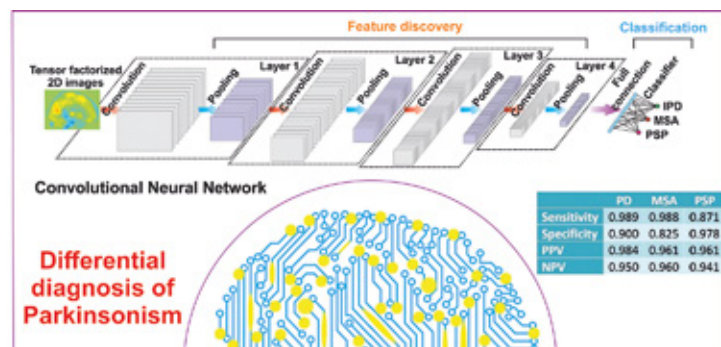
### Selected Competitive Grants

- Uni Bern Forschungsstiftung
- Deutsche Forschungsgemeinschaft (DFG)

### Selected Publications

- Afshar-Oromieh A, Sattler LP, Steiger K, Holland-Letz T, da Cunha ML, Mier W, Neels O, Kopka K, Weichert W, Haberkorn U. Tracer uptake in mediastinal and paraaortal thoracic lymph nodes as a potential pitfall in image interpretation of PSMA ligand PET/CT. *Eur J Nucl Med Mol Imaging*. 2018 Jul;45(7):1179-1187. doi: 10.1007/s00259-018-3965-8. Epub 2018 Mar 1
- Afshar-Oromieh A, Debus N, Uhrig M, Hope TA, Evans MJ, Holland-Letz T, Giesel FL, Kopka K, Hadaschik B, Kratochwil C, Haberkorn U. Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018 Nov;45(12):2045-2054. doi: 10.1007/s00259-018-4079-z. Epub 2018 Jul 7
- Grimmer T, Shi K, Diehl-Schmid J, Natale B, Drzezga A, Förster S, Förstl H, Schwaiger M, Yakushev I, Wester HJ, Kurz A, Yousefi BH. 18F-FIBT may expand PET for  $\beta$ -amyloid imaging in neurodegenerative diseases. *Mol Psychiatry*. 2018 Aug 17. doi: 10.1038/s41380-018-0203-5. [Epub ahead of print]
- Guo T, Dukart J, Brendel M, Rominger A, Grimmer T, Yakushev I. Rate of beta-amyloid accumulation varies with baseline amyloid burden: implications for anti-amyloid drug trials. *Alzheimers Dement*. 2018 Nov;14(11):1387-1396. doi: 10.1016/j.jalz.2018.05.013. Epub 2018 Jul 4
- Brendel M, Jaworska A, Overhoff F, Blume T, Probst F, Gildehaus F, Carlsen J, Bartenstein P, Haass C, Herms J, Willem M, Rominger A. Efficacy of chronic BACE1 inhibition in PS2APP mice depends on the regional A $\beta$  deposition rate and Plaque Burden at Treatment Initiation. *Theranostics*. 2018 Sep 9;8(18):4957-4968. doi: 10.7150/thno.27868. eCollection 2018

Portfolio of research projects of artificial intelligence including characterization of lesions on PSMA PET, early differential diagnosis of pancreatic cysts, differential diagnosis of parkinsonian syndromes.



# Department of Obstetrics and Gynecology

Inselspital, Bern University Hospital  
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## Division of Obstetrics and Feto-Maternal Medicine



Prof. Daniel Surbek  
Director and  
Head Research



Prof. Luigi Raio  
Deputy Director  
Group Leader



PD Dr. Beatrice Mosimann  
Group Leader



PD Dr. Marc Baumann  
Group Leader



PD Dr. Andreina Schoeberlein  
Co-Head  
Research  
Laboratory  
Prenatal Medicine  
Group Leader



PD Dr. Martin Müller  
Group Leader

### Research Partners

- Department of Ob-Gyn and Reproductive Sciences, Yale University, New Haven, USA
- Department of Neonatology, Maastricht University, Maastricht, The Netherlands
- Departments of Pediatrics / Neonatology, Cardiology, and Rheumatology, University of Bern, Bern, Switzerland
- Bern University Hospital Biobank, Switzerland
- Swiss Blood Stem Cell Registry, SRK, Bern, Switzerland
- Biolncept, LLC, Cherry Hill NJ, USA

### Research Profile

We have a strong research focus in the following fields of research:

- Stem cells and perinatal Neuroregeneration
- Prediction and prevention of Preeclampsia
- Clinical research in preterm birth biomarker, induction of labor, postpartum hemorrhage and patient blood management, prenatal ultrasound, fetal diagnosis and therapy, hybrid cord blood stem cell banking

Preclinical research infrastructure includes the Laboratory for Prenatal Medicine which is integrated in the Department for Biomedical Research.

#### *Stem cells and Neuroregeneration*

The mechanisms leading to perinatal injury and neuroregeneration in the neonatal brain and the potential of human umbilical cord tissue stem cells, exosomes and PIF for neuroregeneration are investigated.

#### *Preeclampsia, Metabolic and cardiovascular complications during pregnancy and long term outcome*

We study the molecular mechanisms of preeclampsia pathophysiology and investigate the role of specific placental transport mechanisms, and its longterm effects on cardiovascular and metabolic diseases after an intrauterine preeclampsia exposition. Furthermore clinical studies evaluate novel biomarkers for prediction and prevention of preeclampsia.

### Highlights 2018

Prices for best abstracts at congress of German Society of Obstetrics and Gynecology DGGG, Berlin, November 2018:

- Lüscher B et al. Placental uric acid transport system and its impact on fetal development

- Spinelli M. et al. Preimplantation Factor promotes Neuroprotection by modulating long-non coding RNA

### Selected Competitive Grants

- Swiss National Science Foundation (grant No. 149958)
- National Institute of Health, Small Business Technology Transfer (STTR) Program
- Gottfried and Julia Bangerter-Rhyner Foundation
- EU-Grant COST Action CA17116: International Network for Translating Research on Perinatal Derivatives

### Selected Publications

- Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and pHlGFBP-1 tests: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2018 Oct;52(4):442-451. doi: 10.1002/uog.19119
- Bolla D, Weissleder SV, Radan AP, Gasparri ML, Raio L, Müller M, Surbek D. Misoprostol vaginal insert versus misoprostol vaginal tablets for the induction of labour: a cohort study. *BMC Pregnancy Childbirth.* 2018 May 10;18(1):149. doi: 10.1186/s12884-018-1788-z
- Joerger-Messerli MS et al. Extracellular Vesicles Derived from Wharton's Jelly Mesenchymal Stem Cells Prevent and Resolve Programmed Cell Death Mediated by Perinatal Hypoxia-Ischemia in Neuronal Cells. *Cell Transplant.* 2018 Jan;27(1):168-180. doi: 10.1177/0963689717738256
- Huang X et al. Identification of placental nutrient transporters associated with intrauterine growth restriction and pre-eclampsia. *BMC Genomics.* 2018 Mar 2;19(1):173. doi: 10.1186/s12864-018-4518-z
- Mosimann B et al. Reference Ranges for Fetal Atrioventricular and Ventriculoatrial Time Intervals and Their Ratios during Normal Pregnancy. *Fetal Diagn Ther.* 2018;44(3):228-235. doi: 10.1159/000481349
- Spinelli M et al. The Vermian-Crest Angle: A New Method to Assess Fetal Vermis Position within the Posterior Fossa Using 3-Dimensional Multiplanar Sonography. *Fetal Diagn Ther.* 2018 Dec 5:1-8. doi: 10.1159/000494721
- Spinelli M et al. Nomograms of the Fetal Sylvian Fissure and Insular Lobe throughout Gestation: A Multicentric, Ultrasonographic Cross-Sectional Study. *Fetal Diagn Ther.* 2018 Jul 12:1-7. doi: 10.1159/000490242. [Epub ahead of print]



## Division of General Gynaecology, Oncologic Gynaecology and Urogynaecology



Prof. Michael Mueller  
Director and  
Head Research



PD Dr. Andrea Papadia



Prof. Annette Kuhn



Dr. Sara Imboden



Prof. Nick Bersinger

### Research Partners

- Department of Obstetrics and Gynaecology, Institute for Molecular Biosciences, Queensland, Australia
- Center for Gender Variance, University of Basel, Basel University Hospital, Basel, Switzerland
- Berner Fachhochschule, Bern, Switzerland
- Dell Medical School, University of Texas, Austin, USA
- Croydon University Hospital, London, UK
- Department of Obstetrics and Gynaecology, Skane University, Lund, Sweden
- Department of Urogynaecology, Princess-N-Hospital, Southampton, UK

### Research Profile

We have a strong research focus in the following fields of research:

- ICG sentinel detection in gynaecologic cancers
- Inflammation and endometriosis
- Genetic influences in breast cancer
- Quality of life studies in urogynaecology
- Physiologic and pathophysiologic changes of the pelvic floor during exercises and everyday activities
- Transgender studies

#### *ICG in gynaecologic Oncology*

Recent advances in gynaecologic oncology were remarkably influenced by our publications analyzing the efficacy of sentinel ICG markers for sentinel lymph nodes. With this method, the detection of the sentinel lymph nodes is facilitated and radiating substances are avoided.

#### *Inflammation and endometriosis*

Inflammatory markers are analyzed in patients with endometriosis and biological pathways a being developed looking at peritoneal fluid after laparoscopy and specific endometriotic lesions.

#### *Quality of life-studies in urogynecology*

Our clinical studies focus on quality of life before and after urogynaecologic interventions. To note, we are looking at an elderly population and the development of pathways after urogynaecologic operations in an elderly group of female patients. We aim at looking after this group of patients interdisciplinarily including geriatricians, internal medicine and gynaecology. Furthermore we investigate the effect of several sports activities on the pelvic floor in continent and incontinent women.

### Teaching Profile

The Department of Gynaecology is performing clinical and pre-clinical teaching medical student with masters, MD and PhD level. Additionally, we look after PhD students from the

Bfh Bern and the University of Maastricht. Apart from that, we have programs for fellows from abroad and nationally.

### Highlights 2018

The excellent integration of ICG sentinel lymph node (= SLN) detection and minimal invasive surgery represents a cornerstone of a new area in gynaecological oncology. The adoption of ICG as a tracer has substantially accelerated the detection of the SLN comparable to systematic lymphadenectomy. Publications from our department have confirmed both the non-inferiority and superiority of ICG compared to isosulfan blue dye as a new standard in SLN. A new radio ablative method for the treatment of uterine fibroids has received the video prize at the Swiss annual meeting 2018 (Sonata).

For the first time an international joint report on the terminology of the assessment of sexual health in women with pelvic floor dysfunction has been established. The use of this terminology is essential for future studies and it is accepted by gynaecologic, urologic and urogynaecologic societies.

### Selected Competitive Grants

- Swiss National Science Foundation
- Contura AG, Copenhagen, Denmark

### Educational Grants

- Astella AG, Wallisellen, Switzerland
- Clinical-experimental oncologic Foundation
- Swiss Cancer Society
- Bernese Cancer Association

### Selected Publications

- Nirgianakis K, et al. Obstetric complications after laparoscopic excision of posterior deep infiltrating endometriosis: a case-control study. *Fertil Steril.* 2018 Aug;110(3):459-466. doi: 10.1016/j.fertnstert.2018.04.036
- Gasparri ML, Mueller MD, Papadia A. Instead of feeling blue, go green! *Lancet Oncol.* 2018 Oct;19(10):1273-1274. doi: 10.1016/S1470-2045(18)30514-X
- Papadia A et al. The impact of different doses of indocyanine green on the sentinel lymph-node mapping in early stage endometrial cancer. *Cancer Res Clin Oncol.* 2018 Nov;144(11):2187-2191. doi: 10.1007/s00432-018-2716-3
- Papadia A et al. Retrospective validation of the laparoscopic ICG SLN mapping in patients with grade 3 endometrial cancer *J Cancer Res Clin Oncol.* 2018 Jul;144(7):1385-1393. doi: 10.1007/s00432-018-2648-y
- Papadia A et al. The combination of preoperative PET/CT and sentinel lymph node biopsy in the surgical management of early-stage cervical cancer. *J Cancer Res Clin Oncol.* 2017 Nov;143(11):2275-2281. doi: 10.1007/s00432-017-2467-6



## Department of Ophthalmology

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Prof. Sebastian Wolf  
Director



Prof. Beatrice Früh  
Anterior Segment



Prof. Martin Zinkernagel  
Outpatient Department



Prof. Mathias Abegg  
Orthoptic Goldman Foundation



Prof. Volker Enzmann  
Research Laboratories

### Research Partners

- ARTORG, University of Bern, Bern, Switzerland
- Department of Biology, University of Fribourg, Switzerland
- Department of Anatomy, University of Bern, Switzerland
- Schepens Eye Research Institute/Massachusetts Eye and Ear, Boston, MA, USA
- Department of Ophthalmology, Harvard Medical School, Boston, MA, USA
- Department of Ophthalmology and Visual Sciences, University of Louisville, Louisville, KY, USA
- Hôpital Ophtalmique Jules-Gonin, Université de Lausanne, Switzerland
- Lab for Retinal Cell Biology, Department of Ophthalmology, University of Zürich, Switzerland
- Department of Ophthalmology, University Hospital Basel, Switzerland
- Department of Ophthalmology, University Hospital Regensburg, Regensburg, Germany

### Research Profile

The Department of Ophthalmology was founded in 1834 and is involved in clinical and basic research in the field of visual sciences and ophthalmology. Several clinical research groups are involved in the investigation of the pathophysiology and treatment of vitreoretinal diseases, glaucoma, neuro-ophthalmologic disorders and external disease. Clinical research includes phase I-IV studies as well as the development of new imaging modalities for retinal diseases. The Bern Photographic Reading Center (BPRC) is an internationally renowned center for coordination and independent evaluation of images obtained in clinical multicenter trials. Research projects in cooperation with the ophthalmic technology group at the ARTORG-Center explore new deep-learning approaches for image evaluation. The research groups involved in basic research use state-of-the-art molecular, cellular and imaging techniques for in vitro, cell culture, ex vivo and in vivo studies. Research projects in Experimental Ophthalmology focus on the potential of stem cells and progenitor cells in restoring visual function, in ocular immunology and the influence of the microbiome on inflammatory eye diseases, as well as on new avenues to treat them. The ophthalmogenetics group continuously strives to identify new phenotype-genotype correlations in inherited eye diseases by molecular diagnostic and to understand their impact on eye development.

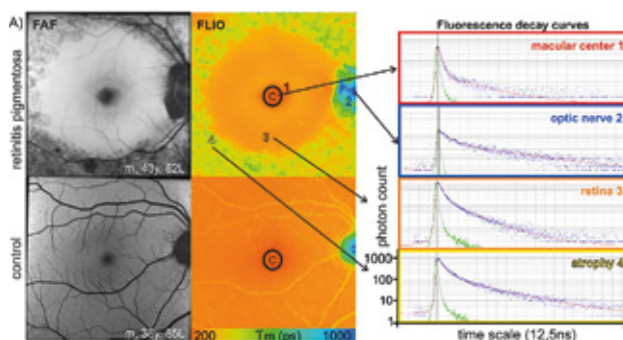
### Teaching Profile

The Dept. Ophthalmology participates in University teaching programs for students of medicine, biomedicine, neuroscience and biology.

### Highlights 2018

#### *Fundus Autofluorescence Lifetime Patterns in Retinitis Pigmentosa*

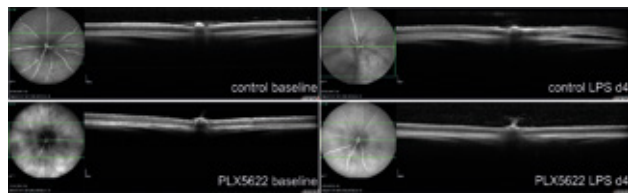
Retinal autofluorescence lifetime imaging (FLIO) combined with qualitative autofluorescence intensity measurements provides a tool for visualization of specific retinal features, such as the RPE and photoreceptor integrity. Thereby fluorescence lifetimes can be analyzed and compared qualitatively by investigating the map of fluorescence lifetime distribution, quantitatively by comparing specific lifetime values, within fluorescence decay histograms among subjects, and within follow-up examinations. FLIO in patients with Retinitis Pigmentosa (RP) potentially provides information about the integrity and function of the outer retinal layers.



Fluorescence lifetime values in the macular center. Qualitative FAF intensity and autofluorescence lifetime images are shown for a patient with RP (Above) and a healthy subject (Below; FLIO LSC: color range, 200–1000 ps). Corresponding fluorescence decay curves of specific locations are shown besides (Nr 1–4; blue dots, measured decay trace; red line, fitting curve; green line, instrument response function). Mean fluorescence lifetime data was averaged in the indicated field C within the macular center (diameter  $\frac{1}{4}$  1 mm).

*Colony-stimulating factor 1 receptor inhibition prevents disruption of the blood retina barrier during chronic inflammation*

Repeated systemic challenge with lipopolysaccharide leads to activation and proliferation of retinal microglia and breakdown of the blood-retina barrier. The breakdown of the blood-retina barrier can be visualized by optical coherence tomography where accumulation of sub-retinal fluid is seen. Lipopolysaccharide induced breakdown of the BRB is highly reproducible but transitory. Inhibition of the CSF-1R by PLX5622 results in depletion of retinal microglia, suppression of cytokine production in the retina, and prevention of BRB breakdown. Our findings suggest that microglia/macrophages play an important role in the pathology of retinal disorders characterized by breakdown of the BRB. (Kokona et al. *Journal of neuroinflammation*: in press).



Infrared images and vertical B-scans at baseline and after 4 daily LPS injections, in mice fed with normal (control) or PLX5622 chow. Arrows indicate accumulation of sub-retinal fluid as sign of BRB breakdown.

