SCIENTIFIC REPORT 2019-2020

SECTION MEDICINE

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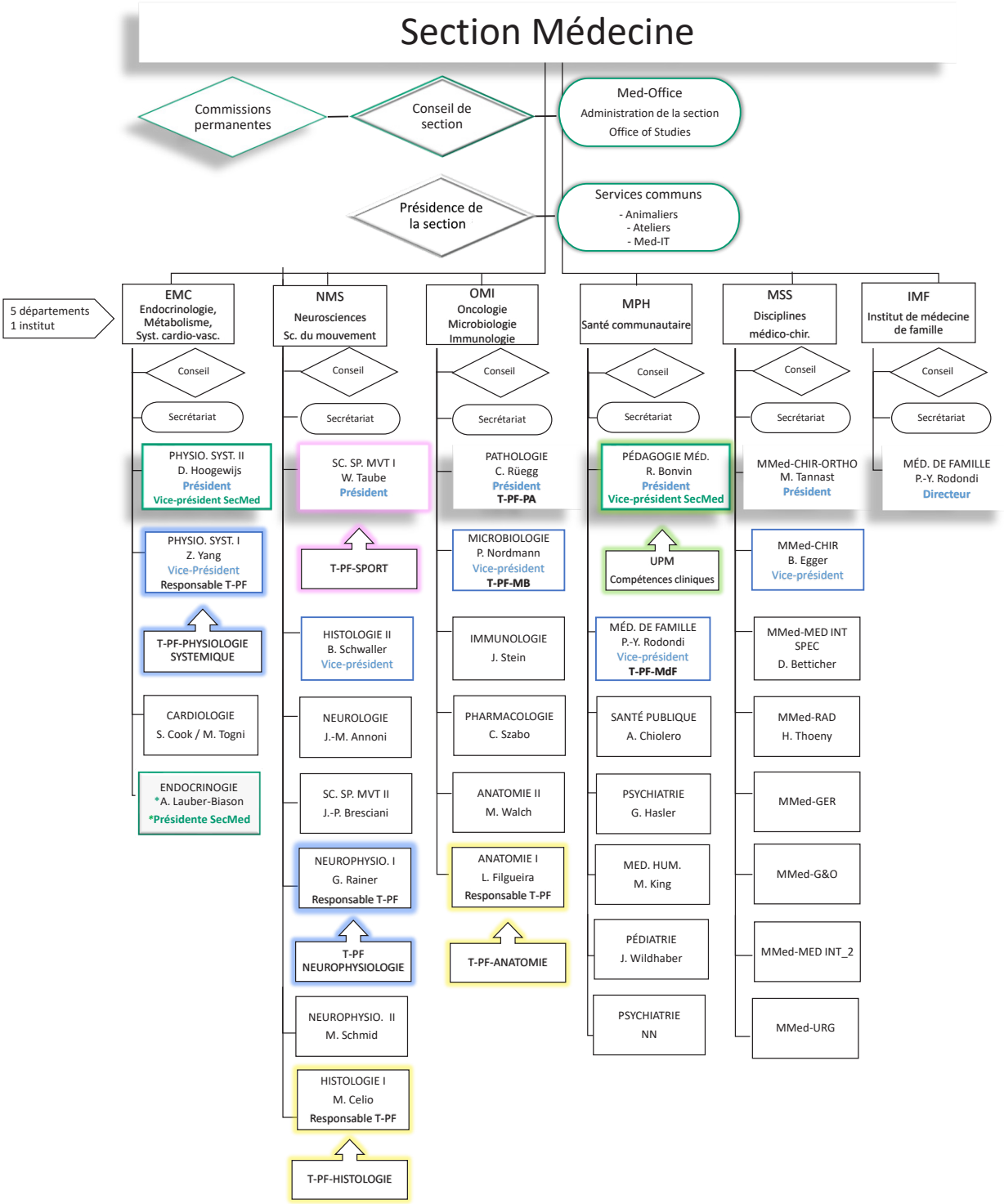

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CONTENTS

When I was asked to write the introduction to this 2019 and 2020 report as President of the Section of Medicine, I was very embarrassed because I could not identify any positive event as if 2019 had been blurred in the COVID-fog that was 2020.
Ignoring this situation is impossible for me and so allow me some perhaps sentimental reflections as a woman and also of a certain age.

Despite the difficulties more than 14 million CHF in Grants were obtained by members of the Section, we acquired a powerful microscope thanks to a SNF- R'Equip funding in collaboration with the Dept. Biology and we could extend our machine park with investments around 150k Swiss Francs.

We introduced novel animal models as alternative to the classical models and we started to use the fruit fly Drosophila melanogaster to study mechanism of disease in humans (Lauber-Biason, EMC). Our new colleague Yann Ravussin (EMC) will increase our knowledge of the mechanisms regulating weight maintenance.
In 2019 we could welcome Mario Prsa as Eccellenza recipient (NMS) , and the new colleagues Michael Schmid (NMS), Moritz Tannast and Berhard Egger (MSS), Gregor Hasler, Arnaud Chiolero and Johannes Wildhaber (MPH) who started in 2019.

The corona pandemic gave us also opportunities like expansion of the NARA (National Reference Center for Emerging Antibiotic Resistance (NARA Prof. Nordmann, OMI https://www.unifr.ch/med/nara/de/), CoronaImmunitas (Profs Chiolero and Rodondi MPH) and the installation of the testing facilities at the HFR.

Our Section, represented by Prof. Pierre-Yves Rodondi, (MPH) is part of the project "Sex and Gender integration in the Swiss Medical Curriculum", This project aims to guide and support the integration of these objectives in the Swiss medical and nursing schools. This is a joint project developed by 6 medical schools (Lausanne, Zürich, Geneva, Fribourg, Bern, Basel) and one nursing school (University of Applied Sciences of Southern Switzerland, SUPSI-DEASS) in Switzerland. It includes two main activities: 1) the development of a structural concept for integration of sex and gender dimensions in medicine and of a core curriculum including specific teaching/learning materials; 2) the creation of a platform to share resources, namely teaching materials, pedagogical tools and literature reviews.
(https://events.unifr.ch/dies/de/news/news/24708/trad?&cat=3).
This initiative is financed by Swissuniversities within the" Diversity, Inclusion and Equal Opportunity (Equity) in University Development 2021-2024" project.

The resilience, courage, determination, and passion of all of us has allowed us to continue to do our research and ensure the teaching of our bachelor's, master's, and post-graduate students.
The tireless work of the members of MedOffice, MedIT and all the fellow professors with their teams have managed to organize a new life, never seen before by our generations.
This is for me the most extraordinary achievement of 2019-2020.