### Selected Competitive Grants

- Swiss National Science Foundation: A pragmatic, randomized, non-inferiority trial comparing the effectiveness of Botulinum toxin-based treatment with conventional strabismus surgery in acquired esotropia (No. 33IC30\_173533)
- Swiss National Science Foundation: Molecular mechanisms of NR2E3-linked retinal degenerations (No. 31003A\_169237)

### Selected Publications

- Munk, Marion; Arendt, Petra; Yu, Siqing; Ceklic, Lala; Huf, Wolfgang; Ebnetter, Andreas; Wolf, Sebastian; Zinkernagel, Martin (2018). The Impact of the Vitreomacular Interface in Neovascular Age-Related Macular Degeneration in a Treat-and-Extend Regimen with Exit Strategy. *Ophthalmology retina*, 2(4), S. 288-294
- Berger V; Munk MR; Lersch F; Wolf S; Ebnetter A; Zinkernagel MS (2018). Association of Intravitreal Injections With Blood Pressure Increase: The Following Excitement and Anxiety Response Under Intravitreal Injection Study. *JAMA Ophthalmol*. 2018 Nov 1. doi: 10.1001/jamaophthalmol.2018.4892. [Epub ahead of print]
- Dysli M; Ebnetter A; Menke M; Zinkernagel MS; Wolf S; Grabe H; Abegg M (2018). Patients with Epiretinal Membranes Display Retrograde Maculopathy after Surgical Peeling of the Internal Limiting Membrane. *Retina*. 2018 Aug 29. doi: 10.1097/IAE.0000000000002266. [Epub ahead of print]
- Dysli C; Schürch K; Escher P; Wolf S; Zinkernagel MS (2018). Fundus Autofluorescence Lifetime Patterns in Retinitis Pigmentosa. *Invest Ophthalmol Vis Sci*. 2018 Apr 1;59(5):1769-1778. doi: 10.1167/iovs.17-23336.
- Yu S; Früh BE; Steinmair D; Ebnetter A; Wolf S; Zinkernagel MS; Munk M (2018). Cataract significantly influences quantitative measurements on swept-source optical coherence tomography angiography imaging. *PLoS One*. 2018 Oct 2;13(10):e0204501. doi: 10.1371/journal.pone.0204501. eCollection 2018

## Department of Orthopedic Surgery and Traumatology

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Prof. Klaus A. Siebenrock  
Chairman



Prof. Matthias Zumstein  
Vice Chairman  
Head Shoulder, Elbow and Sports



Prof. Lorin M. Benneker  
Head Spine Surgery



Prof. Moritz Tannast  
Research Leader  
Hip Surgery



PD Dr. Frank M. Klenke  
Head Knee Surgery and Tumor Surgery



PD Dr. Fabian Krause  
Head Foot and Ankle Surgery



PD Dr. Johannes Bastian  
Orthogeriatrics



PD Dr. Sven Hoppe  
Translational Medicine and Spine Research

### Research Partners

- Institute for Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
- Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland
- Department of Small Animals, Division of Diagnostic Imaging, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland
- AO Research Institute, Davos, Switzerland
- RMS Foundation, Bettlach, Switzerland
- SUVA, Switzerland
- Institute for Forensic Medicine, University of Bern, Bern, Switzerland
- Institute for Topographic and Clinical Anatomy, University of Bern, Bern, Switzerland
- Institute of Pathology, University of Bern, Bern, Switzerland

### Research Profile

The Department of Orthopedic Surgery consists of six research groups. In each specific field, we perform clinical as well as pre-clinical and basic research. Hip research focus on the development of osteoarthritis and pre-arthritis deformities like femoroacetabular impingement. 3D MRI is used to simulate pre-arthritis deformities and access early stages of chondral lesions. In a sheep model, different impingement morphologies and its treatment can be simulated.

Spine research is focused on disc degeneration models and tissue-engineered disc regeneration and the treatment of osteoporotic fractures. The main focus of knee research is the regenerative treatment of the anterior cruciate ligament. Prosthetic infections and anti-infectious implants are also research topics. The shoulder and elbow team is working on statistical shape modeling of shoulder morphology, rotator cuff regeneration incl. stem cells and the investigation of surgical techniques and implants. Arthrosis of the ankle joint, innovative treatment of ankle fractures and AMIC plastic in osteochondral lesions is the main focus in foot and ankle research. Orthogeriatrics investigates the impact of orthogeriatric pathways and rehabilitations protocols on the clinical outcome in geriatric patients. Translational medicine is the latest research field which will come to focus the during the next years.

### Teaching Profile

The Department participates in University teaching programs for students of medicine, physiotherapy, nursing and sports. Moreover, we are active in advanced training for general practitioners and emergency physicians as well as for orthopedic surgeons. The Department is certified teaching facility of the AO Foundation, the largest community of musculoskeletal disorders, and constantly hosts several fellows in all sub-disciplines.



## Highlights 2018

*First swiss orthogeriatric day, 31.10.2018*

The number of elderly patients in orthopaedics and traumatology is steadily increasing and represents a new challenge in interdisciplinary and interprofessional treatment. Hosted by the Inselspital in Bern by PD Dr. med. J.D. Bastian and Prof. A. E. Stuck the "1<sup>st</sup> Swiss Orthogeriatrics Day" provided the framework to discuss this new clinical challenge with the inclusion of all interdisciplinary and interprofessional treating groups, from all regions of Switzerland. The program included specialist contributions by established speakers from the various centres in German and French speaking Switzerland as well as a guest speaker from Germany and was divided into three consecutive sessions:

- Session 1: Standards and controversies in the treatment of elderly patients
- Session 2: Key note session - Geriatric anaesthesiology
- Session 3: Co-management - Experience reports

187 guests from 16 different cantons joined this truly interdisciplinary event and made it a great success. For 2019 the 2<sup>nd</sup> orthogeriatric day is already scheduled for October 31<sup>st</sup> and will take place in Bern at the Inselspital again.



## Selected Competitive Grants

- Krause F, Kurze C, Seidel A, Kolp D, Attinger M: "Prospective, randomized multicenter study to compare pain, function and return to work in conservative vs. operative treated stable fractures of the lateral malleolus" (SUVA CHF 131'000)
- Hoppe S, Benneker L: „10 years results after vertebroplasty of vertebral compression fractures" (Lindenhofstiftung 2017-2019: CHF 65'000)
- Maniglio M, Zumstein M, Künzler M, Bolliger L, Flückiger R, Thay QL "The effects of the ulnar styloid fractures site on the ap-translation of the distal radio ulnar joint and comparison of different fixation techniques in a biomechanical model" (Hans Neuenschwander Fonds 2017-2018: CHF 69'000)

## Selected Publications

- Zumstein MA, Schiessl P, Ambuehl B, Bolliger L, Weihs J, Maurer MH, Moor BK, Schaer M, Raniga S. New Quantitative Radiographic Parameters for Vertical and Horizontal Instability in Acromioclavicular Joint Dislocations. *Knee Surg Sports Traumatol Arthrosc.* 2018 Jan;26(1):125-135. doi: 10.1007/s00167-017-4579-6
- May C, Egloff M, Butscher A, Keel MJB, Aebi T, Siebenrock KA, Bastian JD Comparison of Fixation Techniques for Acetabular Fractures Involving the Anterior Column with Disruption of the Quadrilateral Plate: A Biomechanical Study. *J Bone Joint Surg Am.* 2018 Jun 20;100(12):1047-1054. doi: 10.2106/JBJS.17.00295
- Albers CE, Schott PM, Ahmad SA, Benneker LM, Nieuwkamp N, Hoppe S. Vertebral Body Lavage Reduces Hemodynamic Response to Vertebral Body Augmentation With PMMA, *Global Spine Journal* 10.2018 <https://doi.org/10.1177/2192568218803106>
- Schmid T, Krause F, Penner MJ, Veljkovic A, Younger ASE, Wing K. Effect of Preoperative Deformity on Arthroscopic and Open Ankle Fusion Outcomes. *Foot Ankle Int.* 2017 Dec;38(12):1301-1310. doi: 10.1177/1071100717729491



## Department of Osteoporosis

Inselspital, Bern University Hospital  
Freiburgstrasse, 3010 Bern



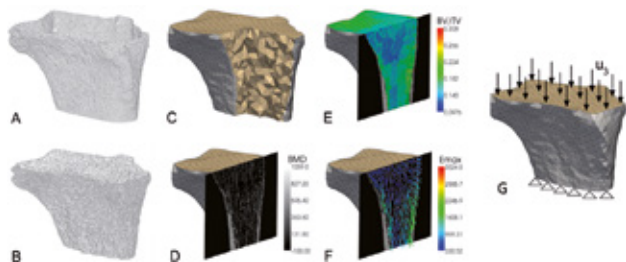
Prof. Kurt  
Lippuner  
Chairman and  
Head

### Research Partners

- AO Research Institute Davos, AO Foundation, Davos, Switzerland
- Department of Orthopaedic Surgery, Bern University Hospital, University of Bern, Bern, Switzerland
- ETH Zurich, Institute for Biomechanics, Zürich, Switzerland
- Free University of Amsterdam (ACTA), Amsterdam, the Netherlands
- Institute of Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
- Radboud University Medical Center, Nijmegen, the Netherlands
- Swiss Paraplegic Centre, Clinical Trial Unit, Nottwil, Switzerland
- Service of Bone Diseases, Department of Rehabilitation and Geriatrics, University Hospitals of Geneva, Geneva, Switzerland
- Bone and Joint Department, University of Lausanne, Lausanne, Switzerland
- Zhejiang Chinese Medical University, Hangzhou, China

### Research Profile

The research activities of the Department of Osteoporosis cover a broad range of aspects within the field of metabolic bone diseases including clinical and translational projects. Research areas comprise the epidemiology and socio-economic burden of osteoporotic fractures, the refinement of fracture risk prediction through novel general (e.g. FRAX®-Score) and local osteoporotic diagnostics including the evaluation and establishment of new bone-densitometry sites and techniques. Current experimental/ translational research priority among the latter is the establishment of bone strength prediction via finite element analysis using



Framework for the generation of a FE model from HR-pQCT data. Separation of cortical (A) and trabecular bone (B); Mesh (C) with image-based cortical thickness (D); Image-based material properties of each element with bone volume fraction (E) and trabecular anisotropy (F); (G) Boundary conditions (Images adapted from Varga P1, Dall'Ara E, Pahr DH, Pretertklieber M, Zysset PK, *Biomech Model Mechanobiol.* 2011, 10(4):431-44).

high-resolution peripheral quantitative CT (HR-pQCT) at the forearm and distal tibia (collaborative project with ISTB, University of Bern). Targeted stimulation of bone anabolism through local therapeutic intervention at high risk topographic sites (spine and hip), is the main topic of our research group at the DBMR supervised by Prof. Ernst B. Hunziker (see highlights 2018).

Another clinical project under the joint leadership of the ETH Zurich and our clinic on local remodeling and mechanoregulation of bone fracture healing in healthy, aged, and osteoporotic humans has been granted by the SNSF. Patient recruitment has started recently. Last but not least, our department has been internationally acknowledged and awarded for many years as a research site for phase II and III trials relating to the pharmacological treatment of primary and secondary osteoporosis in men and women.

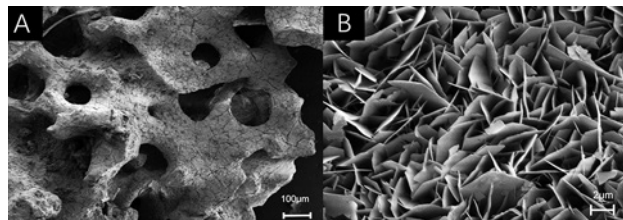
### Teaching Profile

Undergraduate teaching (osteoporosis lectures in the context of geriatrics as well as lectures on calcium phosphate metabolism), and practical courses on pharmaceutical medicine are given to students of human medicine. For students of biomedical engineering a module of the course "Biomechanics Labs" (responsible coordinator: Prof. Ph. Zysset, ISTB, Univ. Bern) with practical teaching on measurement technologies in Biomechanical Engineering is held. The department of osteoporosis is a postgraduate training site for residencies in General Internal Medicine, Endocrinology (Lab), and Pharmaceutical Medicine (the sole residency program of that speciality at the University Hospital in Bern).

### Highlights 2018

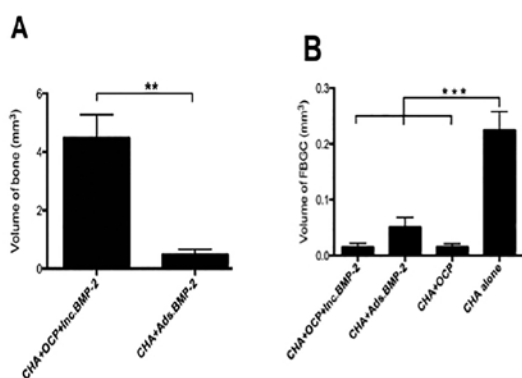
*Enhanced biocompatibility and improved osteogenesis of coralline hydroxyapatite modified by bone morphogenetic protein 2 incorporated into a biomimetic coating.*

The objective of this study was to determine whether the low-degree of biocompatibility of coralline hydroxyapatite (CHA) granules (A), used as a carrier for bone induction, could be improved by (1) using an octacalcium phosphate



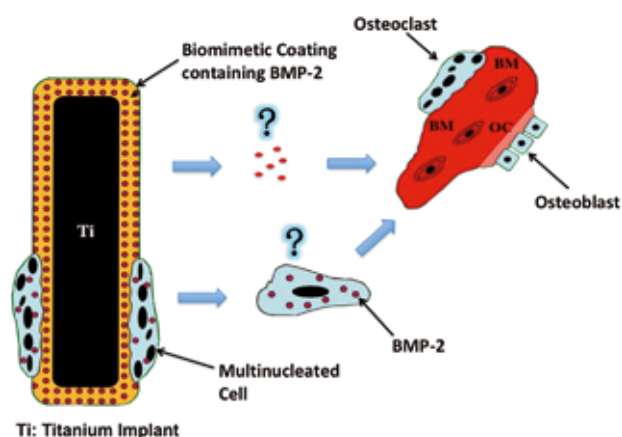
(OCP) coating layer (B), and (2) could be functionalized with bone morphogenetic protein-2 (BMP-2), and (3) to investigate if BMP-2 incorporated into this coating is able to enhance its osteoinductive efficiency, in comparison to its surface-adsorbed delivery mode. An appropriate *in vivo* experiment was performed in adult rats.

The OCP coating-incorporated depot of BMP-2 showed the highest volume and quality of bone (A), and the highest osteoinductive efficacy. OCP coating was able to reduce inflammatory responses (improve biocompatibility) (see reduction of foreign body giant cells (FBGCs)). The biocompatibility of CHA granules (reduction of inflammation (FBGCs)) was thus significantly improved by coating with a layer of OCP. Higher osteoinductivity and improved biocompatibility of CHA can thus be obtained when a layer of BMP-2 functionalized OCP is deposited on the surfaces of CHA granules.



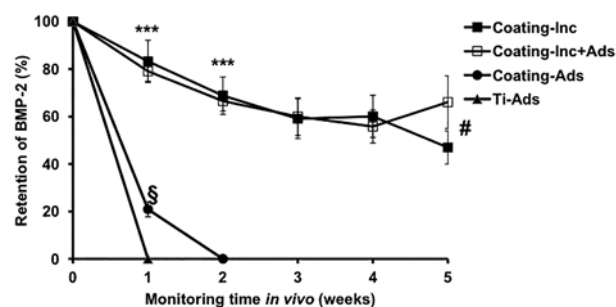
#### The kinetics and mechanism of BMP-2 release from calcium phosphate-based implant-coatings

Biomimetically-deposited calcium phosphate-based coatings of prostheses can serve as a vehicle for the targeted delivery of growth factors to the local implant environment. Based on indirect evidence in previous studies we hypothesize that such agents are liberated gradually from the coating via a cell-mediated degradation. In the present study, we tested this hypothesis by investigating the release mechanism



Graphical Summary of our delayed-release system that is able to deliver a growth factor slowly and cell-dependent over a long period of time. This is the first direct evidence for this system that *in vivo* the postulated slow release is indeed the case, and that in the absence of carrier-resorbing cells the growth factor is not released. This release system has great potential to deliver other factors/drugs and even for much more extensive time periods at low-concentration delivery levels, and thus has a potential for use for other tissues than bone, i.e. for diverse growth-factor directed tissue engineering applications.

and its kinetics by use of a radiolabelled osteogenic agent (<sup>131</sup>I-BMP-2) under conditions in which native cell populations with a coating-degradative potential were either absent or present. The release of <sup>131</sup>I-BMP-2 was monitored for 5 weeks, either *in vitro* or after implantation at an ectopic (subcutaneous) site in rats *in vivo*. Only from implants that bore a coating-incorporated depot of BMP-2 was the agent released slowly and steadily over 5 weeks, i.e. 50% of the loaded dose was liberated *in vivo* (5 to 10% weekly), as against 14.6% *in vitro* (less than 1% weekly). The coatings bearing an incorporated depot of BMP-2 underwent significant cell-mediated degradation, whereas under cell-free conditions no degradation occurred, and the spontaneous release of BMP-2 was negligible. Our findings confirm this carrier system to be a suitable vehicle for the sustained and cell-mediated delivery of BMP-2.



#### Selected Competitive Grants

- SNF 320030L\_170205 (D-A-CH): Local remodelling and mechanoregulation of bone fracture healing in healthy, aged, and osteoporotic humans. Collaborative Project with ETH Zurich, Medical University Innsbruck, University Hospital Ulm. 2017-2020; 372'000 CHF
- SNF no 165510: Micro-Meso Scale Transition of Bone Strength. 2016-2019; 381000 CHF
- China Scholarship Council, Scholarship for Dr. Hairong Huang. (2014 - 2017; 110000 CHF)

#### Selected Publications

- Lin X, Hunziker EB, Liu T, Hu Q, Liu Y. Enhanced biocompatibility and improved osteogenesis of coralline hydroxyapatite modified by bone morphogenetic protein 2 incorporated into a biomimetic coating. *Mater Sci Eng C Mater Biol Appl.* 2019 Mar;96:329-336. doi: 10.1016/j.msec.2018.11.017
- Liu Y, Schouten C, Boerman O, Wu G, Jansen JA, Hunziker EB. The kinetics and mechanism of bone morphogenetic protein 2 release from calcium phosphate-based implant-coatings. *J Biomed Mater Res A.* 2018 Sep;106(9):2363-2371. doi: 10.1002/jbm.a.36398
- Hunziker EB, Spiegl-Habegger M, Rudolf S, Liu Y, Gu Z, Lippuner K, Shintani N, Enggist L. A Novel Experimental Dental Implant Permits Quantitative Grading of Surface-Property Effects on Osseointegration. *Int J Oral Maxillofac Implants.* 2018 Sep/Oct;33(5):967-978. doi: 10.11607/jomi.6348
- Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, Miyauchi A, Maddox J, Chen L, Horlait S. A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis. *J Clin Endocrinol Metab.* 2018 Sep 1;103(9):3183-3193. doi: 10.1210/nc.2017-02163

## Department of Pediatrics

University Children's Hospital, Inselspital  
Freiburgstrasse, 3010 Bern



Prof. Christoph  
Aebi  
Infectiology



Prof. Christa  
Flück  
Endocrinology



Prof. Maja  
Steinlin  
Neurology



Prof. Sabina  
Gallati  
Genetics



Prof. Philipp  
Latzin  
Pulmonology



Prof. Jochen  
Rössler  
Hematology/Oncology

### Department Profile

The Department of Pediatrics is one of the largest clinics within the Medical Faculty of the University of Bern and one of the most diverse, comprising all medical specialties (apart from cardiology). There is one Director ad interim (Prof. Steffen Berger), five Extraordinaria, and several associated and assistant professors leading research groups whose activities are presented. The Ordinarius position is currently vacant. The Department is also strongly involved in teaching at the medical faculty. Most students receive their teaching in Pediatrics at our Children's Hospital Inselspital.

### Division of Pediatric Infectious Diseases

#### Research topics

Current research aims at a multi-angle approach to pediatric sepsis within the Swiss Pediatric Sepsis Study (SPSS) headquartered at our institution. In 2018, activities focused on host genetics (whole exome analysis in previously healthy children with sepsis), clinical data management and the microbiology/epidemiology of causative pathogens. In addition, the PERFORM study (EU consortium for the development of novel biomarkers for the diagnostics of fever) continues to recruit patients.

#### Highlight of the year

The SPSS embarks on new collaborations with national and EU partners interested in the use of the SPSS clinical data-bank and biobanking.

### Division of Pediatric Endocrinology, Diabetology and Metabolism

#### Research topics

Research in endocrinology is focused on translational and basic studies on steroid and growth hormones, specifically the regulation of androgen biosynthesis and the understanding of genetic mutations in human disease. Likewise mitochondrial and urea cycle disorders are subjects of studies of our team. Furthermore, we participated in (inter-)national register studies for obesity, diabetes, rare metabolic disorders and disorders of sex development (DSD). The Swiss DSD Cohort Study is being led by our unit in which eight major children's hospitals are participating.

#### Highlight of the year

Prof. Christa Flück was awarded the prestigious Research Award of the European Society of Pediatric Endocrinology 2018.

### Division of Neuropediatrics, Development and Rehabilitation

#### Research topics

During the last year we have continuously followed on our research in the different areas: pediatric stroke (Swiss national pediatric stroke registry, SNPSR), reorganisation after stroke (HERO study), training and its effect after oncological problems (BRAINFIT study) and consequences after preterm birth (NEMO Study). Prof. Heather Fullerton visited from UCSF for a guest professorship, helping to design a transatlantic study in the area of focal arteriopathy in childhood stroke. Sebastian Grunt who finished his Habilitation (pediatric neurorehabilitation) this year is involved in the new Swiss Registry on Cerebral Palsy and became the president of this consortium.

#### Highlights of the year

- Second prize for thesis (Medical Faculty University of Bern) for Andrea Dulcey
- Anna Müller Grocholsky prize (Swiss Society of Neuropediatrics) for Rebekka Leistner
- Anna Müller Grocholsky prize (Swiss Academy of Childhood disability) for Valentin Benzing

### Division of Human Genetics

#### Research topics

Main research focus was on the functional characterization of novel nuclear mitochondrial genes in order to improve the understanding of the pathomechanisms of mitochondrial disorders. Another topic was the identification and characterization of the primary genetic defects in patients with Moebius syndrome and, still ongoing, genotype-phenotype association studies in patients with cystic fibrosis diagnosed by the newborn screening.

#### Highlight of the year

Within the scope of a national collaboration in Human Genetics Bern is part of the SPHN project "SwissGenVar – a platform for clinical grade interpretation of genetic variants to foster personalized health care in Switzerland".

### Division of Pediatric Pulmonology and Allergy

#### Research topics

Main research focus was lung development and variability of lung function by sensitive measurement techniques, e.g. multiple breath washout, and novel functional lung MRI imaging techniques. Two large cohort studies are led

by the Children's Hospital Bern (BILD; Bern-Basel infant lung development and SCILD; Swiss cystic fibrosis infant lung development cohort). In addition, the full spectrum of diagnostic tests for primary ciliary dyskinesia (PCD) has been established together with the Institute for Anatomy in the newly funded PCD UNIBE center.

#### *Highlight of the year*

Sophie Yammine, MD-PhD was awarded an SNF-Ambizione Research Fellowship to follow up former preterm children at adolescence using novel lung function and imaging.

### **Division of Pediatric Hematology and Oncology**

#### *Research topics*

The clinical research focuses on the performance of international diagnostic and therapeutic trials with specific emphasis on high dose chemotherapy followed by autologous stem cell transplantation. A multicenter randomized controlled clinical trial on fever in neutropenia, led by Bern, has been successfully completed. Translational and basic laboratory studies on mechanisms of genomic instability and clonal hematopoiesis in hematological malignancies in cooperation with the German Cancer Research Center (DKFZ). Furthermore, a registry for lymphatic anomalies has been initiated.

#### *Highlight of the year*

Initiation of a new preclinical research group to study new targets and drug delivery options for pediatric sarcoma

### **Selected Publications**

- Infectious diseases: Martín-Torres F, Salas A, Rivero-Calle I, Cebey-López M, Pardo-Seco J, Herberg JA, Boeddha NP, Klobassa DS, Secka F, Paulus S, de Groot R, Schlapbach LJ, Driessen GJ, Anderson ST, Emonts M, Zenz W, Carrol ED, Van der Flier M, Levin M; EUCLIDS Consortium. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. *Lancet Child Adolesc Health*. 2018 Jun;2(6):404-414. doi: 10.1016/S2352-4642(18)30113-5. Epub 2018 Apr 28
- Endocrinology: Fernández-Cancio M, Camats N, Flück CE, Zalewski A, Dick B, Frey BM, Monné R, Torán N, Audi L, Pandey AV. Mechanism of the Dual Activities of Human CYP17A1 and Binding to Anti-Prostate Cancer Drug Abiraterone Revealed by a Novel V366M Mutation Causing 17,20 Lyase Deficiency. *Pharmaceuticals (Basel)*. 2018 Apr 29;11(2). pii: E37. doi: 10.3390/ph11020037
- Neurology: Bigi S, Dulcey A, Gralla J, Bernasconi C, Melliger A, Datta AN, Arnold M, Kaesmacher J, Fluss J, Hackenberg A, Maier O, Weber J, Poloni C, Fischer U, Steinlin M. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol*. 2018 Jun;83(6):1125-1132. doi: 10.1002/ana.25242
- Genetics: Jackson CB, Huemer M, Bolognini R, Martin F, Szinnai G, Donner BC, Richter U, Battersby BJ, Nuoffer JM, Suomalainen A, Schaller A. A variant in MRPS14 (uS14m) causes perinatal hypertrophic cardiomyopathy with neonatal lactic acidosis, growth retardation, dysmorphic features and neurological involvement. Jackson CB et al., *Hum Mol Genet*. 2018 Oct 24. doi: 10.1093/hmg/ddy374. [Epub ahead of print]

- Pulmonology: Nyilas S, Bauman G, Pusterla O, Sommer G, Singer F, Stranzinger E, Heyer C, Ramsey K, Schlegtendal A, Benzrath S, Casaulta C, Goutaki M, Kuehni CE, Bieri O, Koerner-Rettberg C, Latzin P. Structural and Functional Lung Impairment in Primary Ciliary Dyskinesia. Assessment with Magnetic Resonance Imaging and Multiple Breath Washout in Comparison to Spirometry. *Ann Am Thorac Soc*. 2018 Dec;15(12):1434-1442. doi: 10.1513/AnnalsATS.201712-967OC
- Oncology: Karow A, Wilhelm A, Ammann RA, Baerlocher GM, Pabst T, Mansouri Taleghani B, Roessler J, Leibundgut K. Peripheral blood progenitor cell collection in pediatric patients optimized by high pre-apheresis count of circulating CD34+ cells and high blood flow. *Bone Marrow Transplant*. 2018 Oct 23. doi: 10.1038/s41409-018-0353-8. [Epub ahead of print]



## Department of Pediatric Surgery

University Children's Hospital, Inselspital  
Freiburgstrasse, 3010 Bern



Prof. Steffen  
Berger  
Director



PD Dr. Elizaveta  
Fasler-Kan



PD Dr. Thoralf  
Liebs



PD Dr. Kai  
Ziebarth



PD Dr. Ulf  
Kessler

### Research Partners

- Division of Cytogenetics, University of Bern, Bern, Switzerland
- Zahnmedizinische Kliniken, University of Bern, Bern, Switzerland
- Pharma Center, University of Basel, Basel, Switzerland
- Department of Biomedicine University of Basel, Basel, Switzerland
- School of Pharmacy, University of Kent, Canterbury, UK
- Department of Human Genetics and USA Computation Institute, University of Chicago, Chicago, USA
- Children's Hospital, Harvard Medical School, Boston, USA
- Group Prof. von Gunten, Institute of Pharmacology, University of Bern, Bern, Switzerland

### Research Profile

- Oncobiology (laboratory research in childhood malignancies). Study of the expression of Tim-3 and Gal-9 molecules and their roles in leukemia and in pediatric solid tumors: PD Dr. E. Fasler-Kan.
- Another project of this group is dealing with study of the expression profiles of several genes potentially involved in the pathogenesis of cleft lip/palate in collaboration with ZMK Bern: Dr. I. Schnyder, PD Dr. E. Fasler-Kan.
- Necrotizing enterocolitis of the newborn (Hosting of the Swiss national NEC registry): Prof. S. Berger, PD Dr. U. Kessler, Dr. M. Kordasc
- Pathophysiology of appendicitis: PD Dr. U. Kessler
- Health related quality of life after pediatric extremity fractures (clinical research and follow up studies): PD Dr. T. Liebs
- Development of new operative strategies in pediatric hip surgery and clinical outcome research after surgical treatment of pediatric hip and knee diseases, including slipped capital femoral epiphysis and ruptured anterior cruciate ligaments. PD Dr. K. Ziebarth

### Teaching Profile

The Department for Pediatric Surgery participates in University teaching programs for students of medicine (PBL-teaching, bedside teaching, practical year, surgical rotation for students).

### Highlights 2018

#### *Oncobiology group*

Continued collaboration with Prof. Sumbayev, School of Pharmacy (University of Kent, UK), resulting in several further publications in 2018.

#### *NEC Group*

The national registry database has been established in 2017. During 2018, several Swiss centers began to enter their retrospective and prospective datasets. By now data of >300 patients were entered.

#### *Orthopedic Group*

Habilitation of Dr. K. Ziebarth (group leader) in December 2018. The project for the detection of health-related quality of life (HRQL) in patients who have sustained an extremity fracture during childhood or adolescence analyzed the responses from more than 3200 patients so far. First, fractures of the upper extremity (supracondylar fractures, clavicular fractures and distal forearm fractures) were investigated as to the association of demographic, clinical and radiological risk factors with the clinical outcome.

#### **Selected Competitive Grants**

- "Batzebär" grants PD Dr. Fasler-Kan, PD Dr. Liebs
- AO foundation grants PD Dr. Ziebarth, Dr. Slongo

#### **Selected Publications**

##### Oncobiology group

- Yasinska IM, Gonçalves Silva I, Sakhnevych SS, Ruegg L, Hussain R, Siligardi G, Fiedler W, Wellbrock J, Bardelli M, Varani L, Raap U, Berger S, Gibbs BF, Fasler-Kan E, Sumbayev VV: High mobility group box 1 (HMGB1) acts as an "alarmin" to promote acute myeloid leukaemia progression. *Oncoimmunology*. 2018 Feb 27;7(6):e1438109. doi: 10.1080/2162402X.2018.1438109. eCollection 2018
- Yasinska IM, Ceccone G, Ojea-Jimenez I, Ponti J, Hussain R, Siligardi G, Berger SM, Fasler-Kan E, Bardelli M, Varani L, Fiedler W, Wellbrock J, Raap U, Gibbs BF, Calzolari L, Sumbayev VV. Highly specific targeting of human acute myeloid leukaemia cells using pharmacologically active nanoconjugates. *Nanoscale*. 2018 Mar 29;10(13):5827-5833. doi: 10.1039/c7nr09436a
- Degen M, Wiederkehr A, La Scala GC, Carmann C, Schnyder I, Katsaros C. Keratinocytes isolated from individual cleft lip/palate patients display variations in their differentiation potential in vitro. *Front Physiol*. 2018 Nov 29;9:1703. doi: 10.3389/fphys.2018.01703. eCollection 2018

##### NEC Group

- Hau E, Meyer S, Berger S, Goutaki M, Kordasz M, Kessler U. Gastrointestinal sequelae after surgery for necrotizing enterocolitis: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2018 Jun 26. pii: fetalneonatal-2017-314435. doi: 10.1136/archdischild-2017-314435. [Epub ahead of print]

- Kessler U, Hau EM, Kordasz M, Haefeli S, Tsai C, Klimek P, Cholewa D, Nelle M, Pavlovic M, Berger S. Congenital heart disease increases mortality in neonates with necrotizing enterocolitis. *Front Pediatr.* 2018 Oct 23;6:312. doi: 10.3389/fped.2018.00312. eCollection 2018

Trauma/orthopedic group

- Lerch TD, Novais EN, Schmaranzer F, Ziebarth K, Steppacher SD, Tannast M, Siebenrock KA. What Is the Prevalence of Cam deformity after prophylactic pinning of the contralateral asymptomatic hip in unilateral slipped capital femoral epiphysis? A 10-year minimum followup study. *Clin Orthop Relat Res.* 2018 Dec 13. doi: 10.1097/CORR.0000000000000592. [Epub ahead of print]
- Liebs TR, Ziebarth K, Berger S. Randomized controlled trials for arthroscopy in degenerative knee disease: Was conservative therapy appropriately tried prior to arthroscopy? *Arthroscopy.* 2018 May;34(5):1680-1687.e6. doi: 10.1016/j.arthro.2017.12.016. Epub 2018 Feb 1

## Department for Plastic and Hand Surgery

Inselspital, Bern University Hospital  
Freiburgstrasse 10, 3010 Bern



Prof. Mihai  
Constantinescu



Prof. Esther  
Vögelin

### Research Partners

- Cardiovascular Research Group, Department for BioMedical Research, University of Bern, Bern, Switzerland
- Department of Pharmaceutical Technology, Institute of Pharmacy, University of Jena, Germany
- Department of Plastic Surgery and Hand Surgery, University Hospital Zürich, University of Zürich, Zürich, Switzerland
- Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels, Belgium
- Institute for Stem Cell Biology and Regenerative Medicine (inStem), Bangalore, India
- Institute of Anatomy, University of Bern, Bern, Switzerland
- Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH Zürich, Zürich, Switzerland
- Institute of Pathology, University of Bern, Bern, Switzerland
- Swiss Federal Laboratories for Materials Science and Technology, St Gallen, Switzerland
- University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

### Research Profile

The University Clinic for Plastic and Hand Surgery at the Inselspital Bern exists since 1979. The clinic is conducting clinical and basic research in the fields of Plastic, Reconstructive and Aesthetic Surgery, under the direction of Prof. Mihai Constantinescu, and Hand Surgery and Surgery of the Peripheral Nerve, under the direction of Prof. Esther Vögelin. The Plastic Surgery clinical research focuses on the implementation of 3D models of aesthetic tissue reconstruction and innovative strategies for the diagnosis and treatment of critical ischemic tissue and malignant skin tumors. Hand surgery research is oriented to develop new treatment modalities for hand injuries by application of new drugs and evaluation of innovative modalities for repair of peripheral-nerve injuries. The clinic is also conducting several basic research projects in the field of vascularized composite allotransplantation (VCA). In this field, the interests of the group focus on the use of site-specific immunosuppression to reduce off-target systemic toxicity and increase compliance, and to characterize the role of the lymphatic system in allograft rejection. Moreover, the group is investigating the possibility to use vascularized composite tissue-engineering (VCE) and innovative nanoparticle-based modalities for the treatment of nerve injuries and surgical complications.

### Teaching Profile

The clinic participates in University teaching programs for students of Medicine, Biomedical Science and Molecular Life Science. Moreover, we are involved in outreach activities for education of young students, such as the Swiss Youth in Science program and the mentoring of Matura Projects of the Swiss Academy of Science.

### Highlights 2018

*A prospective, experimental, single center, observational study to analyse the concentration of the antiseptic Octenisept® in hand wounds due to high performance liquid chromatography (HPLC)*

Deep open injuries to the hands are treated in our clinic by exploration and surgical debridement to detect injuries to tendons, nerves or blood vessels. The antiseptic of choice for open wounds is Octenisept®, as it causes little pain due to its low tissue irritation. Prepping a wound with swabs soaked with Octenisept® is unproblematic, but it is known that the injection or pressurized rinsing of wound cavities with Octenisept® leads to toxic tissue reactions. These lead clinically to inflammations, some of which are difficult to distinguish from bacterial infections. These inflammatory reactions can persist for up to one year after use and are difficult to treat. If the underlying problem is not recognized, repeated, sometimes mutilating operations and a protracted postoperative treatment, which are connected with suffering for the patients and high costs, may result. Beside the anamnesis high performance liquid chromatography (HPLC) measurement of the Octenisept® concentration in the tissue helps to establish the correct diagnosis. The purpose of this study is to test whether and in what concentration Octenisept® can be detected in 10 patients after standardized disinfection of open wounds in samples of injured tissue using HPLC. The correct detection of Octenisept® in open wounds avoids frequent frustrating surgical revisions and the unnecessary use of antibiotics.