Prof. Anna Lauber-Biason

President Section of Medicine

Cardiovascular, Metabolism and Endocrinology

David Hoogewijs

Integrative oxygen physiology

Stéphane Cook
Mario Togni

Cardiology

Marie-Noëlle Giraud

Cardiac repair cell therapy

Anna Lauber-Biason

Experimental and translational endocrinology

David Hoogewijs

Integrative oxygen physiology

Introduction

The maintenance of oxygen homeostasis is an essential physiological challenge for all large animals. Reduced oxygen supply (hypoxia) induces gene expression alterations, serving for the adaptation to the environmental conditions at the cellular, local and systemic level.

At the cellular level changes in oxygen availability are sensed by a group of enzymes that directly control the cellular response to low oxygen by destabilizing hypoxia-inducible factor (HIF) α subunits, the master transcriptional regulators of the hypoxic response. Our group explores the molecular mechanisms of cellular adaptation to hypoxia and aims to understand the differential regulation between the transcription factors HIF-1 and HIF-2 in response to hypoxia with a strong focus on distal regulatory regions and oxygen-dependent erythropoietin transcription.

At the systemic level oxygen transport and storage is assured via heme-containing globins. These oxygen-binding proteins are among the most intensively studied of all proteins. The field has been revolutionized recently by major advancements in our understanding of these proteins. Genomic information accrued over the last 20 years has greatly expanded the established repertoire of mammalian globins, beyond the familiar hemoglobin and myoglobin. Using a wide variety of molecular techniques complemented by bioinformatical approaches we investigate the regulation and physiological role of novel oxygen-binding proteins.

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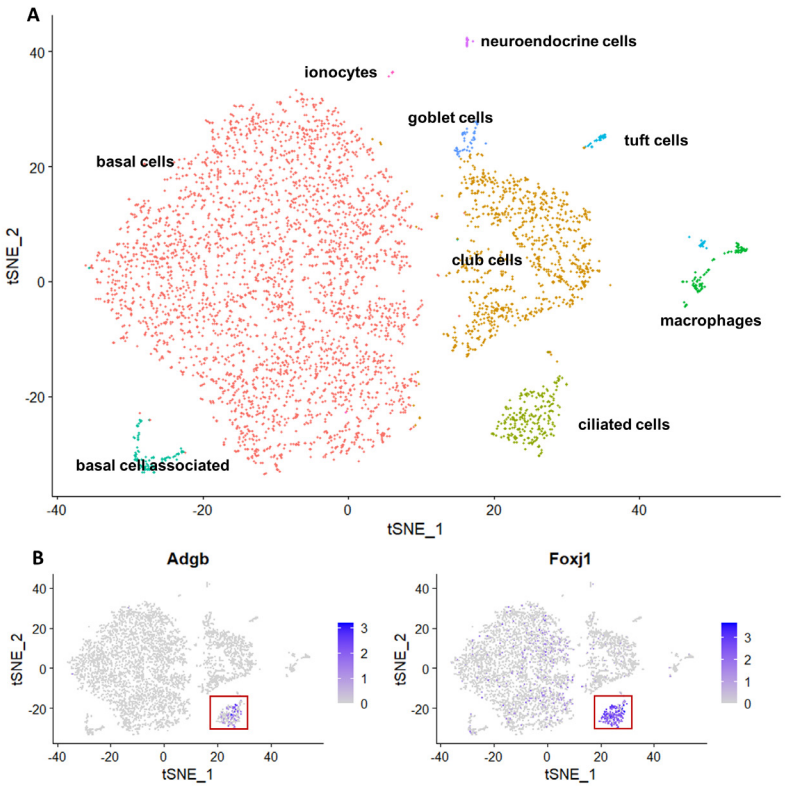
Novel oxygen-binding globins

Globins are small globular metallo-proteins containing a heme prosthetic group, by which they can reversibly bind gaseous ligands like O_2, CO and NO. Most known globins fulfil respiratory functions. Over the last two decades evidence has accrued indicating that globins exhibit additional, novel functions as enzymes, sensors and signaling molecules (Keppner et al. 2020). Genomic analyses have considerably altered and extended our view of the globin family in mammals, leading to the discovery of novel globin types like neuroglobin and cytoglobin. More recently, we identified androglobin (ADGB) as fifth mammalian globin, with most abundant expression levels in testis. Remarkably, ADGB has a chimeric nature with an N-terminal calpain-like domain and its internal globin domain is circularly permuted, an unprecedented feature in the globin field. Ongoing research, funded by the German Research Foundation, the SNSF and the NCCR Kidney.CH aims at elucidating the physiological role of this novel globin type.

Single-cell RNA-sequencing data analysis from mammalian tissues revealed that -in addition to testes- ADGB is prominently expressed in the female reproductive tract, lungs and brain, specifically being associated with cell types forming motile cilia. Correlation analysis suggested co-regulation of ADGB with FOXJ1, a crucial transcription factor of ciliogenesis. Investigating the transcriptional regulation of the ADGB gene, we characterized its promoter using epigenomic datasets, exogenous promoter-dependent luciferase assays, chromatin immunoprecipitation assays and CRISPR/dCas9-VPR-mediated activation approaches, all confirming a FOXJ1-dependent regulation. The complex transcriptional regulation of the ADGB locus was further illustrated by identifying a distal enhancer, responsible for synergistic regulation by FOXJ1 and RFX2, another key transcription factor in ciliogenesis. Furthermore, cell culture studies indicated an ADGB-dependent increase in the number of ciliated cells, suggesting a ciliogenesis-associated role of ADGB in mammals (Koay et al. *in press*).

Additional mammalian globin studies identified cytoglobin (CYGB) as implicated in chronic kidney disease. By using a Cygb-deficient mouse model we demonstrated a Cygb-dependent reduction in renal function, coinciding with a reduced number of podocytes. Employing numerous podocyte cellular models, we could show that CYGB-deficient cells display an increase in cell death, accumulation of ROS, an impaired cellular bioenergetic status and upregulation of multiple genes involved in apoptosis and redox balance, indicating an anti-oxidative role of CYGB in podocyte cell lines (Randi et al. 2020).

Figure 1. Clustering analysis of single cell RNA-Seq data from murine lungs.