*The role lymph nodes' transfer in vascularized composite allotransplantation*

Vascularized composite allotransplantation (VCA), such as hand transplantation, has the potential to restore esthetic and function in patients with severe injuries. However, adverse effects of chronic high-dose immunosuppression regimens strongly limit the access to procedures in the clinic. The lymphatic system plays an important role in modulating

inflammation and autoimmune disease, along with organ immune-rejection processes. The aim of this study was to assess the role of regional lymph nodes in VCA rejection. 16 Brown-Norway to Lewis rats hind-limb transplantations were performed. 8 rats received grafts containing lymph nodes (popliteal and inguinal), while the other 8 received lymph node-depleted grafts. The rats with lymph nodes showed increased B- and T-cell chimerism in recipient lymph nodes and spleen, but unchanged rejection scores. These results underline the potential of specifically targeting lymphatic vessels and lymph nodes to influence VCA rejection that could minimize the need for immunosuppressive therapy.

*Bioactive nanoparticle-based formulations promote survival of perforator flaps in a rat model*

Distal flap necrosis is a common complication of perforator flaps in plastic surgery. Advances in nanotechnology offer exciting new therapeutic approaches. Anti-inflammatory and neo-angiogenetic properties of certain metal oxides may promote flap survival. In this study we investigated the effect of different nanoparticle formulations on the survival of perforator flaps in a rat model. The nanoparticle formulations contained bioglass, bioglass/cerioxide and zinc-doped strontium-substituted bioglass/cerioxide. All groups treated with nanoparticles showed a larger survival area of the flap than the control group, which received only 1 ml saline solution. Blood flow measurements with laser Doppler also showed increased peripheral perfusion in the flaps treated with nanoparticles. The tissue analysis showed a higher number of blood vessels and increased VEGF expression, while the inflammatory markers (CD31 and MCP-1) were lowered. Bioglass-based nanoparticles exert local anti-inflammatory and neo-angiogenetic effects on the distal part of a perforator flap and thus increase its survival. These results show a potential benefit of these nanoparticles in the clinical setting.

**Awards**

- Euraps Research Council: Ioana Lese was elected as one of the Euraps Research Council's best paper of the 7th Euraps Research Council Annual Meeting, May 2018, Madrid, Spain with „The role lymph nodes' transfer in vascularized composite allotransplantation“.
- Award for Ioana Lese for the best oral presentations EPSRC (European plastic surgery research council) August 2018 Hamburg for „The role of lymph nodes' transfer and lymphangiogenesis in vascularized composite allotransplantation“
- Ioana Lese has won the SGPRÄC Science Award 2018 for the work: "Bioactive nanoparticle-based formulations promote survival of perforator flaps in a rat model"
- Catherine Tsai has won the award for the best free communication (basic research), also at SGPRÄC.

**Selected Competitive Grants**

- Decellularized vascularized nerve scaffolds for the repair of peripheral nerves. - Foundation for Surgery of the Hand (AFSH) Award 1926 (Dr. Damian Sutter)
- Decellularized vascularized nerve scaffolds for the repair of peripheral nerves. - Förderpreis Schweizerische Gesellschaft für Handchirurgie SGH 2018 (Dr. Damian Sutter)
- Site-specific immunosuppression for long-term maintenance of vascularized composite allotransplantation: validation of efficacy and safety in a clinically relevant large animal model - Medicine Main Discipline: 30702 Surgery University Universität Bern - Swiss National Science Foundation Grant (Dr. Radu Olariu)

**Selected Publications**

- Leclère, Franck-Marie Patrick; Kohl, Sabine; Varonier, Cédric; Unglaub, Frank; Vögelin, Esther. Range of motion, postoperative rehabilitation and patient satisfaction in MCP and PIP joints affected by Dupuytren Tubiana stage 1-3: collagenase enzymatic fasciotomy or limited fasciectomy? A clinical study in 52 patients. Arch Orthop Trauma Surg. 2018 Nov;138(11):1623-1631. doi: 10.1007/s00402-018-3034-6
- Dzhonova, Dzhuliya Vihrenova; Olariu, Radu; Leckenby, Jonathan Ian; Banz Wälti, Yara; Prost, Jean-Christophe; Dhayani, Ashish; Vemula, Praveen K; Vögelin, Esther; Taddeo, Adriano; Rieben, Robert. Local injections of tacrolimus-loaded hydrogel reduce systemic immunosuppression-related toxicity in vascularized composite allotransplantation. Transplantation. 2018 Oct;102(10):1684-1694. doi: 10.1097/TP.0000000000002283
- Duisit, Jérôme; Amiel, Hadrien; Wüthrich, Tsering; Taddeo, Adriano; Dedriche, Adeline; Destoop, Vincent; Pardoën, Thomas; Bouzin, Caroline; Joris, Virginie; Magee, Derek; Vögelin, Esther; Harriman, David; Dessy, Chantal; Orlando, Giuseppe; Behets, Catherine; Rieben, Robert; Gianello, Pierre; Lengelé, Benoît. Perfusion-decellularization of human ear grafts enables ECM-based scaffolds for auricular vascularized composite tissue engineering. Acta Biomater. 2018 Jun;73:339-354. doi: 10.1016/j.actbio.2018.04.009
- Schönfeld, Annemarie; Constantinescu, Mihai Adrian; Peters, Kirsten; Frenz, Martin. Electrospinning of highly concentrated albumin patches by using auxiliary polymers for laser-assisted vascular anastomosis. Biomed Mater. 2018 May 29;13(5):055001. doi: 10.1088/1748-605X/aac332
- Puga Yung, Gisella; Bongoni, Anjan K; Pradier, Amandine; Madelon, Natacha; Papaserafeim, Maria; Sfriso, Riccardo; Ayares, David L; Wolf, Eckhard; Klymiuk, Nikolai; Bähr, Andrea; Constantinescu, Mihai Adrian; Vögelin, Esther; Kiermeir, David; Jenni, Hansjörg; Rieben, Robert; Seebach, Jörg D. Release of pig leukocytes and reduced human NK cell recruitment during ex vivo perfusion of HLA-E/human CD46 double-transgenic pig limbs with human blood. Xenotransplantation. 2018 Jan;25(1). doi: 10.1111/xen.12357



## Department for Pulmonary Medicine

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Prof. Thomas Geiser



Prof. Christophe von Garnier



Dr. Manuela Funke



Dr. Anne-Kathrin Brill



Dr. Jacqueline Pichler Hefti



Dr. Nikolay Pavlov



Dr. Sabina Guler



Dr. Amiq Gazdhar



PD Dr. Fabian Blank

### Research Partners

- Prof. Guenat, Organ-on-chip, ARTORG, University of Bern, Switzerland
- Prof. Lars Knudsen, Institute of Functional and Applied Anatomy, Hannover Medical School, German Center for Lung Research, Hannover, Germany
- PD Dr. Katrin Hostettler, Pulmonary Division, Basel University Hospital, Switzerland
- Prof. Phil Stumbles, Murdoch University, Western Australia
- Sleep-Wake-Epilepsy Center, Inselspital, Bern University Hospital, University of Bern, Switzerland
- Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom
- Prof. Bruno Crestani, Pulmonary Division, Hôpital Bichat, Paris, France
- Pulmonary Medicine, MGH, Harvard, Boston, USA
- Pediatric Pulmonology, Department for Pediatric Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
- Institute of Clinical Chemistry, University of Bern, Switzerland
- Dr. Alexander Eggel, Department for Rheumatology, Immunology and Allergology, Inselspital, Bern University Hospital, University of Bern, Switzerland

### Research Profile

The research activities of the Department for Pulmonary Research are based on experimental, translational and clinical research. In experimental research, we run three research groups concentrating on lung injury, inflammation/immunity and fibrosis. One group focuses on the role of stem cells in lung injury, fibrosis and repair. We established the generation of induced pluripotent stem cells (iPSC) in our laboratory and are interested in the therapeutic potential in iPSC and their secretome in acute and chronic lung injury (acute lung injury, lung fibrosis, emphysema, Prof. Th. Geiser/Dr. A. Gazdhar). Another group pays particular attention to the regulation of pulmonary immune responses by designing liposomes and virosomes that are administered to the respiratory tract (Prof. Ch. von Garnier/ PD Dr. F. Blank). The potential of such biomimetic particles are tested in models of asthma and chronic obstructive pulmonary

disease (COPD). Dr. M. Funke studies pathomechanisms in lung fibrosis and new treatment approaches. Finally, we participate in the development of novel in vitro technology (lung-on-chip) in close collaboration with Prof. O. Guenat and his team (ARTORG).

Clinical study focuses are sleep medicine, asthma/COPD, interstitial lung diseases and pulmonary hypertension. In sleep medicine and non-invasive ventilation we are involved in several clinical studies on sleep disordered breathing and stroke, cardiac conditions and treatment options for respiratory failure (Dr. AK Brill/PD Dr. S. Ott). In interstitial lung diseases we conduct investigator driven pharmacological studies to treat patients with idiopathic pulmonary fibrosis. We also initiate Swiss cohort studies with biobanking for new biomarker discovery for patients with idiopathic interstitial pneumonias (Dr. M. Funke). Dr. J. Pichler Hefti started her research group focusing on new biomarkers in patients with pulmonary hypertension and Dr. S. Guler will also set up her own research after a postdoc at the University of British Columbia, Vancouver on biomarkers and frailty in interstitial lung diseases. Dr. N. Pavlov performs clinical research on the effects of e-cigarette smoking, testing novel lung function parameters (Lung Clearance Index).

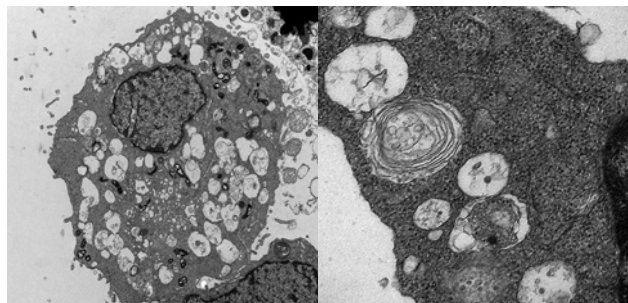
### Teaching Profile

The Department for Pulmonary Medicine provides training in respiratory medicine for students in medicine, biomedicine, dentistry, sport sciences and biomedical research. Furthermore, we teach physiotherapists at the Bern University of applied sciences and the Swiss neurophysiologists in respiratory medicine. Another activity is to train specialists in respiratory medicine and to provide post-graduate training for other specialists and general practitioners.

### Highlights 2018

*Award by the American Physiological Society APS 2018 for the publication "Generation of an alveolar epithelial type II cell line from induced pluripotent stem cells" by Tamò et al*  
In 2018, our work was awarded by the American Physiological Society APS as one of the best recent publications in physiological research 2018. We established an alveolar type II epithelial cell line from induced pluripotent

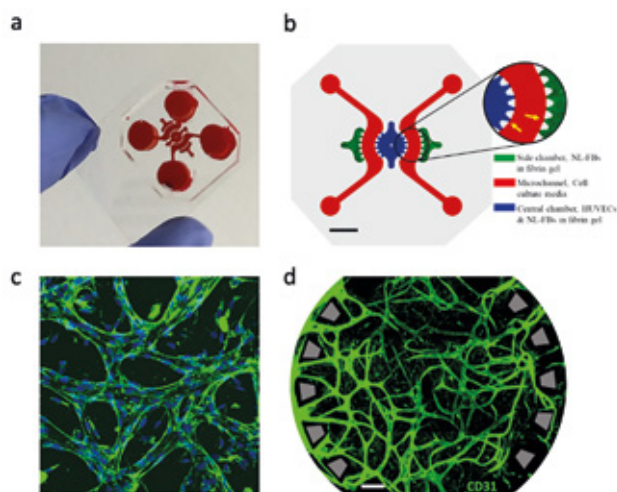
stem cells. This is considered as a break-through in alveolar biology research since it has almost been impossible to culture primary human alveolar type II epithelial cells so far. This novel cellular model obtained from human induced pluripotent stem cells will allow to study alveolar epithelial cell biology in lung health and disease and hopefully to reduce the number of lab animals in the future.



EM images from the newly created alveolar epithelial type II cell line from induced pluripotent stem cells (with typical surfactant producing, onion shaped lamellar bodies).

#### Award for the best presentation at the International Organ-On-Chip Symposium 2018 in Eindhoven

An in vitro 3D perfusable lung microvasculature-on-chip was developed in order to study neovascularisation and perfusion in lung capillaries on chip and for drug testing. These novel models represent an exciting approach because they allow to study the effect of drugs on isolated human microvessels and cell-cell interactions in greater detail than in vivo.



#### Novel non-invasive approaches to evaluate patients with idiopathic pulmonary fibrosis

Prediction of disease course and assessment of severity is challenging in patients with idiopathic pulmonary fibrosis (IPF). In collaboration with the University Institute of Clinical Chemistry, we were able to distinguish metabolic profiles in serum from IPF patients compared to controls. The possible molecular structure is lysophosphatidylcholin (LysoPC), which is a known precursor of the profibrotic pathway lysophosphatidylacid (LPA). The transformation from LysoLPC to LPA is mediated by autotaxin - a molecule, which is currently targeted in clinical studies and might represent future therapeutic options for patients with IPF. In collaboration with the Department for Pediatric Pulmonology, we evaluated multiple breath washout as a new lung functional tool to

assess disease severity in IPF patients. We could not only assess disease severity but also predict disease course. Lung functional measurements further correlated with alterations on radiological imaging and might represent a novel assessment tool for IPF.

#### Enhanced adverse health effects of multi-walled carbon nanotubes (MWCNTs) in the course of COPD

There is increasing concern about possible adverse health-effects of inhaled occupational nanoparticles, such as MWCNTs, particularly in the respiratory tract in persons suffering from chronic obstructive pulmonary disease (COPD). We published our results showing fiber-related changes in pulmonary macrophage and dendritic cell populations with an increased effect of MWCNTs seen in the presence of COPD in a mouse model. These data contribute to the discussion of safety of inhaled nanoparticles in a COPD-injured lung.

#### Selected Competitive Grants

- Lungenliga Schweiz (Nr. 2018-14)
- Swiss National Science Foundation (SINERGIA SNF Grant Nr. CRSII3\_160704/1)
- Swiss National Science Foundation (Nrs. 320030-149752; 320030- 166827)
- Lungenliga Schweiz (Nr. 2015-06)
- Lungenliga Schweiz (Nr. 2014-15)
- Johanna Dürmüller-Bol DBMR Research Grant Award 2017

#### Selected Publications

- Tamò L, Hibaoui Y, Kallol S, Alves MP, Albrecht C, Hostettler KE, Feki A, Rougier JS, Abriel, H, Knudsen L, Gazdhar A, Geiser T. Generation of an alveolar epithelial type II cell line from induced pluripotent stem cells. *Am J Physiol Lung Cell Mol Physiol*. 2018 Sep 13. doi: 10.1152/ajplung.00357.2017. [Epub ahead of print]
- Zeinali S, Bichsel CA, Hobi N, Funke M, Marti TM, Schmid RA, Guenat OT, Geiser T. Human microvasculature-on-a chip: Anti-neovascularogenic effect of nintedanib in vitro. *Angiogenesis*. 2018 Nov;21(4):861-871. doi: 10.1007/s10456-018-9631-8
- Beyeler S, Chortarea S, Rothen-Rutishauser B, Petri-Fink A, Wick P, Tschanz SA, von Garnier C, Blank F. Acute effects of multi-walled carbon nanotubes on primary bronchial epithelial cells from COPD patients. *Nanotoxicology*. 2018 Sep;12(7):699-711. doi: 10.1080/17435390.2018.1472310
- Rindlisbacher B, Schmid C, Geiser T, Bovet C, Funke-Chambour M. Serum metabolic profiling identified a distinct metabolic signature in patients with idiopathic pulmonary fibrosis – a potential biomarker role for LysoPC. *Respir Res*. 2018 Jan 10;19(1):7. doi: 10.1186/s12931-018-0714-2
- Nyilas S, Schreder T, Singer F, Poellinger A, Geiser TK, Latzin P, Funke M. Multiple breath washout: A new and promising lung function test for patients with idiopathic pulmonary fibrosis. *Respirology*. 2018 Aug;23(8):764-770. doi: 10.1111/resp.13294
- Boehringer S, Ruzgys P, Tamò L, Šatkauskas S, Geiser T, Gazdhar A, Hradetzky D. A new electrospray method for targeted gene delivery. *Sci Rep*. 2018 Mar 5;8(1):4031. doi: 10.1038/s41598-018-22280-2

## Department of Radiation Oncology

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Prof. Daniel M. Aebersold  
Director



Dr. Kristina Lössl



Dr. Evelyn Herrmann



Dr. Olgun Eliçin



Prof. Steffen Eychmüller



PD Dr. Peter Manser



Prof. Michael K. Fix



Prof. Yitzhak Zimmer



PD Dr. Michaela Medova

### Research Partners

- Department of Otolaryngology, Head and Neck Surgery, Inselspital, University of Bern, Bern, Switzerland
- Institute for Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
- Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
- Swiss Group for Clinical Cancer Research, Bern, Switzerland
- GEC-ESTRO-Breast-Working-Group, Brussels, Belgium
- Paul Scherrer Institute, Villigen, Switzerland
- Institute for Biomedical Engineering, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland
- Princess Margaret Cancer Center, Toronto, Canada
- Institute of Molecular Systems Biology, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland
- The Netherlands Cancer Institute, Amsterdam, The Netherlands

### Research Profile

The Department of Radiation Oncology along with its three alliance centers represents the largest provider of radiation therapy in Switzerland. Three main branches of research are established as follows: (A) Clinical research with roughly 20 open clinical trials, among them six trials initiated and chaired by the department; (B) Research in medical physics, headed by the division of medical physics; (C) Research in radiation biology, conducted in three research groups.