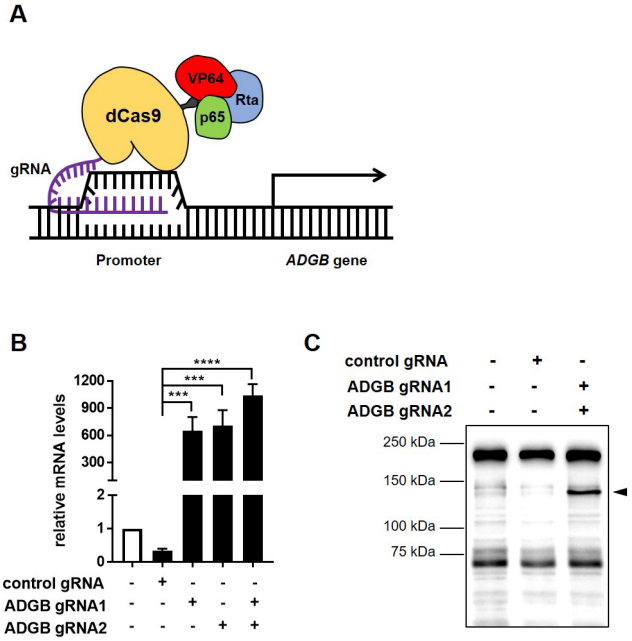


*(**A**) tSNE (t-distributed stochastic neighbor embedding) representation of cell clusters (**B**) Visualization of all clusters expressing mRNA of Adgb and Foxj1. Adgb expression is restricted to ciliated cells in murine lung epithelia.*

Hypoxia-dependent gene regulation

An additional research theme of our group represents the study of various aspects of the oxygen sensing pathway. Hypoxia stabilizes HIFα subunits which together with the constitutive HIFβ subunit form the active HIF-1 and HIF-2 transcriptions factors, inducing several hundred genes following a drop in oxygen availability. While HIF-1α is ubiquitously expressed and regulates a broad variety of target genes, HIF-2α expression is more specific and regulates erythropoietin (Epo) (Watts et al. 2020). Recently, we found that multiple, distal and proximal, hypoxia response elements cooperate in oxygen-regulated *EPO* gene expression and that *EPO* regulation in renal cells may have more in common with neuronal cells than with hepatic cells, illustrating the context-dependent complexity of *EPO* regulation (Orlando et al. 2020).

Figure 2. CRISPR/Cas9-based activation of the ADGB promoter.



*(**A**) Graphical illustration of the dCas9-VPR system displaying the tripartite VPR activator consisting of VP64-p65-Rta activation domains fused in tandem to nuclease-deficient dCas9. Guide RNA (gRNA) sequences direct dCas9-VPR to the endogenous ADGB promoter region, leading to the recruitment of transcriptional machinery for gene activation. (**B**) HEK293 cells were transfected with dCas9-VPR along with ADGB promoter-targeting gRNAs (gRNA1 and/or gRNA2), and relative ADGB transcript levels were quantified by RT-qPCR using a negative control gRNA as reference. Single-guide activation of the ADGB promoter with gRNA1 and gRNA2 results in substantial increment in ADGB transcript levels. Simultaneous expression of gRNA1 and gRNA2 leads to synergistic activation of endogenous ADGB expression. Data represent mean ± S.E.M. ***p<0.001, **** p<0.0001. (**C**) Immunoblotting of protein lysates from HEK293 cells after gRNAs-dCas9-VPR-activation detects endogenous ADGB expression (arrow).*

Selected Publications

Keppner A, Maric D, Correia M, Koay TW, Orlando IMC, Vinogradov SN, **Hoogewijs D.** *(2020).*

Lessons from the post-genomic era: globin diversity beyond oxygen binding and transport. Redox Biol. 37:101687.

Randi E, Vervaet B, Tsachaki M, Porto E, Vermeylen S, Lindenmeyer MT, Thuy LT, Cohen CD, Kistler A, Devuyst OD, Szabo C, Kawada N, Hankeln T, Odermatt A, Dewilde S, Wenger RH, **Hoogewijs D**. *(2020).*

The anti-oxidative role of cytoglobin in podocytes: implications for a role in chronic kidney disease. Antioxid Redox Signal. 32: 1155-1171.

Stéphane Cook
Mario Togni

Cardiology

Introduction

Interventional cardiology is a rapidly evolving field that has made considerable progress throughout the last decades. From simple percutaneous balloon dilation of coronary arteries, such as performed in the beginnings of interventional cardiology in 1977, to the implantation of fully bioresorbable coronary stents, these advances have allowed to optimize patient care and significantly diminish dismal clinical events as e.g. cardiac death or myocardial infarction.

Despite of the multitude of innovations in the field, some challenges remain yet to be opposed: ranging from prevention of coronary artery disease over an optimization in treatment of patient subpopulations to adverse clinical events related to coronary device implantation.

This research is multifaceted, includes preclinical and clinical research.

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Clinical Research (Research Leader - PD Dr. Serban Puricel)

During the years 2019 and 2020 the unit continued its heavy involvement in international multicenter randomized controlled trials and large-scale registries. Several subgroup analyses and sub-studies from e.g. SENIOR, EVOPACS and BIOSCIENCE were published over the course of the last 2 years.

The unit conducted a randomized controlled trial investigating the efficacy of a handheld ECG-device for the detection of AF in patients in hospital without a prior diagnosis of AF. The final results will be published in 2021.

Registry data were analyzed to publish a quantitative analysis of the local STEMI network (EVALFAST). Furthermore, analyses regarding bleeding outcomes in patients undergoing PCI and particularly in those patients at high bleeding risk were carried out and are currently being prepared for publication. The safety and efficacy of various intracoronary devices for the treatment of coronary artery disease was assessed using data from the local Cardio-FR registry.

In the face of the COVID pandemic, the research unit has devoted time and effort to better understand the cardiovascular impact and implication of this novel disease. The research is primarily focused on the role and utility of biomarkers in the management of COVID patients. So far, several of the unit's publications have contributed to the growing body of evidence regarding COVID such as interesting COVID cases or e.g. the utility of detecting antibodies to the novel coronavirus in cardiology caregivers. A comprehensive analysis scrutinizing the characteristics of cardiovascular diseases during COVID and the potential role of related biomarkers is currently ongoing.

Preclinical Research (Research Leader – PD PhD Marie-Noëlle Giraud)

An acute cardiac ischemic injury damages the myocardial tissue and has serious consequences including an impairment of the ventricular function as well as a chronic remodelling of the heart, that finally lead to life-threatening heart failure (HF). HF had become a rapidly growing public health issue with an estimated prevalence between 1.3 to 6.7% globally. The prevention and management of chronic HF urgently requires new therapeutic approaches. The expected success of novel therapy are increased exercise performance and quality of life of the patient, a reduced rate of rehospitalization and mortality, as well as a delay or suppression of cardiac remodelling and consequent end-stage HF. To address the increasing demand for HF treatment, we investigate cell-based therapy strategies. A large number of clinical trials for cell therapy has flourished for the past two decades and have revealed several challenges. Ongoing still opened questions are related to the source of the cells, their delivery mode and their survival, the patient selection, the mechanistic understanding of the biological effect and finally the efficacy of the treatment.