#### Clinical Research

- Prostate cancer: salvage radiotherapy in biochemical failure, metabolomic signatures
- Head neck cancer: Role of upfront neck dissection in the context of primary radiotherapy; outcome of immune checkpoint inhibitor and chemotherapy followed by dose and volume adapted chemo-radiotherapy
- Breast cancer: Partial breast irradiation with multi-catheter brachytherapy
- Brain tumor: Automatic segmentation of brain tumors, postoperative radiosurgery
- Palliative care: Advanced care planning/anticipation; best care for the dying; community palliative care

#### Medical Physics

- Dynamic trajectory radiotherapy (DTRT) and modulated electron beam radiotherapy (MERT)
- Independent dose calculation and radiation protection in the context of robotic stereotactic radiotherapy
- Efficient quality assurance for external beam radiotherapy and accurate dose calculation for brachytherapy
- Medical imaging related research topics

#### Radiation Biology

- Omics-related (transcriptomics, phosphoproteomics and single-cell proteomics, metabolomics) studies on receptor-tyrosine kinase (MET) signaling, radiation therapy response and resistance and head and neck squamous cell carcinoma (HNSCC)
- Roles of novel posttranslational modifications (phosphorylations, ubiquitinations, acetylations) in cellular responses to DNA-damaging agents and targeted therapies
- Translational research to explore new prognostic and predictive biomarkers
- Radiobiological impact of dose rate

#### Teaching Profile

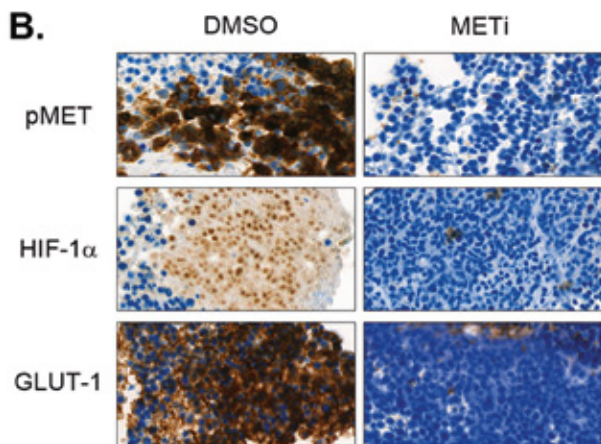
Undergraduate lectures are provided for students in medicine, biomedical engineering, molecular and biomedical sciences as well as in dental medicine at the University of Bern. Undergraduate teaching does also include practical training for medical students. Postgraduate lectures in medical physics are given at the department of physics at the Swiss Federal Institute of Technology in Zurich. A CAS program for palliative care is run in cooperation with various faculties of the University of Bern and the Bern University of Applied Sciences. Various PhD and MD-PhD positions are provided in radiation biology and medical physics.

#### Highlights 2018

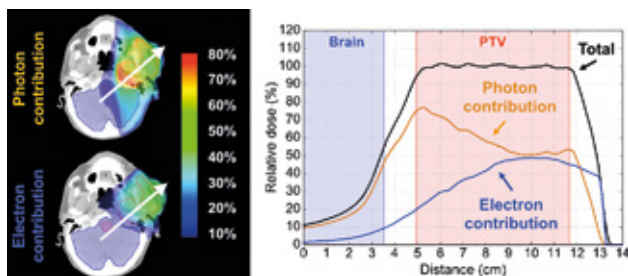
Glück AA, Orlando E, Leiser D, Poliaková M, Nisa L, Quintin A, Gavini J, Stroka DM, Berezowska S, Bubendorf L, Blaukat A, Aebersold DM, Medová M, Zimmer Y. Identification of a MET-*elF4G1* translational regulation axis that controls HIF-1 $\alpha$  levels under hypoxia. *Oncogene* 2018 37(30):4181-4196  
The detailed molecular mechanisms underlying MET



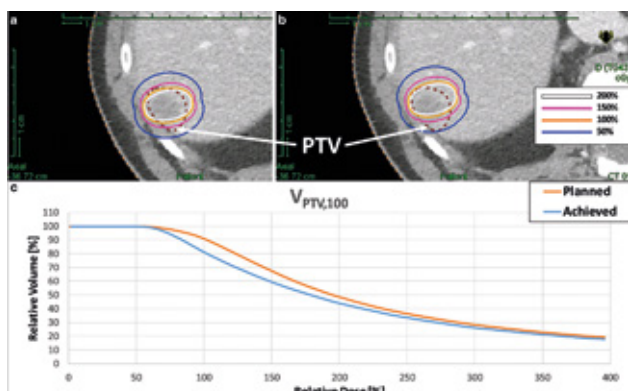
signaling under clinically-relevant hypoxic conditions remain largely unknown. In order to close this gap, this study elucidates the molecular effects of the MET receptor tyrosine kinase inhibition on MET-overexpressing cancer cells in hypoxic environment and identifies a novel MET-eIF4G1 axis as an important regulator of these effects.



S. Mueller, et al. *Dynamic mixed beam radiotherapy (DYMBER): Photon dynamic trajectories combined with modulated electron beams. Med Phys* 2018 45(9): 4213-4226  
 Dynamic trajectory radiotherapy (DTRT) combines non-coplanar beam directions with intensity modulated photon fields and has a huge potential to improve dose distributions for linac based radiotherapy. When DTRT is additionally combined with modulated electron beams leading to dynamic mixed beam radiotherapy (DYMBER), the compactness of the dose to the tumor region could be further improved while simultaneously sparing the organs at risk.



Herrmann E, Terribilini D, Manser P, Fix MK, Toporek G, Candinas D, Weber S, Aebersold DM, Loessl K. Accuracy assessment of a potential clinical use of navigation-guided intra-operative liver metastasis brachytherapy-a planning study. *Strahlenther Onkol* 2018 194(11):1030-1038  
 For patients with inoperable liver metastases, intra-operative liver high dose-rate brachytherapy (HDR-BT) is a promising



technology enabling delivery of a high radiation dose to the tumor, while sparing healthy tissue. We have analyzed anonymized CT datasets of patients who underwent open liver surgery (resection and/or ablation) in order to test whether the accuracy of a new image-guidance method specifically adapted for intra-operative HDR-BT is high enough to be used in similar situations and whether patients could potentially benefit from navigation-guided intra-operative needle placement for liver HDR-BT.

### Selected Competitive Grants

- Innosuisse – Swiss Innovation Agency: Brain Tissue and Tumor Segmentation for Radiation Oncology Planning using Advanced Deep Learning Technologies. (M. Reyes, E. Herrmann)
- Stiftung für klinisch-experimentelle Tumorforschung: Panomic-based characterization of the role of Ser1016 phosphorylation, a newly identified site on the MET receptor tyrosine kinase, in MET-mediated oncogenic signaling (M. Medová)
- Master Research Agreement with Varian Medical Systems (P. Manser, M. Fix)
- Swiss Cancer Research and Rising Tide: PROMET - Multicenter, Randomized, Double Blind, Placebo Controlled Phase II Trial of Salvage Radiotherapy +/- Metformin for Patients with Prostate Cancer after Prostatectomy. (A. Dal Pra, D. Aebersold)
- Swiss Cancer Research: Is early palliative care associated with a reduction in intensity and costs of care at the end of life in patients with advanced cancer? A randomized controlled trial. (S. Eychmüller)

### Selected Publications

- Mackeprang PH, Vuong D, Volken W, Henzen D, Schmidhalter D, Malthaner M, Mueller S, Frei D, Stampanoni MFM, Dal Pra A, Aebersold DM, Fix MK, Manser P. Independent Monte-Carlo dose calculation for MLC based CyberKnife radiotherapy. *Phys Med Biol*. 2017 Dec 19;63(1):015015. doi: 10.1088/1361-6560/aa97f8
- Herrmann E, Terribilini D, Manser P, Fix MK, Toporek G, Candinas D, Weber S, Aebersold DM, Loessl K. Accuracy assessment of a potential clinical use of navigation-guided intra-operative liver metastasis brachytherapy-a planning study. *Strahlenther Onkol*. 2018 Nov;194(11):1030-1038. doi: 10.1007/s00066-018-1334-y
- Glück AA, Orlando E, Leiser D, Poliaková M, Nisa L, Quintin A, Gavini J, Stroka DM, Berezowska S, Bubendorf L, Blaukat A, Aebersold DM, Medová M, Zimmer Y. Identification of a MET-eIF4G1 translational regulation axis that controls HIF-1 $\alpha$  levels under hypoxia. *Oncogene*. 2018 Jul;37(30):4181-4196. doi: 10.1038/s41388-018-0256-6
- Nisa L, Barras D, Medová M, Aebersold DM, Medo M, Poliaková M, Koch JP, Bojaxhiu B, Elicin O, Dettmer MS, Angelino P, Giger R, Borner U, Caversaccio MD, Carey TE, Ho L, McKee T, Delorenzi M. Comprehensive Genomic Profiling of Patient-matched Head and Neck Cancer cells: a Preclinical Pipeline for Metastatic and Recurrent Disease. *Mol Cancer Res*. 2018 Dec;16(12):1912-1926. doi: 10.1158/1541-7786.MCR-18-0056
- Mueller S, Manser P, Volken W, Frei D, Kueng R, Herrmann E, Elicin O, Aebersold DM, Stampanoni MFM, Fix MK. Dynamic mixed beam radiotherapy (DYMBER): Photon dynamic trajectories combined with modulated electron beams. *Med Phys*. 2018 Jul 10. doi: 10.1002/mp.13085. [Epub ahead of print]



## Department of Rheumatology, Immunology and Allergology (RIA)

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Prof. Martin F.  
Bachmann



PD Dr. Monique  
Vogel



PD Dr. Alexander  
Eggel



Dr. Daniel Yerly



Prof. Peter M.  
Villiger

### Research Partners

- The Jenner Institute, University of Oxford, Oxford, UK
- Department of Dermatology, Zürich University Hospital, Zürich, Switzerland
- Allergy Therapeutics (UK) Ltd., Dominion Way, Worthing BN14 8SA, UK
- BRSC, Riga, Latvia
- Vetsuisse Faculty, University of Bern, Bern, Switzerland
- Vifor Fresenius Medical Care Renal Pharma Ltd., St. Gallen, Switzerland
- Ludwig Institute, Lausanne, Switzerland
- Nanyang University, Singapore
- Kennedy Institute, University of Oxford, UK
- Tumor-Immunologie, Prof. Dr. med Ochsenbein, DBMR, University of Bern, Bern, Switzerland
- Laboratory of Clinical Immunology Allergy and Advanced Biotechnologies, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy
- University of Piemonte Orientale, Dept. of Translational Medicine, Italy
- Istituto Nazionale di Genetica Molecolare Via Francesco Sforza 35, Milano, Italy
- Prof. Theodore Jardetzky, Stanford University, USA
- Prof. Tony Wyss-Coray, Stanford University, USA
- Immunologie de l'allergie cutanée et vaccination, CIRI, Université Claude Bernard, Lyon, France

### Research Profile

The Immunology is linked to the Department for BioMedical Research (DBMR) at the University of Bern and to the University Clinic of Rheumatology, Immunology and Allergology (RIA) at the Inselspital, Bern. It consists of three independent basic research groups and a clinically oriented research group that investigate immunological mechanisms with the aim of furthering our understanding of immune regulation and the development of potential new therapies in the one health framework. In the first group (Bachmann/Vogel) the research is dominated by the question how T and B cells responses are induced and influenced by innate immunity. Viruses, virus-like particles and parasites are used to probe the protective capacity of the induced immune response. Understanding the cellular networks of the immune system is of significant medical interest since i) prophylactic vaccines, which are the most effective medical intervention known to date, are based on the induction of long-lived immune responses and ii) a deregulated immune system is the underlying cause of many chronic diseases and autoimmunity. Several diseases serve as models i.e. Typ II Diabetes, cancer, neurodegenerative diseases and inflammatory diseases mostly on type 2 immunity such as allergic inflammation of

the skin (e.g. Insect-bite hypersensitivity (IBH)). Monoclonal antibodies and virus-like particles based vaccines are the primary agents developed for therapy. In the field of allergy the focus is on the study of basic and applied aspects of IgE regulation and mast cell biology and the role of CD23 in driving IgE and IgG responses. Development of a vaccine against peanut- as well as cat allergy are also important goals in this field.

The second group (Eggel) focuses on the biologic mechanisms underlying both beneficial as well as pathogenic type 2 immune responses. Key areas of investigation are: 1) how allergies evolve and how treatments directly interfering with the allergic cascade may be developed 2) age-related disorders and how they are linked to alterations in type 2 immune responses.

The focus of the third group (Yerly) is the drug allergy and the understanding of the cellular and molecular mechanisms involved in drug allergies.

The clinical research group (Villiger) is active in the study of pathogenic mechanisms and the testing of novel treatment strategies of large vessel vasculitides such as Giant Cell Arteritis, Takayasuarteritis and Behçet's disease. In addition, there is a long-term interest in the field of pregnancy and rheumatic diseases (Foerger). There is a strong interaction with international groups, in particular with Italy, Germany and the USA.

### Teaching Profile

The Immunology groups participate in university teaching programs for students of medicine, biomedicine and biology. Master students of biology are also coming from foreign universities.

### Highlights 2018

*Treating insect-bite hypersensitivity in horses with active vaccination against IL-5.*

Insect bite hypersensitivity (IBH) is an allergic response to bites of midges (Culicoides) and leads to strong inflammation of the skin. The skin lesions are characterized by massive eosinophil infiltration which correlates with the disease severity. To dampen eosinophil activity, we decided to target the eosinophil-master regulator, IL-5 which is produced mainly by TH2 cells and mast cells and plays a key role in eosinophil activation and release into blood circulation. For that we developed virus-like particle (VLP)-based therapeutic vaccine that induces IL-5 autoantibodies in the host. VLPs derived from Cucumber Mosaic Virus were engineered to incorporate a T-cell-stimulatory epitope derived from Tetanus toxoid to enhance TH cell-dependent IgG responses against antigens displayed on the VLP surface (CuMV-TT).

We showed that the vaccine consisting of equine IL-5 (eIL-5) chemically linked to CuMV-TT VLPs was well tolerated and induced potent anti-eIL-5 antibody response in horses. Strikingly, symptoms of IBH in immunized horses were strongly reduced compared to placebo-horses and to the pretreatment season (1). More recently, we have shown that horses can be immunized over multiple seasons and that protection against IBH remains stable (2). Hence, vaccination against IL-5 in the horse is the first successful immunotherapy against an inflammatory disease in companion animals and might allow the development of a similar vaccine against IL-5 in humans that will protect against asthma, an eosinophil-mediated pathology for the disease of the lung.

#### *The role of IL-3 and monomeric IgE in the regulation of FcεRI and cell survival in primary human basophils*

Binding of allergen-specific IgE to its primary receptor FcεRI on basophils and mast cells represents a central event in the development of allergic diseases. In addition, monomeric IgE has been reported to actively regulate FcεRI surface levels and thereby promote survival of mast cells in the absence of allergen. As basophils and mast cells share many biological commonalities we assessed the role of monomeric IgE binding and IL-3 signaling in FcεRI regulation and cell survival of primary human basophils. Interestingly, surface levels of FcεRI on basophils were passively stabilized but not actively upregulated in the presence of monomeric IgE. In contrast to previous observations with mast cells, monomeric IgE binding did not enhance basophil survival. Moreover, we found that IL-3 transcriptionally regulates surface levels of FcεRI in human primary basophils. Our data suggest that IL-3 but not monomeric IgE regulates FcεRI expression and cell survival in primary human basophils. Thus, blocking of IL-3 signaling in allergic effector cells might represent an interesting approach to diminish surface FcεRI levels and to prevent prolonged cell survival in allergic inflammation.

#### *Oligo-clonality and drug reactivity of T cells found in the blister fluid of patients with toxic epidermo-necrolysis (TEN)*

Together with research partner in Lyon, T cells from blister fluid of skin lesions in patients suffering from Stevens Johnson syndrome (SJS) or TEN could be isolated. Spectral analysis and sequencing of the TCR revealed the oligo-clonality feature of the T cells. In one case the infiltrating T cells were even monoclonal and the corresponding TCR could be cloned and transduced into T cell lymphoma line. Transduced cells could be activated with oxypurinol, the active metabolite of allopurinol, and at higher concentration by allopurinol itself. This reactivity was restricted by the allele HLA-B\*58:01 and followed the pi concept (pharmacological interaction).

#### *Biomarkers may qualify to monitor subclinical disease activity of Giant Cell Arteritis*

Monitoring subclinical disease activity in order to guide treatment and to prevent relapse is an as yet unresolved problem. In follow-up studies of our RCT, published in The Lancet in 2016, we could show that MR-angiography is unreliable, but that certain biomarkers reflect subclinical disease activity. The data will be validated with the GUSTO (GCA treatment with Ultra-Short glucocorticoids and Tocilizumab) study, which started in December and will be performed with the academic center in Reggio-Emilia.

#### **Selected Competitive Grants**

- Cancer Research Switzerland, Bern. Project: Development and exploration of a novel personalized cancer vaccine based on virus-like particles incorporating patient-specific melanoma T-cell epitopes. Project period: 1.1.2018-31.12.2020
- Allergy Therapeutics (UK) Limited, United Kingdom. Project: Investigating the efficacy of MCT and DOPS adjuvants in combination with VLPs-based vaccines in melanoma murine models via different administrative routes. Project period: 1.8.2017-30.7.2019
- Vifor Fresenius Medical Care Renal Pharma Ltd., St. Gallen. Project: Uptake of non-biological complex drugs by immune cells. Project period: 1.6.2017-31.5.2019
- EHVA, Horizon 2020, SBFI, Bern. Project: European HIV Vaccine Alliance (EHVA): a EU platform for the discovery and evaluation of novel prophylactic and therapeutic vaccine candidates. Project period: 1.1.2016-31.12.2020
- Swiss National Science Foundation (SNF), Bern. Project: "Unraveling the role of CD23 in the context of allergy". Project period: 1.04.2018-31.03.2022
- National Institute of Health R01 Subaward with Prof. Theodore Jardetzky from Stanford University, Project: "Suppression of basophil activation by IgE glycovariants". Project period: 15.04.2018-31.03.2022

#### **Selected Publications**

- Fettelschoss-Gabriel A, Fettelschoss V, Thoms F, Giese C, Daniel M, Olomski F, Kamarachev J, Birkmann K, Bühler M, Kummer M, Zeltins A, Marti E, Kündig TM, Bachmann M. Treating insect-bite hypersensitivity in horses with active vaccination against IL-5. *J Allergy Clin Immunol.* 2018 Oct;142(4):1194-1205.e3. doi: 10.1016/j.jaci.2018.01.041
- Cabral-Miranda G, Cardoso AR, Ferreira LCS, Sales MGF, Bachmann MF. Biosensor-based selective detection of Zika virus specific antibodies in infected individuals. *Biosens Bioelectron.* 2018 Aug 15;113:101-107. doi: 10.1016/j.bios.2018.04.058
- Engeroff P, Fellmann M, Yerly D, Bachmann MF, Vogel M. A novel recycling mechanism of native IgE-antigen complexes in human B cells facilitates transfer of antigen to dendritic cells for antigen presentation. *J Allergy Clin Immunol.* 2018 Aug;142(2):557-568.e6. doi: 10.1016/j.jaci.2017.09.024
- Engeroff P, Caviezel F, Storni F, Thoms F, Vogel M, Bachmann MF. Allergens displayed on virus-like particles are highly immunogenic but fail to activate human mast cells. *Allergy.* 2018 Feb;73(2):341-349. doi: 10.1111/all.13268
- Bachmann MF, Zeltins A, Kalnins G, Balke I, Fischer N, Rostaer A, Tars K, Favrot C. Vaccination against IL-31 for the treatment of atopic dermatitis in dogs. *J Allergy Clin Immunol.* 2018 Jul;142(1):279-281.e1. doi: 10.1016/j.jaci.2017.12.994
- Zellweger, F. et al. IL-3 but not monomeric IgE regulates FcεRI levels and cell survival in primary human basophils. *Cell Death Dis.* 2018 May 1;9(5):510. doi: 10.1038/s41419-018-0526-9
- Gloor AD, Yerly D, Adler S, Reichenbach S, Kuchen S, Seitz M, Villiger PM. Immuno-monitoring reveals an extended subclinical disease activity in tocilizumab-treated giant cell arteritis. *Rheumatology (Oxford).* 2018 Oct 1;57(10):1795-1801. doi: 10.1093/rheumatology/key158

## Department of General Thoracic Surgery

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Chief Physician



PD Dr. Gregor Kocher  
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Dr. Roland Kuster  
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Dr. Jon Andri Lutz  
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Dr. Patrick Dorn  
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Dr. Adrian Zehnder  
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PD Dr. Ren-Wang Peng  
Research Group  
Leader



Dr. Sean R. R. Hall  
Research Group  
Leader



Dr. Thomas M. Marti  
Research Group  
Leader

### Research Partners

- Department of Oncology, Bern University Hospital, Bern, Switzerland
- Department of Pulmonology, Bern University Hospital, Bern, Switzerland
- Department of ENT, Head and Neck Surgery, Bern University Hospital, Bern, Switzerland
- Visceral and Transplantation Surgery, Bern University Hospital, Bern, Switzerland
- Department of Radiation Oncology, Bern University Hospital, Bern, Switzerland
- Institute of Pathology, University of Bern, Switzerland
- Swiss Institute of Bioinformatics (Interfaculty Bioinformatics Unit), University of Bern, Switzerland
- Genome Plasticity - Department of Biomedicine, University of Basel, Basel, Switzerland
- Institute General Physiology, University of Ulm, Ulm, Germany
- ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland

### Research Profile

The Department of Thoracic Surgery in Bern is with 27 beds (together with the Department of Pulmonology) and over 170 anatomical resections per year one of the largest centers in Switzerland with a considerable experience in all fields of this specialized medicine area, e.g. oncological surgery, chest wall resection and reconstruction, treatment for chest wall deformities, lung volume reduction surgery, thoracic trauma management, etc.

#### Main Research Goals

- Evaluation and therapeutic improvements by uniportal minimally-invasive thoracic surgery techniques
- Investigation of different clinical and functional parameters with the aim of achieving better outcome and improvement of patient's comfort
- Determine the immunosuppressive potential of the tumor-derived mesenchymal subset, which may serve as a

novel therapeutic target in lung cancer. Further, we are interested in identifying the molecular mechanisms underlying T cell dysfunction in the setting of lung cancer.

- Identify the molecular mechanisms conferring resistance to clinical standard therapies, with the goal to unravel druggable vulnerabilities - the 'Achilles' heel' - of therapy-resistant cancer cells for development of innovative strategies to treat lung cancer and MPM.
- Investigate how the mitochondria-related nucleotide metabolism and the DNA damage response machinery is associated with the tumor initiating capacity and chemotherapy response of NSCLC cancer stem cells.

### Teaching Profile

Teaching at our Department is characterized by a specialized knowledge of team members from different educational sections. Undergraduate teaching is provided for students of medicine, biomedicine and biology. By giving lectures at the University of Medicine, by organizing students courses and bedside-teachings and by supporting students writing their thesis or completing their PhD programs, we offer a wide range of teaching and knowledge support services. We continued to be actively involved in teaching of the Master Program of Biomedical Sciences by giving lectures in the seminar series entitled "Topics in Tumor Biology" and "Stem Cells & Regenerative Medicine" (PD Dr. Ren-Wang Peng & Dr. Thomas M. Marti). Furthermore, since our centre has the largest experience in uniportal, minimally invasive lung resections in Switzerland, this year we organized two courses for thoracic surgeons in Bern, focused on uniportal lung surgery.

### Highlights 2018

Our translational research part focused on 1.) The biology of stem cells in lung development and disease and on 2.) Drug resistance in lung cancer and malignant pleural mesothelioma (MPM). In the clinical context, we investigated functional parameters as prognostic factors for postoperative complication with the future aim for better prediction. We

published 23 original publications, including the following three papers.

*Surgical smoke: still an underestimated health hazard in the operating theatre*

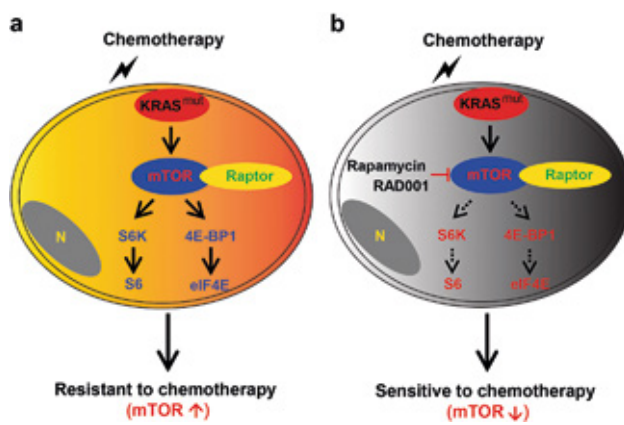
Kocher GJ, Sesia SB, Lopez-Hilfiker F, Schmid RA. Eur J Cardiothorac Surg. 2018 Nov 2. doi: 10.1093/ejcts/ezy356. [Epub ahead of print] PMID: 30388210

Smoke generated from electrocautery dissection contains irritating and/or carcinogenic components. Although smoke evacuation systems may reduce the concentrations of most of the detected volatile organic compounds to a certain amount, especially the carcinogenic substances, butadiene and benzene remained high above exposure limits.

*mTOR mediates a mechanism of resistance to chemotherapy and defines a rational combination strategy to treat KRAS-mutant lung cancer*

Liang SQ, Bühler ED, Berezowska S, Marti TM, Xu D, Froment L, Yang H, Hall SRR, Vassella E, Yang Z, Kocher GJ, Amrein MA, Riether C, Ochsenbein AF, Schmid RA, Peng RW. Oncogene. 2018 Aug 31. doi: 10.1038/s41388-018-0479-6. [Epub ahead of print] PMID: 30171261

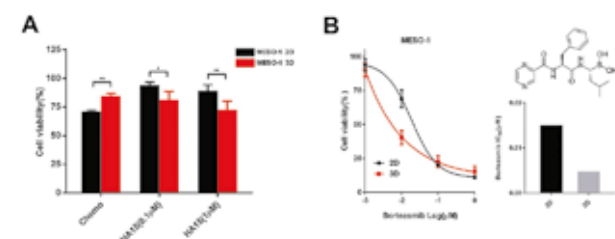
Our data show that KRAS-mutant lung cancer cells rely on dysregulated mTOR pathway to confer resistance to chemotherapy and further define a combination strategy to treat KRAS-mutant lung cancer.



mTORC1 mediates a mechanism of resistance to chemotherapy and defines a rational combination strategy to treat KRAS-mutant lung cancer.

*Increased sensitivity to apoptosis upon endoplasmic reticulum stress-induced activation of the unfolded protein response in chemotherapy-resistant malignant pleural mesothelioma*

Xu D, Liang SQ, Yang H, Lüthi U, Riether C, Berezowska S, Marti TM, Hall SRR, Bruggmann R, Kocher GJ, Schmid RA, Peng RW. Br J Cancer. 2018 Jul;119(1):65-75. doi: 10.1038/s41416-018-0145-3. Epub 2018 Jun 20. PMID: 29921948



Chemotherapy-resistant MPM cells (3D) are hypersensitive to ER stress induced by HA15 (a) or Bortezomib (b).

We provide the first evidence for ER stress and the adaptive UPR signaling in chemotherapy resistance of MPM, which suggests that perturbation of the UPR by altering ER stress is a novel strategy to treat chemotherapy-refractory MPM.

**Selected Competitive Grants**

- Gregor Kocher, Lungenliga Bern, Hazardous surgical smoke: Risk assessment and evaluation of a new smoke extractor system in the surgical unit
- Sean Hall, Boehringer Ingelheim, Analysis of the transcriptome of matched NSCLC patient samples and establishment of pathophysiologically relevant organoid models
- Thomas Marti, Swiss Cancer League, Targeting tumour initiating cells in lung cancer
- Patrick Dorn, Cancer League Bern, Targeting mitochondrial activity to enhance lung cancer therapy
- Ren-Wang Peng, Swiss Cancer League, Unravelling and reversing drug resistance of human lung cancer

**Selected Publications**

- Liang SQ, Bühler ED, Berezowska S, Marti TM, Xu D, Froment L, Yang H, Hall SRR, Vassella E, Yang Z, Kocher GJ, Amrein MA, Riether C, Ochsenbein AF, Schmid RA, Peng RW. mTOR mediates a mechanism of resistance to chemotherapy and defines a rational combination strategy to treat KRAS-mutant lung cancer. Oncogene. 2018 Aug 31. doi: 10.1038/s41388-018-0479-6
- Xu D, Liang SQ, Yang H, Lüthi U, Riether C, Berezowska S, Marti TM, Hall SRR, Bruggmann R, Kocher GJ, Schmid RA, Peng RW. Increased sensitivity to apoptosis upon endoplasmic reticulum stress-induced activation of the unfolded protein response in chemotherapy-resistant malignant pleural mesothelioma. Br J Cancer. 2018 Jul;119(1):65-75. doi: 10.1038/s41416-018-0145-3
- Kocher GJ, Sesia SB, Lopez-Hilfiker F, Schmid RA. Surgical smoke: still an underestimated health hazard in the operating theatre. Eur J Cardiothorac Surg. 2018 Nov 2. doi: 10.1093/ejcts/ezy356. [Epub ahead of print]
- Kocher GJ, Zehnder A, Lutz JA, Schmidli J, Schmid RA. First Rib Resection for Thoracic Outlet Syndrome: The Robotic Approach. World J Surg. 2018 Oct;42(10):3250-3255. doi: 10.1007/s00268-018-4636-4
- Dorn P, Kuhn MA, Schweizer BA, Schmid RA, Kocher GJ. Xiphoidectomy for Intractable Xiphodynia. World J Surg. 2018 May 16. doi: 10.1007/s00268-018-4668-9. [Epub ahead of print]



## Department of Urology

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Prof. Fiona  
Burkard



PD Dr. Marianna  
Kruithof-de Julio



Prof. Katia  
Monastyrskaya



PD Dr. Roland  
Seiler

### Research Partners

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- Alvaro Aytes Institut d'Investigació Biomèdica de Bellvitge, Program Against Cancer Therapeutic Resistance / Prostate Cancer Lab, Barcelona, Spain
- Theodore Alexandrov EMBL-Heidelberg, Structural and Computational Biology / Spatial Metabolomics Lab, Heidelberg, Germany
- Cristina Müller, Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institut, Zürich, Switzerland
- Sylvia LeDevedec, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands
- Rosalyn Adam, Urological Diseases Research Center, Boston Children's Hospital, Boston, USA
- Thomas Grewal, Faculty of Pharmacy, University of Sydney, Sydney, Australia

### Research Profile

#### *Genito-Urinary (GU) Cancer Research Group*

Our research is focused on the role of cancer stem cell and the supportive stroma in the progressive and metastasising GU cancers. We are establishing a personalized GU platform that well integrates effective therapeutic treatments for individual patients, by developing and optimizing different near-patient models (in vitro, in vivo, ex vivo). This platform consists of 1. Patient derived organoids (PDOs), which facilitates the integration of genomic, transcriptomic, proteomic and metabolomics data with drug screening of patients' tumor samples, 2. Patient derived xenografts (PDXs), that allow the growth of tumor material 3. Zebrafish model that allows the (fast) assessment of the metastatic potential of the individual PDO lines.

#### *Bladder Dysfunction Research Group*

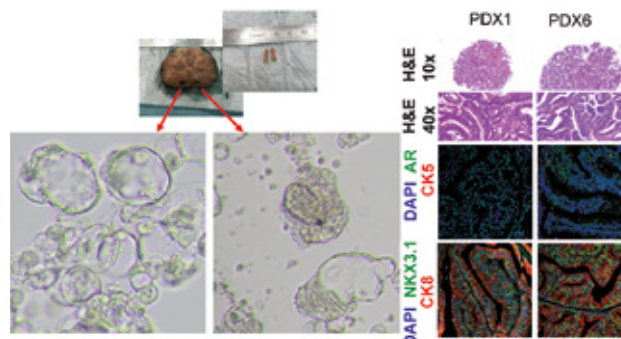
Lower urinary tract dysfunction, characterized by urgency, frequency and incomplete emptying, has multiple causes including bladder outlet obstruction and neurological diseases including spinal cord injury. Our group has pioneered the study of the role of miRNAs in the pathogenesis of lower urinary tract diseases. Our experimental approach combines the analysis of human biopsy material with the in vitro cell-based models. Altered miRNAs serve as biomarkers and might be used to optimise the timing of treatment, and we determined combinations of 3 mRNAs and 3 miRNAs sufficient to discriminate between bladder functional states. We are currently quantifying these miRNAs in urinary exosomes with the aim of developing a non-invasive tool for reliable diagnosis of bladder dysfunction.

### Teaching Profile

The Genito-Urinary group participates in University teaching programs for students of medicine, biomedicine, veterinary medicine and biology.

### Highlights 2018

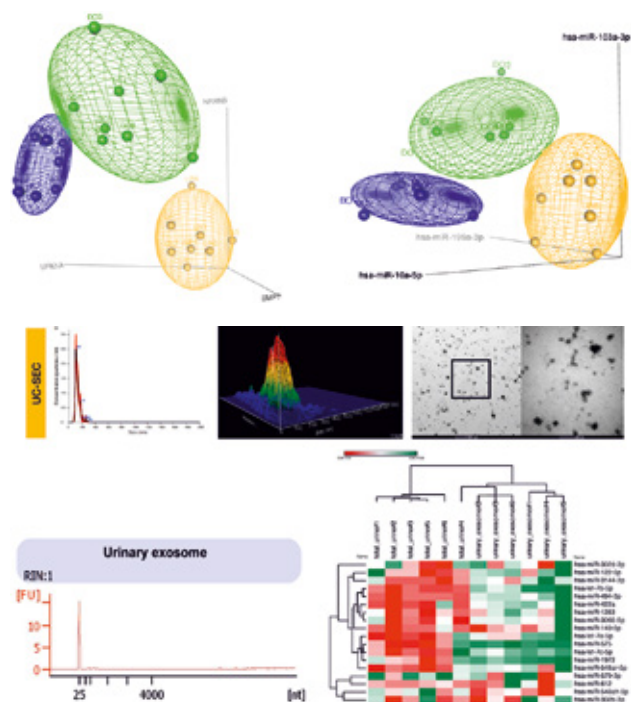
The use of preclinical models is a core component in every aspect of translational cancer research ranging from efforts to understand the biological basis of the disease to the development of new treatments. A major goal of our work has been the understanding of tumor heterogeneity, its role in cancer progression and the development of novel therapies. In order to achieve this, we have used multiple distinct preclinical models including organoids, ex vivo maintenance of needle biopsies, zebrafish xenografts, and microvasculature grown on a chip. These complementary models are robust, fast and provide personalized, clinically relevant information regarding metastasis initiating cells (MICs) and therapy response (Zoni et al. 2017). We have generated patient derived organoids (PDOs) and patient derived xenografts (PDXs) of primary and metastatic PCa and other malignancies or tumor types (Karkampouna et al. 2018). We have also developed and implemented a clinically relevant culture system for studying tumor tissue ex vivo. This technique allows cultivation of tumor slices and needle biopsies in a tissue culture setting without loss of normal architecture, viability, proliferative properties, or expression of specific markers. We have shown that the effects of drug treatment in this system are consistent with those observed on organoids (in vitro) and PDXs (in vivo).



Organoids generated from different lesions of prostate. PDX generated from needle biopsies of penile metastasis from PCa

We have customized a microvasculature-on-a-chip device to mimic the bone microenvironment as a model to study cancer cell extravasation. This methodology is complemented by in vivo characterisation of tumorigenic properties of organoid-forming cells in zebrafish xenografts.

Assessment of specific molecular alterations in the bladder wall could aid diagnosis and optimize timing of treatment. We validated the biomarkers for distinguishing urodynamic BOO phenotypes in an independent patient cohort before and after TURP and found mRNA and/or miRNA combinations, sufficient to accurately discriminate between urodynamic phenotypes before and after relief of obstruction. Specific miRNA and mRNA signatures present a potential tool to evaluate disease progression during BOO and the symptom recovery after surgery. In order to facilitate the assessment of the bladder function, relevant for diagnostic of LUTS and obstruction, we developed an optimized ultracentrifugation and size exclusion chromatography approach for highly reproducible isolation for 50-150 nm uEVs, corresponding to the exosomes, from urine. We profiled the miRNA content of uEVs and total urine from the same samples with the NanoString platform and validated the data using qPCR.