The heart has a low capacity to regenerate. For adult heart, a cellular turnover rate of 0.3 to 1% per year has been evaluated. The failure to generate sufficient cardiomyocytes to replace the lost ones limits the regeneration of the cardiac contractile mass after injury cardiac injury. The loss of a large area of contractile myocardium progressively leads to heart failure. There is an urgent need for novel drugs and therapies for the development of a curative treatment aiming to increase the regeneration of the cardiac myocardium and stabilization or even reversal of heart failure.

Our research team assesses therapeutic strategies to improve cardiac prognosis after MI.

We have assessed the epicardial administration of different cells/matrix combinations in a rodent model of myocardial infarction. We have evidence that the extent of the therapeutic effects depends on the nature of the matrix and its capacity to trigger the cell secretome. We have identified fibrin glue as a bioactive matrix that triggered the bone marrow-derived cell (BMCD) and potentiated their regenerative capacity. We showed that infarcted animals treated with a biopatch (BP) and composed of BMDCs and a fibrin-based substrate demonstrated an improved ejection fraction and a decreased infarct size. In parallel, we validated an in vitro functional assay that evaluates the cardiac regenerative potential of different cell and matrix combination. Using the in vitro model, we showed that the impact on BP on cardiac repair is mediated by the innate immune response. BP alleviates the balance of pro-inflammatory to anti-inflammation macrophage.

The potential of modulating the inflammatory status of the infarcted heart is promising to promote the repair of the damaged myocardium.

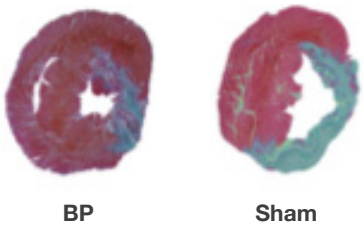

Figure 1. *Goldner Staining of a cross section of an infarcted heart treated with cell/matrix biopatch (**BP**) or no treatment (**sham**) and showing a reduced fibrotic scar after BP treatment.*

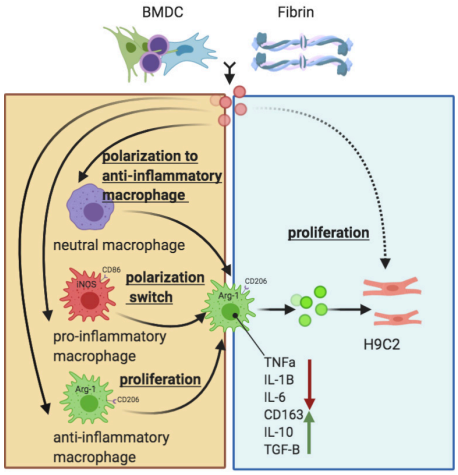

Figure 2. *Role of cells (BMDC) and matrix (fibrin) in cardiac repair. Fibrin primed cell-conditioned medium stimulated (i) the anti-inflammatory macrophage proliferation, (ii) the phenotype switch of macrophages towards an anti-inflammatory phenotype. The proliferation of cardiomyoblasts is augmented by the secretomes of cell/fibrin and anti-inflammatory macrophages.*

Selected Publications

Patet C, Ryckx N, Arroyo D, **Cook S**, *Goy JJ. (2019).*

Efficacy of the SEPARPROCATH® radiation drape to reduce radiation exposure during cardiac catheterization: A pilot comparative study. Catheter Cardiovasc Interv. doi: 10.1002/ ccd.28130.

Zellweger M, Xiao Y, Jain M, **Giraud MN**, *Pitzschk, A, de Kalbermatten M, Berger E, van den Bergh H,* **Cook S**, *Wagnières G (2020).*

Optical characterization of an intra-arterial light and drug delivery system for photodynamic therapy of atherosclerotic pllaque. Appl Sci. 10: 4304.

Frobert A, Ajalbert G, Valentin J, **Cook S**, **Giraud MN**. *(2019).*

High-resolution ultrasound imaging system for the evaluation of the vascular response to stent or balloon injuries in the rabbit liiac arteries. Animal Models in Medicine and Biology. http://dx.doi.org/10.5772/intechopen.88656.

Schukraft S, Mancinetti M, Hayoz D, Faucherre Y, **Cook S**, *Arroyo D, Puricel S. (2019).*

Handheld ECG tracking of in-hospital atrial fibrillation the HECTO-AF trial clinical study protocol. doi: 10.1186/s13063-019-3189-7.

Anna Lauber-Biason

Experimental and Translational Endocrinology

Introduction

Sex development is a complex process involving various genes and hormones (Fig. 1). Disorders/differences of sex development (DSD) in patients are heterogeneous and not as rare as previously thought since genital anomalies occur in 1:3500-5000 births. Several challenges delay progress and the lack of a proper model system for the single patient severely hinders advances in understanding these diseases. Mouse models are often not entirely appropriate, making innovative approaches for the interpretation of whole exome/genome sequencing an urgent priority. We exploit the versatility of induced pluripotent stem cells (iPSCs) and the largely untapped potential of the fruit fly, *Drosophila melanogaster*, for functional investigation of findings from next-generation sequencing.

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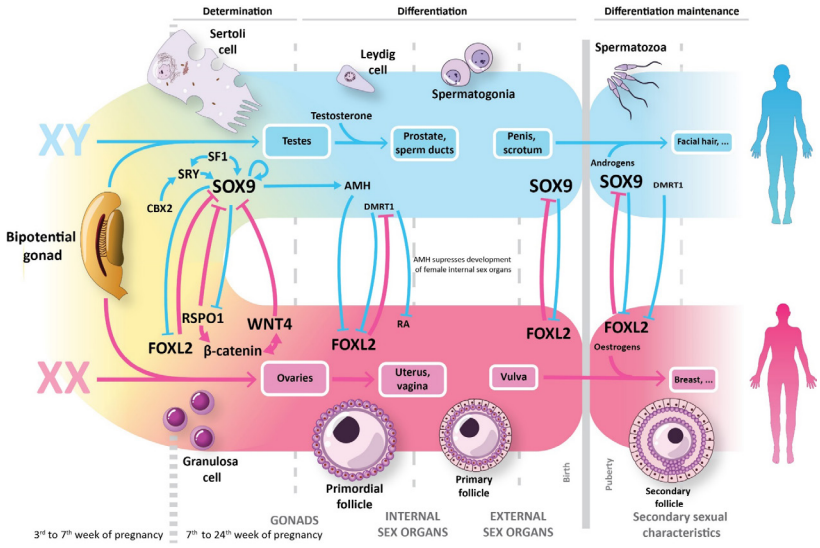
Figure 1. Human sex development.



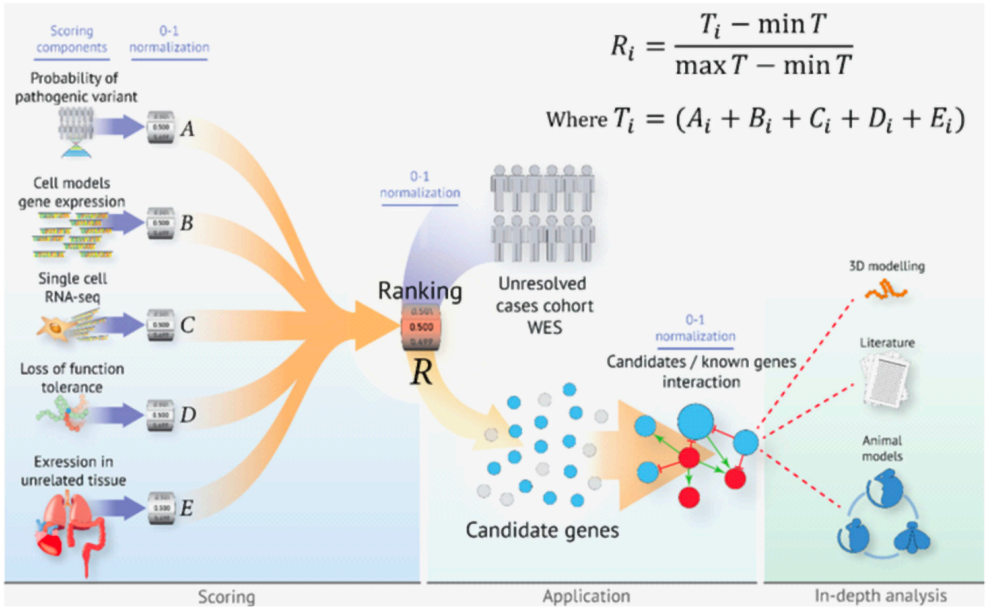
In blue the male pathway, in pink the female. Abbreviations: AMH: Anti-Müllerian Hormone. CBX2: Chromobox2; FOXL2: ForkheadboxL2; RSPO1: Root-plate specific Spondin1; SF1/ NR5A1: Steroidogenic Factor 1; WT1: Wilms' Tumour suppressor 1; SOX9: SRY- box9; SRY: Sex determining Region Y; WNT4: Wingless Type MMTV integration site family, member 4; FGF9: Fibroblast Growth Factor 9; GATA4: GATA binding protein 4.

Selected Research Results :

Combining big data science with clinics: Novel approach for understanding human sex development and its variants

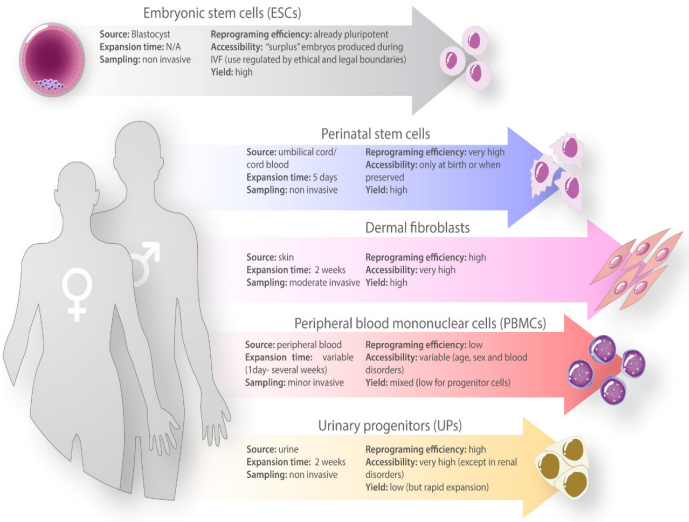
Whole exome sequencing (WES) revolutionized clinical genetics in patients with differences of sex development (DSD). However, the value of WES relies on our ability of interpreting it correctly, which in DSD is complicated by our incomplete understanding of the mechanisms involved. Once the known factors are excluded, the challenge is to "prune" the big data sets and identify the best candidates for further studies. Thus, we created an algorithm that scores potential candidates combining RNA-Seq and single cells transcriptomics of human male gonadal cells we created by differentiation of iPSC (see below), WES data from our cohort of genetically male (46,XY) DSD-patients and connections to sex-development relevant networks. This translational approach advances our knowledge of human sex development and potentially improves diagnosis and management of its variants.

Figure 2. Schematic representation of the scoring system.



Differentiation of human induced pluripotent stem cells into functional gonadal cells

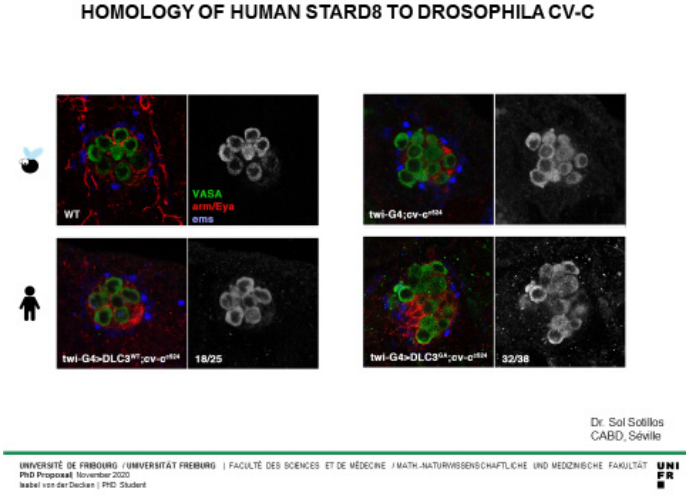
Sertoli and granulosa cells are main players in the gonads development and their study may shed light on disorders of sex development. We succeeded in differentiating Sertoli-like cells from fibroblast-derived iPSCs and granulosa cells from urinary progenitor cells. These gonadal cells are an excellent source of patient-specific Sertoli and granulosa cells that could be of paramount benefit for both basic research and personalized medicine in sex development and reproductive medicine.



Drosophila melanogaster as an unconventional model to study human sex development.

We continued in our translational approach by combining clinical/genetic data from patients and basic research. When the traditional mouse model we created failed to recapitulate the human phenotype, we recreated a mutant phenotype present in three DSD patients in Drosophila melanogaster.

We found gonadal defects in male fly embryos similar to those in patients and are currently dissecting the possible mechanism leading to the gonadal defect. Given the relative simplicity of genetic manipulation in flies and the collaboration with a strong Drosophila team at the Faculty (Simon Sprecher's group) we use the Drosophila model to screen the consequences of genetic variants found in patients with DSD.



Selected Publications

Sproll P. Eid W, **Biason-Lauber A**. *(2019)*

CBX2-dependent transcriptional landscape: implications for human sex development and its defects. Sci Rep. doi: 10.1038/s41598-019-53006-7.

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The transcriptional regulator CBX2 and ovarian function: A whole genome and whole transcriptome approach. Sci Rep. doi: 10.1038/s41598-019-53370-4.