Scatterplots show high discriminative potential of mRNA and miRNA signatures. Urinary exosome isolation and characterization.

We have validated pathway analysis and confirmed the role of TNF-alpha as a major driver of pathological changes, including the loss of contractility, during BOO. Compensatory up-regulation of important miRNAs, decreased by TNF application, might have therapeutic potential.

### Selected Competitive Grants

- Swiss National Science Foundation (grant No. 31003A\_169352; 310030\_175773/1; 320030\_179265)
- HORIZON 2020 (Marie Skłodowska-748836 - STOPCa):
- Novartis (grant No. 17B076)
- PHRT (301)
- KWF (grant No. UL2015-7599)

### Selected Publications

- Karkampouna S, van der Helm D, Gray PC, Chen L, Klima I, Grosjean J, Burgmans MC, Farina-Sarasqueta A, Snaar-Jagalska EB, Stroka DM, Terracciano L, van Hoek B, Schaapherder AF, Osanto S, Thalmann GN, Verspaget HW, Coenraad MJ, Kruithof-de Julio M. CRIPTO promotes an aggressive tumour phenotype and resistance to treatment in hepatocellular carcinoma. *J Pathol.* 2018 Jul;245(3):297-310. doi: 10.1002/path.5083
- Gheinani AH, Vögeli M, Baumgartner U, Vassella E, Draeger A, Burkhard FC, Monastyrskaya K. Improved isolation strategies to increase the yield and purity of human urinary exosomes for biomarker discovery. *Sci Rep.* 2018 Mar 2;8(1):3945. doi: 10.1038/s41598-018-22142-x
- Koeck I, Hashemi Gheinani A, Baumgartner U, Vassella E, Bruggmann R, Burkhard FC, Monastyrskaya K. Tumor Necrosis Factor- $\alpha$  Initiates miRNA-mRNA Signaling Cascades in Obstruction-Induced Bladder Dysfunction. *Am J Pathol.* 2018 Aug;188(8):1847-1864. doi: 10.1016/j.ajpath.2018.05.008
- Zoni E, Chen L, Karkampouna S, Granchi Z, Verhoef EI, La Manna F, Kelber J, Pelger RCM, Henry MD, Snaar-Jagalska E, van Leenders GJLH, Beimers L, Kloen P, Gray PC, van der Pluijm G, Kruithof-de Julio M. CRIPTO and its signaling partner GRP78 drive the metastatic phenotype in human osteotropic prostate cancer. *Oncogene.* 2017 Aug 17;36(33):4739-4749. doi: 10.1038/onc.2017.87
- Gheinani AH, Kiss B, Moltzahn F, Keller I, Bruggmann R, Rehauer H, Fournier CA, Burkhard FC, Monastyrskaya K. Characterization of miRNA-regulated networks, hubs of signaling, and biomarkers in obstruction-induced bladder dysfunction. *JCI Insight.* 2017 Jan 26;2(2):e89560. doi: 10.1172/jci.insight.89560

# Department for Visceral Surgery and Medicine

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Visceral Surgery



Prof. Guido Beldi  
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Hepatology



PD Dr. Lukas Brügger  
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Chief Physician  
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Prof. Beat Gloor  
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Chief Physician  
Gastroenterology



PD Dr. Philipp C. Nett  
Senior Physician  
Bariatric and  
Metabolic  
Surgery



PD Dr. Beat Schnüriger  
Senior Physician  
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Prof. Nasser Semmo  
Senior Physician  
Hepatology

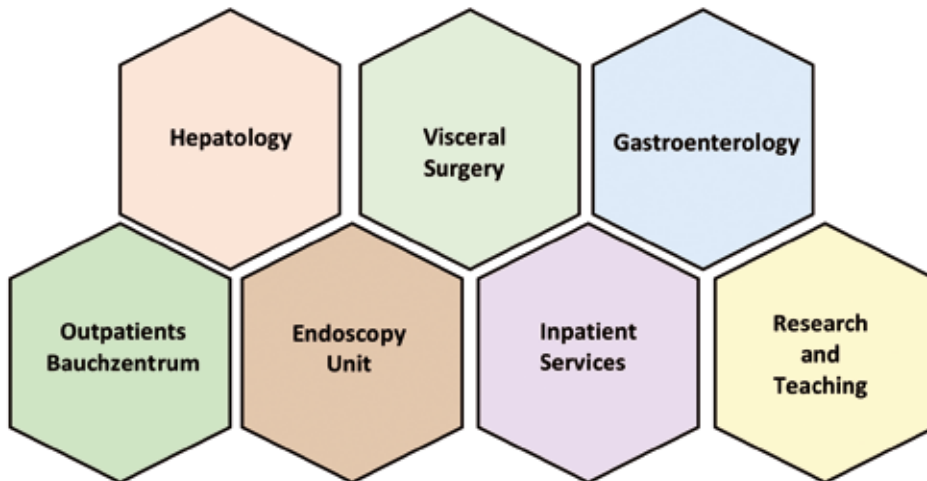


Prof. Deborah Stroka  
Head Research  
Lab Visceral  
Surgery



Prof. Reiner Wiest  
Chief Physician  
Gastroenterology

## Structure Profile



## Research Partners

- ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland
- Systems Biology, ETH Zürich, Zürich, Switzerland
- Department of Surgery, Karolinska Institutet, Stockholm, Sweden
- Molecular Biology, University of Geneva, Geneva, Switzerland
- Department of Psychology, University of Neuchâtel, Neuchâtel, Switzerland
- Clinic for Hepatology, University of Freiburg, Freiburg, Germany
- SCCS (Swiss Hepatitis C Cohort Study)
- FLIP Kohorte (European Fatty Liver: Inhibition of Progression)

- CLIF Consortium (European Foundation for the Study of Chronic Liver Failure)
- VALDIG Consortium (Worldwide Vascular Liver Disease Group)

## Research Profile

The research interests of Visceral Surgery include regenerative medicine and the image guidance of surgical procedures. Specific topics of interest within regenerative medicine include the molecular basis of liver regeneration and sphincter muscle augmentation and regeneration. For both aspects, elements of adult liver stem cell physiology are explored in detail in order to enhance the regrowth of hepatic parenchymal cells, and of the various compartments of sphincter muscle. In Gastroenterology the main research

interests are interactions between bacteria and host in health and diseases. Therefore new genetically engineered bacterial strains have been developed. Such bacteria are used to measure antibody response against commensals, and whether the immune system in the gut 'remembers' previous encounters with commensal bacteria and generates a stronger response on the second occasion (as in medical vaccinations).

We play a leading role in liver disease research (liver cancer, hepatitis, liver cirrhosis, etc.) with the aim of providing our outpatient and inpatient patients with the best possible treatment, and our students and assistants the latest in liver research. Our liver research team covers all areas of hepatology and looks after patients before and after liver transplantation. We explore vascular diseases such as portal hypertension in a cirrhotic and non-cirrhotic liver. A main focus is novel treatments of hepatocellular carcinoma and non-alcoholic steatohepatitis for which we currently include patients in multiple trials.

### Teaching Profile

Training in our clinic is offered with fellowships in visceral surgery, gastroenterology and hepatology. In visceral surgery the fellows receive a training in highly specialized procedures for all visceral and endocrine organs and profit from our team structures. For students we offer a broad spectrum ranging from basic teaching in the field to specialized tuition.

### Highlights 2018

In the past year our collaborators won several prestigious awards and prizes and were engaged in a multitude of panels and committees, both at national and international level. In particular, we are very proud on the international dissemination of our research contributions and on the highly successful acquisition of substantial and prestigious competitive grants from both the SNF and the EU.

### Selected Competitive Grants

- SNF Project Grant 173157 Fuelling hepatic resistance against irradiation-induced damage and disease. (CHF 255'892, Prof Deborah Stroka)
- SNF Project Grant 156882 Impact of structured communication in the operating room on surgical site infections. A multicenter study. (CHF 600'000, Prof Guido Beldi)
- HHMM-Noenates-EU-Grant: (CHF 2'200'000, Prof Andrew Macpherson)
- SNF: The sequence of functional public and private antibody repertoire development in response to transient exposures to non-pathogenic intestinal microbes. (CHF 1'300'701, Prof Andrew Macpherson)
- EU-Grant: Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) (CHF 522'000, Prof Jean-François Dufour)
- SNF: Metabolic control of hepatocytes proliferation in regeneration and cancer (CHF 431'137.00, J-F. Dufour)

### Selected Publications

- Bauché D, Joyce-Shaikh B, Jain R, Grein J, Ku KS, Blumenschein WM, Ganal-Vonarburg SC, Wilson DC, McClanahan TK, Malefyt RW, Macpherson AJ, Annamalai L, Yearley JH, Cua DJ. LAG3(+) Regulatory T Cells Restrain Interleukin-23-Producing CX3CR1(+) Gut-Resident Macrophages during Group 3 Innate Lymphoid Cell-Driven

Colitis. *Immunity*. 2018 Aug 21;49(2):342-352.e5. doi: 10.1016/j.immuni.2018.07.007

- Uchimura Y, Fuhrer T, Li H, Lawson MA, Zimmermann M, Yilmaz B, Zindel J, Ronchi F, Sorribas M, Hapfelmeier S, Ganal-Vonarburg SC, Gomez de Agüero M, McCoy KD, Sauer U, Macpherson AJ. Antibodies Set Boundaries Limiting Microbial Metabolite Penetration and the Resultant Mammalian Host Response. *Immunity*. 2018 Sep 18;49(3):545-559. doi: 10.1016/j.immuni.2018.08.004
- Macpherson AJ, Yilmaz B, Limenitakis JP, Ganal-Vonarburg SC. IgA Function in Relation to the Intestinal Microbiota. *Annu Rev Immunol*. 2018 Apr 26;36:359-38. doi: 10.1146/annurev-immunol-042617-053238
- Studer P, Horn T, Haynes A, Candinas D, Banz VM. Quality of life after hepatic resection. *Br J Surg*. 2018 Feb;105(3):237-243. doi: 10.1002/bjs.10735
- Keller S, Tschan F, Semmer NK, Holzer E, Candinas D, Brink M, Beldi G. Noise in the Operating Room Distracts Members of the Surgical Team. An Observational Study. *World J Surg*. 2018 Dec;42(12):3880-3887. doi: 10.1007/s00268-018-4730-7
- Kohler A, Lavanchy JL, Lenoir U, Kurmann A, Candinas D, Beldi G. Effectiveness of Prophylactic Intraperitoneal Mesh Implantation for Prevention of Incisional Hernia in Patients Undergoing Open Abdominal Surgery: A Randomized Clinical Trial. *JAMA Surg*. 2018
- Saran U, Guarino M, Rodríguez S, Simillion C, Montani M, Foti M, Humar B, St-Pierre MV, Dufour JF. Anti-tumoral effects of exercise on hepatocellular carcinoma growth. *Hepatol Commun*. 2018 Mar 22;2(5):607-620. doi:10.1002/hep4.1159
- Rajasekaran R, Felser A, Nuoffer JM, Dufour JF, St-Pierre MV. The histidine triad nucleotide-binding protein 2 (HINT-2) positively regulates hepatocellular energy metabolism. *FASEB J*. 2018 Sep;32(9):5143-5161. doi: 10.1096/fj.201701429R
- Rodrigues SG, Sixt S, Abrales JG, De Gottardi A, Klingler C, Bosch J, Baumgartner I, Berzigotti A. Systematic review and meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. *Aliment Pharmacol Ther*. 2019 Jan;49(1):20-30. doi: 10.1111/apt.15044
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- Gorecka A, Salemi S, Haralampieva D, Moalli F, Stroka D, Candinas D, Eberli D, Brügger L. Autologous transplantation of adipose-derived stem cells improves functional recovery of skeletal muscle without direct participation in new myofiber formation. *Stem Cell Res Ther*. 2018 Jul 17;9(1):195. doi: 10.1186/s13287-018-0922-1
- Sommer N, Schnüriger B, Candinas D, Haltmeier T. Massive Transfusion Protocols in Non-Trauma Patients: A Systematic Review and Meta-Analysis. *J Trauma Acute Care Surg*. 2018 Oct 29. doi: 10.1097/TA.0000000000002101. [Epub ahead of print]
- Fabbiano S, Suárez-Zamorano N, Chevalier C, Lazarević V, Kieser S, Rigo D, Leo S, Veyrat-Durebex C, Gaïa N, Maresca M, Merkle D, Gomez de Agüero M, Macpherson A, Schrenzel J, Trajkovski M. Functional Gut Microbiota Remodeling Contributes to the Caloric Restriction-Induced Metabolic Improvements. *Cell Metab*. 2018 Dec 4;28(6):907-921.e7. doi: 10.1016/j.cmet.2018.08.005



# University Hospital of Old Age Psychiatry and Psychotherapy

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Prof. Stefan Klöppel  
Director and Head  
of Research



Dr. Jessica Peter  
Group Leader

## Research Partners

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- Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Switzerland
- Inria, Centre Hospitalier Universitaire de Nice, Centre de Memoire, Nice, France
- German Research Center for Artificial Intelligence, Saarbrücken, Germany

## Research Profile

Being a component unit of the University Psychiatry Department (UPD), the University Hospital of Old Age Psychiatry and Psychotherapy attends to psychiatric conditions in elderly patients. The two associated research groups, headed by Prof. Stefan Klöppel and Dr. Jessica Peter, conduct clinically focused research on cognition in healthy elderly as well as patients with neurodegenerative pathologies, with special emphasis on dementia processes. To ultimately improve patient care, our efforts range from providing early and differential diagnoses as well as prognoses with regard to the therapeutic effect by means of MRI-based machine learning algorithms (currently deployed in the interdisciplinary rapport at the local Memory Clinic) to exploring novel personalised treatment options. Concerning the latter, the primary focus is on non-invasive brain stimulation methods, such as auditory stimulation and transcranial electric stimulation (tES), applied independently or in combination with computerized cognitive training. Additionally, we are pursuing more fundamental research questions regarding the underlying neural mechanisms of cognitive processes to later inform practical implementations.

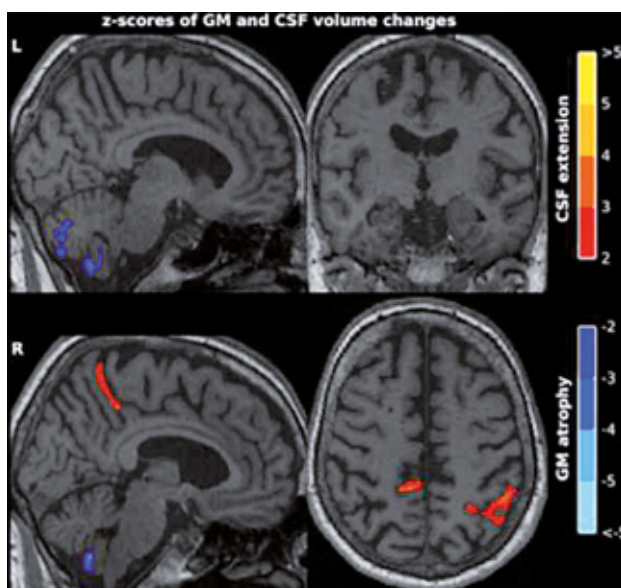
## Teaching Profile

The APP is involved in the University curriculum for students of medicine and psychology, offering master thesis projects for students of medicine and psychology as well as organising seminars and workshops within the curriculum of the Graduate School for Health Sciences (GHS).

## Highlights 2018

*Real-world navigation in amnesic mild cognitive impairment*  
Spatial disorientation, a frequent symptom in Alzheimer's disease (AD) and mild cognitive impairment (MCI), is routinely assessed with 2D visuoconstructive tasks. The question whether the performance in those tasks reliably predicts real-world navigation skills has been addressed in one of our studies. Therein, MCI patients and healthy controls learned an indoor route and were subsequently asked to retrieve the route in physical space, recognize landmarks, and draw the route on paper. Comparisons to standard visuoconstructive tasks revealed that only performance in a more complex visuospatial task served as a valid predictor of navigation performance whereas more standard visuoconstructive tasks did not suffice to detect navigational disabilities. This finding implies that standard clinical assessments need to be extended to increase the sensitivity for predicting navigational impairments in elderly (Peter et al., 2018, Neuropsychologia).

*Visual aid for detection of pathological atrophy in MRI scans*  
The accurate identification of neurodegenerative disorders based on MRI scans relies on the integration of structural information across different brain regions. Since this expertise is often lacking outside specialized centres, this study tested



the value of integrating computer-based visual atrophy ratings to support non-experts in their diagnostic process. To this end, quantitative atrophy scores of grey matter reduction and cerebrospinal fluid extension were calculated and displayed alongside the structural scans. Even though the displayed atrophy scores did not increase the agreement of visual ratings among non-experts, the raters reported subjective benefits on time and confidence. Furthermore, the atrophy scores had a high agreement with the atrophy rating of the experts, implying their usefulness in a fully automated process (Klöppel et al. (2018); *NeuroImage Clin*).

#### *Detection of Delirium in the Emergency Room*

In collaboration with the department of Emergency Medicine, University of Freiburg, Germany, we evaluated two screening test (Nu-DESC and bCAM) in a German speaking emergency room. As both tests showed good specificity coupled with poor sensitivity we suggested modified versions which we intend to evaluate in subsequent studies (Baten et al. (2018); *Acad Emerg Med*).