Rodriguez D, **Biason-Lauber A**. *(2019)*

Pluripotent cell models for gonadal Research. Int J Mol Sci. doi: 10.3390/ijms20215495.

Neurosciences and sciences of sport and movement

Beat Schwaller

The role of parvalbumin in neurodevelopmental and neuropsychiatric diseases and of calretinin in cancer biology

Jean-Marie Annoni

Motor language interaction; pain management and neurodegeneration biomarkers

Gregor Rainer

Basal forebrain neural circuit contributions to sensory processing, memory formation and regulation of behavioral state

Michael Schmid

Visual system function in health and disease

Marco Celio

Functional role of two newly recognized brain sites: parvafox and nucleus papilio. Role in defensive behavior and REM-sleep

Lucas Spierer

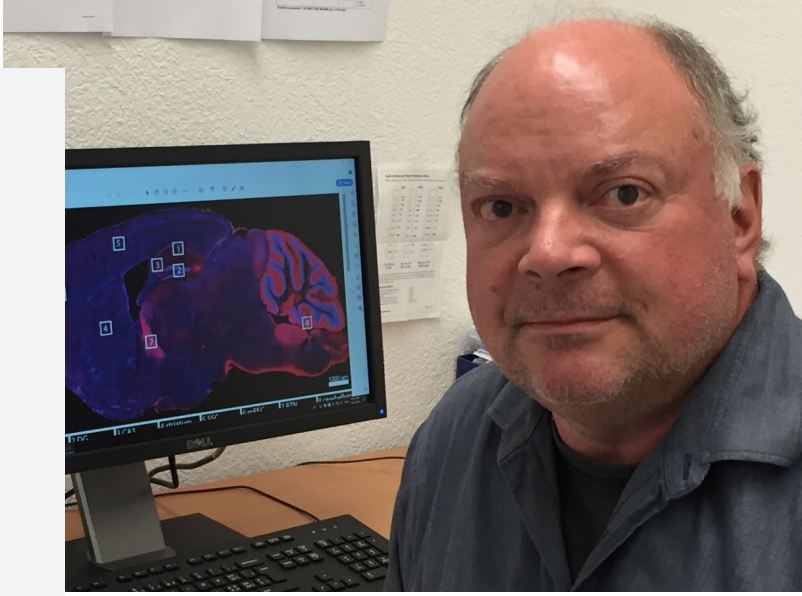
Neurorehabilitation and cognitive enhancement

Mario Prsa

Neuronal mechanisms of upper limb somatosensation and motor control

Beat Schwaller

The role of parvalbumin in neurodevelopmental and neuropsychiatric diseases and of calretinin in cancer biology



Introduction

Ca^{2+}-binding proteins including parvalbumin (PV) and calretinin (CR) mostly function as modulators of intracellular (cytosolic) Ca^{2+} signals. CR has additional Ca^{2+} sensor roles by interacting with target proteins, e.g. Ca^{2+} channels. In the brain, these 2 proteins exist in largely non-overlapping populations of functionally distinct GABAergic interneurons.

In **Topic 1**, we investigate the role of CR in malignant mesothelioma (MM), an asbestos exposure-associated aggressive and still incurable cancer type. CR downregulation by genetic approaches (e.g. shRNA) impairs viability and proliferation of MM cells *in vitro* and *in vivo*, but CR function is difficult to target by pharmacological tools. Thus, we focus on inhibiting the function of septin 7, an interaction partner of CR. Initial results indicate that such a strategy might allow to inhibit growth of MM tumors *in vivo*.

In **Topic 2** we have gained mechanistic insight, how neurons expressing PV (Pvalb neurons) cope with a decrease or complete loss of PV. Reduced levels of PV induce mitochondria biogenesis, organelles with slow-onset Ca^{2+} buffering capacity similar as PV. The increase in mitochondria also leads to augmented dendritic branching and increased ROS production.

In **Topic 3**, we provide evidence that decreased levels of PV lead to autism-like behavior in mice.

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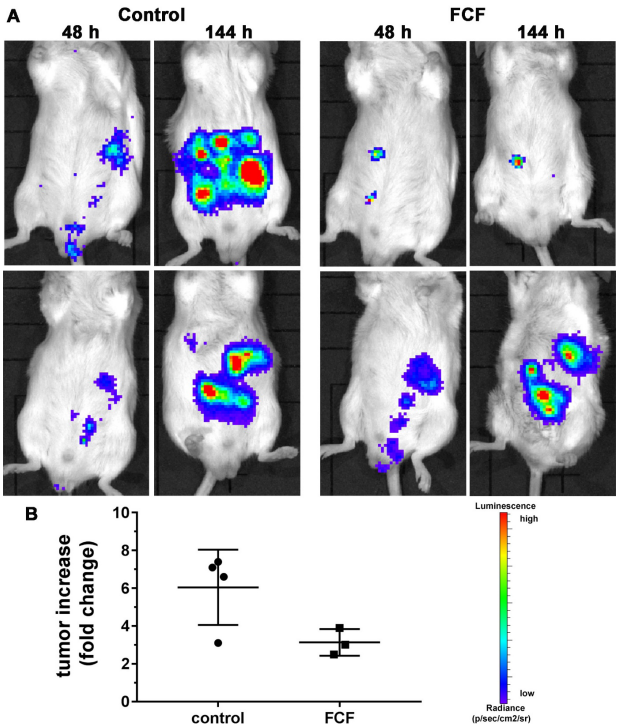
1) In search of novel substances for the treatment of malignant mesothelioma (MM): studies with MM cell lines *in vitro* and *in vivo* experiments with mice

Malignant mesothelioma (MM) is a currently incurable cancer type most strongly associated with exposure to asbestos fibers. Thus, the urgency of finding novel therapeutic approaches to treat mesothelioma is evident. In collaboration with the group of Prof. Christian Bochet, Department of Chemistry, testing the effect of the plant-growth regulator forchlorfenuron (FCF), an inhibitor of septin function(s) in mammalian cells, revealed an impairment of the viability and proliferation of human- and mouse-derived MM cells in a concentration-dependent manner. FCF treatment (IC_{50}: ~20-60 µM) leads to cell cycle arrest and cell death, as does shRNA-mediated downregulation of septin 7, a presumably essential target of FCF. The growth of MM cells is also inhibited in vivo, evidenced by injecting mouse MM cells in the peritoneum followed by FCF application **(Fig. 1)**. FCF's rather low systemic toxicity warrants for an extended search for novel related and possibly more potent FCF analogues to target MM and putatively other septin-dependent tumors.

Figure 1. MM tumor growth in vivo *(Blum, Henzi et al. 2019).*



A) Mice injected with AB12-LV-hRluc MM cells were treated with FCF (or saline in control mice). Tumor growth was monitored by in vivo bioluminescence imaging (BLI) at 48h (before FCF treatment) and at 144h corresponding to 96h FCF treatment. B) The fold increase in BLI signal intensity is lower in FCF-treated mice than in control mice. Color code: from blue (low signal) to red (high signal).

2) Absence of parvalbumin (PV) increases mitochondria volume and branching of dendrites in Pvalb neurons *in vivo*: a point of convergence of autism spectrum disorder (ASD) risk gene phenotypes

Previous work of our group has demonstrated that absence of PV in PV-/- mice, as well as in other cell model systems *in vitro* results in mitochondria upregulation, most likely resulting from the similar delayed Ca^{2+} sequestering/buffering capacity of mitochondria, a function normally exerted by PV. Here, we report that in PV-/- Pvalb neurons present in the somatosensory and medial prefrontal cortex, striatum, thalamic reticular nucleus, and cerebellum, the mitochondria volume is increased. The augmentation is positively correlated with the PV concentration in the corresponding wildtype Pvalb neurons. Moreover, PV-deficiency leads to an increase in dendrite length and branching, as well as thickness of proximal dendrites of selected Pvalb neuron populations **(Fig. 2)**. The extended dendritic branching might lead to hyper-connectivity, a hypothesis previously postulated with respect to ASD etiology (see **#3**).

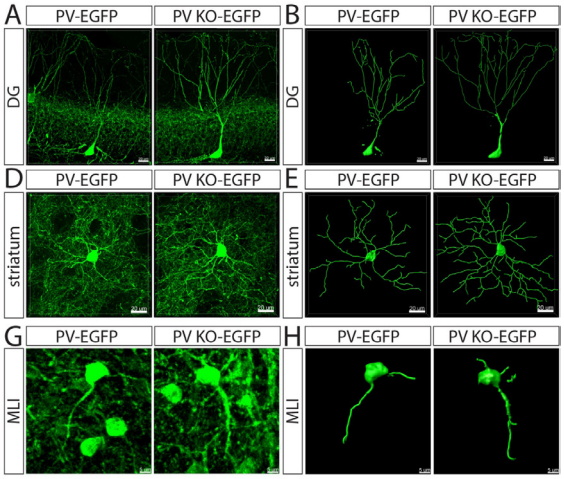
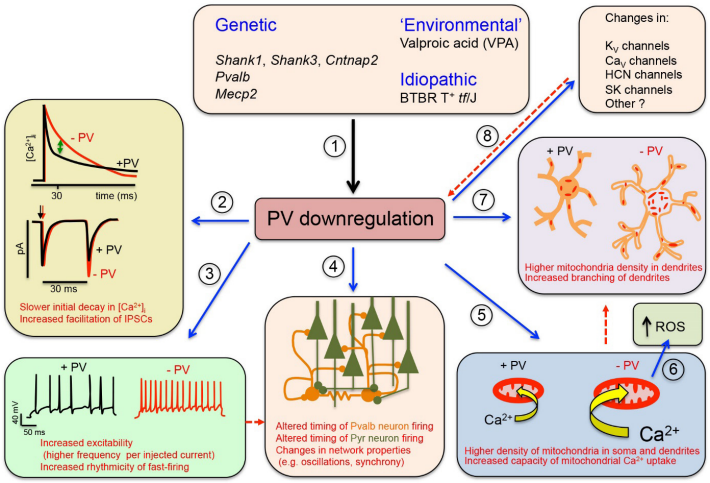


Figure 2. *Increased size of the dendritic tree of PVKO Pvalb neurons in the hippocampal dentate gyrus (DG) (a–b), striatum (d–e), and cerebellar molecular layer (g–h). Confocal images (a,d,g) and 3D-reconstructions (b,e,h) of the same neurons using the Imaris software (image modified from (Janickova, Rechberger et al. 2020).*

3) 'Perturbation experiments' in mice identify Pvalb as an ASD susceptibility gene

Two approaches were used to manipulate PV expression levels in Pvalb neurons of mice *in vivo*, in order to detect changes in ASD-like behavior linked to altered PV levels. In the first, PV expression in PV+/- mice was boosted to ~90% of wildtype mice at PND25 by treatment with 17-β-estradiol (E2) from PND5–15 (Filice, Lauber et al. 2018). In the second we developed a system to efficiently downregulate Pvalb mRNA and PV protein (by ~50% at PND25) in an inducible and moreover reversible manner *in vivo*. In the first case PV upregulation by E2 decreases the ASD-like phenotype observed in constitutive PV+/- mice at PND25, while in the second model, IPTG-induced PV downregulation leads to the appearance of an ASD-like phenotype evidenced in the 'reciprocal social interaction' and 3-chamber assay (Filice, Janickova et al. 2020). These results have led us to formulate 'The Parvalbumin Hypothesis of ASD **(Figure 3)**.

Figure 3. The Parvalbumin Hypothesis of ASD (Filice, Janickova et al. 2020).



__1)__ Decreased PV levels reported in genetic and 'environmental' mouse ASD models __2)__ (Upper) A change in the kinetics of $[Ca^{2+}]_i$ decay caused by absence of PV (red) in Pvalb neurons leads to increased residual Ca^{2+} (green arrow). Differences are largest in the time window of ~20–50 ms after peak $[Ca^{2+}]_i$. (Lower) Larger amounts of residual Ca^{2+} promotes stronger GABA release during further stimulation in this time window, leading to increased facilitation in the paired-pulse protocol. __3)__ Absence of PV alters other electrophysiological properties: it increases the excitability of Pvalb neurons and results in more regular firing within AP trains (reduced 'jitter'). __4)__ Lower PV levels not only affect Pvalb neuron properties, but also of pyramidal cells, and modifies network properties such as oscillations and synchrony. __5)__ Decreased PV levels alter Ca^{2+}-dependent excitation/transcription coupling resulting in increased mitochondria biogenesis. __6)__ Increased mitochondria volume enhances mitochondrial Ca^{2+}-buffering/sequestration capacity, thereby promoting ROS production. __7)__ see __#2__ and __Fig. 2.__ __8)__ Absence of PV perturbs the expression of other putative ASD susceptibility genes. Solid arrows indicate a causal relationship between events—e.g., altered Ca^{2+} concentration (±PV) and short-term modulation of synaptic plasticity. Dashed lines indicate putative (indirect) mechanism(s) via as yet unknown pathways.

Selected Publications

Blum W, Henzi T, Pecze L, Diep KL, Bochet CG, **Schwaller B**. *(2019).*

The phytohormone forchlorfenuron decreases viability and proliferation of malignant mesothelioma cells in vitro and in vivo. Oncotarget. 10: 6944-6956

Filice F, Blum W, Lauber E, **Schwaller B**. *(2019).*

Inducible and reversible silencing of the Pvalb gene in mice: an in vitro and in vivo study. Eur J Neurosci. 50:2694-2706.