#### **Selected Competitive Grants**

- Novartis Foundation (Grant #17C195)
- Velux Foundation (Grant #17/1163)
- UniBE Initiator Grant (IG 2018)
- Swiss National Science Foundation (Grant #173880)
- German Alzheimer Forschung Initiative e.V. (AFI-Grant #16040)

#### **Selected Publications**

- Baten V, Busch HJ, Busche C, Schmid B, Heupel-Reuter M, Perlov E, Bricht J, Klöppel S. Validation of the Brief Confusion Assessment Method for screening delirium in elderly medical patients in a German emergency department. *Acad Emerg Med*. 2018 May 8;11:1251-62. doi: 10.1111/acem.13449
- Peter J, Sandkamp R, Minkova L, Schumacher LV, Kaller CP, Abdulkadir A, Klöppel S. Real-world navigation in amnesic mild cognitive impairment: the relation to visuospatial memory and volume of hippocampal subregions. *Neuropsychologia*. 2018 Jan 31;109:86-94. doi: 10.1016/j.neuropsychologia.2017.12.014
- Klöppel S, Yang S, Kellner E, Reiser M, Heimbach B, Urbach H, Linn J, Weidauer S, Andres T, Bröse M, Lahr J, Lützen N, Meyer PT, Peter J, Abdulkadir A, Hellwig S, Egger K. Alzheimer's Disease Neuroimaging Initiative. Voxel-wise deviations from healthy aging for the detection of region-specific atrophy. *NeuroImage Clin*. 2018;20:851-860. doi: 10.1016/j.nicl.2018.09.013
- Klöppel S, Kotschi M, Peter J, Egger K, Hausner L, Frölich L, Förster A, Heimbach B, Normann C, Vach W, Urbach H, Abdulkadir A. Alzheimer's Disease Neuroimaging Initiative. Separating Symptomatic Alzheimer's Disease from Depression based on Structural MRI. *J Alzheimers Dis*. 2018;63(1):353-363. doi: 10.3233/JAD-170964
- Scheller E, Schumacher LV, Peter J, Lahr J, Wehrle J, Kaller CP, Gaser C, Klöppel S. Brain Aging and APOE ε4 Interact to Reveal Potential Neuronal Compensation in Healthy Older Adults. *Front Aging Neurosci*. 2018 Mar 20;10:74. doi: 10.3389/fnagi.2018.00074. eCollection 2018

# University Hospital of Child and Adolescent Psychiatry and Psychotherapy

Universitäre Psychiatrische Dienste, University Hospital Bern  
Bolligenstrasse 111, 3000 Bern 60



Prof. Michael  
Kaess  
Director and  
Head of Research

## Research Partners

- Translational Research Center, University Hospital of Psychiatry, University of Bern, Bern, Switzerland
- Division of Pediatric Hematology & Oncology, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
- Department of Child and Adolescent Psychiatry, Psychiatric Clinics of the University of Basel, Basel, Switzerland
- Institute of Pharmacology and Toxicology, University of Zürich, Zürich, Switzerland
- Developmental Clinical Psychology Research Unit, Faculty of Psychology and Educational Sciences, University of Genève, Genève, Switzerland
- Department of Child and Adolescent Psychiatry, Heidelberg University, Heidelberg, Germany
- Department of Child and Adolescent Psychiatry and Psychotherapy, University of Ulm, Ulm, Germany
- Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria
- Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Australia

## Research Profile

Research at the University Hospital of Child and Adolescent Psychiatry and Psychotherapy addresses the antecedences and consequences of psychiatric disorders with an onset during childhood and adolescence up to emerging adulthood. The main focus of our research is on clinical outcomes and neurobiological mechanisms associated with risk-taking and self-injurious behaviour in adolescents as well as the development of personality disorders. Other projects address the topics: early psychosis, sleep and psychiatric disorders, and Internet-related disorders. We apply research methods across the spectrum of behavioural paradigms, neuroimaging, ecological momentary assessment, psychophysiology and neuroendocrinology in clinical as well as experimental studies.

## Teaching Profile

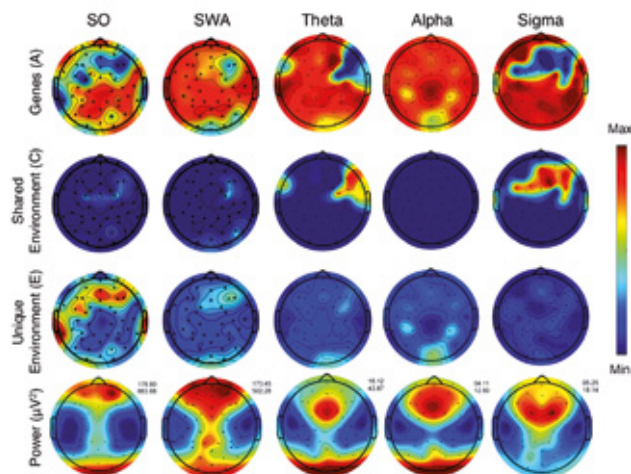
This department participates in University teaching for students of Medicine and Psychology at all educational levels.

## Highlights 2018

### *Brain Region-Specific Inheritance of Sleep Neurophysiology in Adolescence*

During sleep our brain generates unique oscillations that are a marker of thalamocortical and corticocortical functioning and thus provide a unique opportunity to measure

the integrity of these neuronal systems. Understanding the relative contribution of genetic factors to sleep oscillations is important for determining whether they constitute useful endophenotypes that mark vulnerability to psychiatric illness. In this study we use a behavioural genetics approach to examine the heritability of sleep neurophysiology using high-density EEG in a sample of early adolescent twins (n=60; 28 females). Findings show a strong influence of both environmental and genetic factors in shaping sleep oscillations, dependent on brain region. To our knowledge this is the first example of a neural phenotype that exhibits a strong influence of nature in one brain region, and nurture in another. Overall, results from the study highlight the utility of the sleep EEG as a reliable and easy to measure endophenotype during adolescence, assessing disease risk in development prior to the onset of a psychiatric disorder.



Variance (%) explained by additive genetic (A), shared environmental (C) and unique environmental (E) in sleep oscillations.

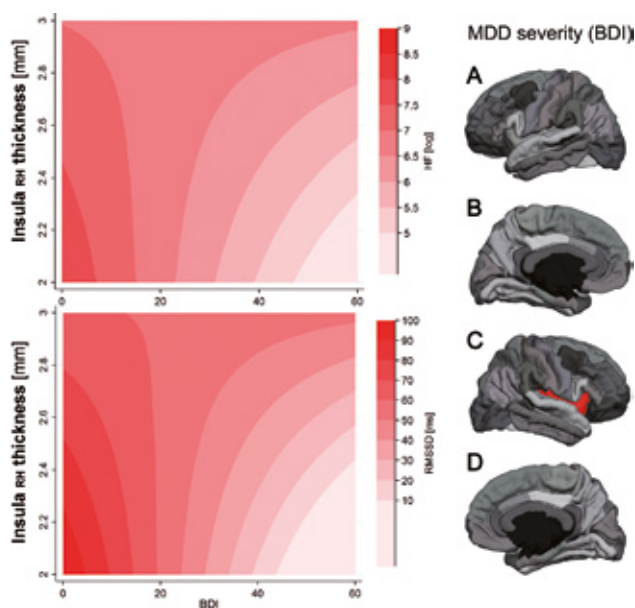
### *Functioning mediates help-seeking for mental problems in the general population*

Absent or delayed help-seeking is considered to aggravate the personal and societal burden caused by mental disorders. In a cross-sectional sample of n = 2683 individuals of the Swiss Canton Bern (16-40 years old, response rate 63.4%) we examined moderators of early help-seeking for mental health problems. Participants were interviewed by telephone for current mental health problems, psychosocial functioning, and help-seeking. In path analyses, help-seeking was associated with the type and severity of mental health problems, and this association was mediated by

functional impairment. Results suggest a gap in help-seeking for mental health problems, such that individuals commonly do not seek help until problems are severe enough to cause problems in occupational and psychosocial functioning. Campaigns promoting early help-seeking, should focus on the importance of psychosocial functioning, alongside early indicators of mental illness.

#### *Brain Structural Concomitants of Altered Autonomic Nervous System Function in Adolescent Depression*

Altered activity of the autonomic nervous system (ANS), indexed by measures of heart rate and its variability (HRV), has been shown in adults with depression. Previously, we were able to replicate these findings in adolescents, illustrating that ANS dysfunction is observed early in the course of depression. However, the underlying neural mechanisms were largely unknown. In a series of studies including adolescents with depression and healthy controls, we were able to show that decreased cortical thickness of the right Insula predicts decreased vagal activity, indexed by HRV, as a function of depression severity. Further, findings in a sub-sample illustrated that alterations of ANS function were reversible after treatment with a selective serotonin reuptake inhibitor, and that changes in ANS function following treatment were mediated by altered brain morphology in areas of the pre-frontal cortex. Results highlight the utility of ANS measures to monitor symptom severity and treatment outcome and provide novel insights into the developmental neurobiology of adolescent depression.



Interaction of Cortical Thickness with Self-Reports of Depression Severity in Predicting Resting State Vagal Activity, indexed by Heart Rate Variability.

#### *Appointment of Dr. Schmidt as Assistant Professor for Clinical Child and Adolescent Psychology*

Dr. Stefanie J. Schmidt was appointed as Assistant Professor for Clinical Child and Adolescent Psychology at the Department of Clinical Psychology and Psychotherapy of the University of Bern in August 2018. Her research will focus on the prevention of mental disorders, the effects of social media use on mental health, and the development of novel internet-based interventions to examine age-specific treatment effects and mechanisms of change.

#### **Selected Competitive Grants**

- Interfaculty Research Cooperation Grant - Decoding Sleep: Sleep subtypes in adolescent depression: Sleep physiology and treatment (PI: Dr. Tarokh)
- SNF Scientific Exchange Grant (182891): The Neurobiological Mechanisms of Auditory Verbal Hallucinations in Youth with Borderline Personality Disorder (PI: Dr. Michel)
- SNF Project Grant (182639): Neurobiological Mechanisms of Pain Dependent Stress-Regulation in Adolescent Non-Suicidal Self-Injury (PIs: Prof. Kaess & Dr. Koenig)

#### **Selected Publications**

- Rusterholz T, Hamann C, Markovic A, Schmidt SJ, Achermann P, Tarokh L. Nature and Nurture: Brain Region-Specific Inheritance of Sleep Neurophysiology in Adolescence. *J Neurosci.* 2018 Oct 24;38(43):9275-9285. doi: 10.1523/JNEUROSCI.0945-18.2018
- Kaess M, Whittle S, O'Brien-Simpson L, Allen NB, Simmons JG. Childhood maltreatment, pituitary volume and adolescent hypothalamic-pituitary-adrenal axis - Evidence for a maltreatment-related attenuation. *Psychoneuroendocrinology.* 2018 Dec;98:39-45. doi: 10.1016/j.psychoneu.2018.08.004
- Kindler J, Schultze-Lutter F, Hauf M, Dierks T, Federspiel A, Walther S, Schimmelmann BG, Hubl D. Increased Striatal and Reduced Prefrontal Cerebral Blood Flow in Clinical High Risk for Psychosis. *Schizophr Bull.* 2018 Jan 13;44(1):182-192. doi: 10.1093/schbul/sbx070
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- Santangelo PS, Koenig J, Kockler TD, Eid M, Holtmann J, Koudela-Hamila S, Parzer P, Resch F, Bohus M, Kaess M, Ebner-Priemer UW. Affective instability across the lifespan in borderline personality disorder - a cross-sectional e-diary study. *Acta Psychiatr Scand.* 2018 Nov;138(5):409-419. doi: 10.1111/acps.12950



# University Hospital of Psychiatry and Psychotherapy

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## Research Partners

- Alzheimer Research Center, Karolinska Institute, Stockholm, Sweden
- Campus Biotech, University of Geneva, Geneva, Switzerland
- Collaborative Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium
- Feinstein Institute for Medical Research, Hofstra University, New York, USA
- Department of Economics, University of Zurich, Zurich, Switzerland
- Department of Neuroscience, University of Groningen, Groningen, The Netherlands
- Department of Psychiatry, Northwestern University, Chicago, USA
- Department of Psychiatry, University of Tokyo, Tokyo, Japan
- Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany
- Department of Psychology, University of Jyväskylä, Jyväskylä, Finland

## Research Profile

The research of the University Hospital of Psychiatry and Psychotherapy is coordinated in the Translational Research Center. Thus, the translational aspect of the research is pivotal and reflected in four research sections, clinical research support, clinical research, systems neuroscience of psychopathology and molecular psychiatry, covering the spectrum from methodological research in neuroimaging, electrophysiology and non-invasive stimulation technologies introducing novel diagnostic criteria improving therapy and prognosis in psychiatry. A large number of independent researchers are covering clinical topics like psychosis, hallucinations, aberrant motoric behaviour, formal thought disturbances, affective disturbances, psychotherapy, sleep and neuroplasticity, molecular psychiatry and addiction. Most of these groups are working transdisciplinary within UPD, Insel University Hospital as well as other faculties at the University of Bern and within international cooperations. Recently it has been

recognized that the currently used diagnostic criteria in psychiatry has led to a deadlock in the clinical development. In the project SyNoPsis we aim to identify neurobiological patterns characteristic for defined psychopathologies and not disease categories and thus to improve prediction outcome and therapy. Innovative therapy studies using novel approaches like transcranial magnetic stimulation as well as deep brain stimulation, partly in close cooperation with the Neurocenter at the Insel University Hospital, have led to alternative therapeutic strategies improving the outcome in patients and reducing the burden of stigma of patients and relatives.

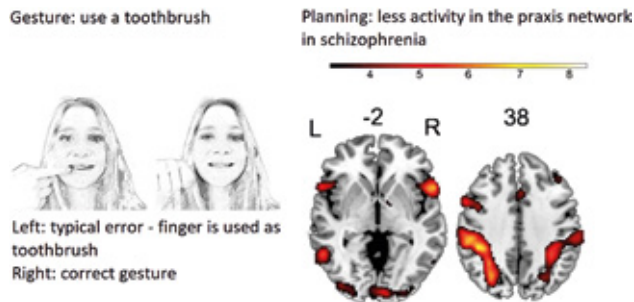
## Teaching Profile

The University Hospital of Psychiatry and Psychotherapy is involved in the University curriculum for students of medicine and psychology including master and doctoral thesis projects. Furthermore, the Department is involved in various Graduate Schools of the University of Bern.

## Highlights 2018

Considering that the unitary model of schizophrenia has failed as a medical diagnosis we focus on a disruptive perspective of psychosis introducing SyNoPsis, a concept where psychopathological symptoms are mapped upon functional neuronal circuits like language, emotion and motor behavior. Several papers have supported our concept. Paranoia, related to emotional perception and behavior, is a central feature of schizophrenia, suggested as determinant for functional outcome. Importantly, paranoid experience is hard to detect in the clinical interview. Our project (SNF Ambizione project grant and the Fondation Frutiger grant) will investigate a hitherto largely neglected topic in neuroscience: the biological mechanism underlying paranoia. We hope this will have heuristic implications by allowing to target paranoia with individualized treatment strategies. Gesturing, in the motor domain, is an important nonverbal communication skill. We detected for the first-time functional neuronal correlates which underlie gesture performance deficits in schizophrenia. The gesture network is hypoactive and subject to limbic

interference during gesture planning in schizophrenia, which contributes to poor gesture performance. In the light of the project results, the research group received the Swiss Brain League Award 2018.



Typical hand gesture error (left) and neural activity during gesture planning in schizophrenia patients compared to healthy controls (right) (Stegmayer et al. 2018).

Schizophrenia is a disorder of high burden for patients, relatives and society. Therefore, one of the aims of our research is an early diagnosis and to start an adequate treatment and thus improving the course of the disease. In a group of subjects with high risk to develop schizophrenia we could demonstrate by MRI that the striatum, an important relay station for neuronal circuits, is already dysfunctional before clinical manifestation and thus a possible early marker for development of schizophrenia.

Regarding sleep animals and humans spend on average one third of their lives in sleep, but its functions remain to be specified. We use non-invasive indices (transcranial magnetic stimulation, TMS, and electroencephalography, EEG) and provide first evidence that sleep promotes both, local strengthening of prior induced plasticity and global network stabilization in the human cortex. The observed reduction of the classic plasticity-stability dilemma might represent an important function of sleep.

In the area of addiction, we could in an EEG study demonstrate that patients with alcohol use disorders suffering from strong craving showed in a Go/No-Go task enhanced and prolonged activation in the posterior cingulate and pre-motor cortical areas when confronted with alcohol-related stimuli. Results indicate a strong conflict making successful behavioral inhibition of urge to drink in high-risk situations more difficult than for patients with low craving. The fMRI part of the study showed comparable results and our group received a poster award at an international congress.

### Selected Competitive Grants

- SNF (320030\_146789, 105319\_159286)
- Schweizerische Stiftung für Alkoholforschung SSA (283)
- University of Bern Interfaculty Research Cooperation - Decoding Sleep (2 subprojects)

### Selected Publications

- Akkus F, Mihov Y, Treyer V, Ametamey SM, Johayem A, Senn S, Rosner S, Buck A, Hasler G (2018). Metabotropic glutamate receptor 5 binding in male patients with alcohol use disorder. *Transl Psychiatry*. 2018 Jan 10;8(1):17. doi: 10.1038/s41398-017-0066-6
- Hubl D, Schultze-Lutter F, Hauf M, Dierks T, Federspiel A, Kaess M, Michel C, Schimmelmann BG, Kindler J (2018). Striatal cerebral blood flow, executive functioning, and fronto-striatal functional connectivity in clinical high risk for psychosis. *Schizophr Res*. 2018 Nov;201:231-236. doi: 10.1016/j.schres.2018.06.018. Epub 2018 Jul 6
- Maier JG, Kuhn M, Mainberger F, Nachtsheim K, Guo S, Bucsenez U, Feige B, Mikutta C, Spiegelhalder K, Klöppel S, Normann C, Riemann D, Nissen C. Sleep orchestrates indices of local plasticity and global network stability in the human cortex. *Sleep*. 2018 Dec 22. doi: 10.1093/sleep/zsy263. [Epub ahead of print]
- Stegmayer K, Bohlhalter S, Vanbellingen T, Federspiel A, Wiest R, Müri R, Strik W, Walther S (2018) Limbic interference during social action planning in schizophrenia. *Schizophr Bull*. 2018 Feb 15;44(2):359-368. doi: 10.1093/schbul/sbx059
- Stein M, Fey W, König T, Oehy J, Moggi F (2018). Context-specific inhibition is related to craving in alcohol use disorders: A dangerous imbalance. *Alcohol Clin Exp Res*. 2018 Jan;42(1):69-80. doi: 10.1111/acer.13532



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