Janickova L, Rechberger KF, Wey L, **Schwaller B**. *(2020).*

Absence of parvalbumin increases mitochondria volume and branching of dendrites in inhibitory Pvalb neurons in vivo: a point of convergence of autism spectrum disorder (ASD) risk gene phenotypes. Mol Autism. 11:47.

Jean-Marie Annoni

Motor language interaction; pain management and Neurodegeneration biomarkers

Introduction

Motor language interaction (JM Annoni): A recent and fruitful line of research suggests that higher-order cognitive processes, such as abstract and conceptual thinking, attitude and belief formation or affective valence attribution, are grounded on sensorimotor and spatial processing. In other words, human cognition seems to be largely embodied. Everyday language, for instance, relies heavily on metaphorical borrowings from highly sensorimotor states as well as spatial appraisals, as this very sentence illustrates. The study of bilingual individuals allows us to investigate the scope and limits of such interactions between language, body and space. In particular, we are interested in whether it could be true, in a non-trivial sense, that bilinguals see the world differently whenever they activate their first or they second language.

Pain Perception (J. Chabwine): Pain is a major public health challenge and the large number of analgesic drugs does not prevent from the high treatment failure rate noticed. A mechanism-based classification of pain could probably help improving treatment efficiency. Several neurotransmitters are involved in nociception including GABA (gamma aminobutyric acid), the major brain inhibitory neurotransmitter, which plays a critical role at different pain processing steps. Since brain GABAergic activity could be reliably measured by EEG β oscillations, our aim is to find an EEG biomarker of the GABAergic component of pain.

Alzheimer biomarkers (L Alberi, JM Annoni): Our research also shows that whole unstimulated saliva shares about a third of the proteome with the cerebrospinal fluid, making it suitable to detect non-invasively neural-derived protein that may reflect impinging neuronal deficits. The overarching aim of this research is to identify salivary fingerprints that are predictive of dementia conversion and can serve to implement preventive strategies in the adult population. In fall 2019, the fruitful collaboration between Prof. Annoni and Dr. Alberi-Auber and their dedication to AD research has served as the foundation for a National Task Force for Dementia for more awareness in the civil society and increased federal funding in this field.

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SUPERVISIONS AND RESEARCH ON NEUROETHICS
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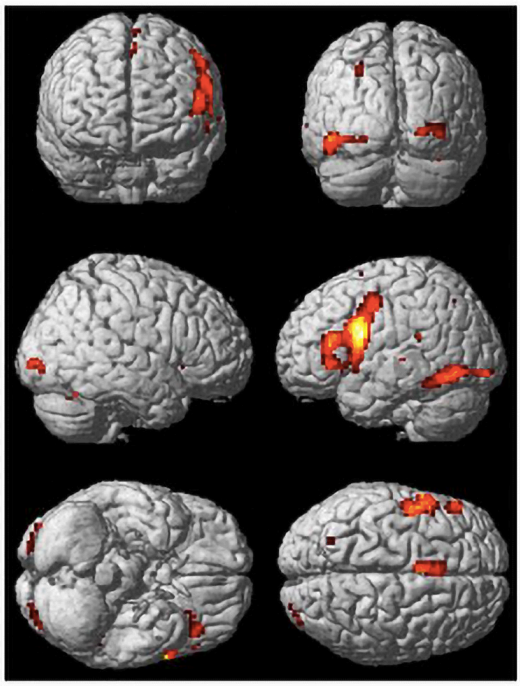
Embodied Semantic:

This project investigating the involvement of the motor cortex in the representation of motor-related vs non-motor related action verbs in L1 and L2, takes advantage of the high spatial resolution of functional Magnetic Resonance Imaging (fMRI).

- Data have been preprocessed and analyzed and a Master thesis has been written on this data.
- We are currently writing the paper to be submitted to a peer-reviewed journal.

1) Main effect of Language in the contrast “L2 vs. L1”, reflected in stronger activation for L2 in the following brain regions:



Brain region	*x, y, z coordinates*	*z-score*
left fusiform (inferior temporal region)	-45, -61, -10	7.64
left inferior frontal gyrus	-51, 5, 26	7.58
left SMA	6, 17, 5	6.26
left superior parietal gyrus	-24, -64, 44	4.98
right cerebellum	27, -64, -25	6.00
right inferior occipital gyrus	21, -94, -4	5.06

A second project investigated the temporal differences in the strength of embodiment in the representation of motor-related vs- non-motor related action verbs in L1 and L2, takes advantage of the high temporal resolution of Electroencephalography (EEG).

A clinical study is currently investigating if a therapy based on embodiment theories improves naming of human motor-related words in chronic bilingual aphasics both in L1 and in L2. It is based on the “action observation therapy” (AOT) that has been used by Marangolo and colleagues (Marangolo et al., 2010, 2012), during which patients are asked to watch video clips of actions and to produce the corresponding verb.

Project D Linguistic, cognitive, and neural predictors in the ability to detect and learn L2 stress: The impact of L1, musical aptitude, phonological awareness, auditory working memory and brain activation (Sandra Schwab & Jean-Marie Annoni)

The main goal was to design and pilot a battery of behavioral and neuroimaging tests that would allow a better understanding of the interindividual variability found in French-speaking participants when learning L2 stress contrasts. Eleven French-speaking participants have completed the entire set of behavioral and fMRI experiments. Concerning behavioral tests, participants performed tests before and after a perceptual training (following the procedure described in Schwab & Dellwo, 2019b). Preliminary results showed that listeners improved by 10% their stress detection performance after a 4-hour training, which was in total agreement with Schwab & Dellwo (2019b). As for fMRI experiments, participants performed a discrimination task where they had to indicate as fast as possible whether two Spanish words were the same or different. The difference between the two words could lie on the final vowel ('vowel' condition; e.g., reparo-repare) or on the stressed syllable ('stress' condition; e.g., reparo-reparó). The two conditions (vowel and stress) were alternatively presented in blocks of 6 auditory word pairs. Preliminary results based on 11 French-speaking participants are described below.

Behavioral results showed first that accuracy was higher for vowel condition (97%) than for stress condition (86%), and that reaction times were shorter for vowel condition (568 ms) than for stress condition (595 ms). These results confirm that stress processing is more difficult than vowel processing, at least for French-speaking participants. Moreover, we can conclude that the task difficulty for stress processing is appropriate since no ceiling effect was observed for stress condition.

As for the activation of brain regions, the comparison between stress and vowel processing revealed that the regions of the bilateral inferior frontal gyrus (IFG) and the bilateral supplementary motor area (SMA) were more engaged during stress processing than vowel processing **(see Figure 1, A)** and particularly in the right hemisphere **(see Figure 1, B)**. This data, compared with other groups'data bringing the question of a certain variability in stress detection, at least for French-speaking listeners.

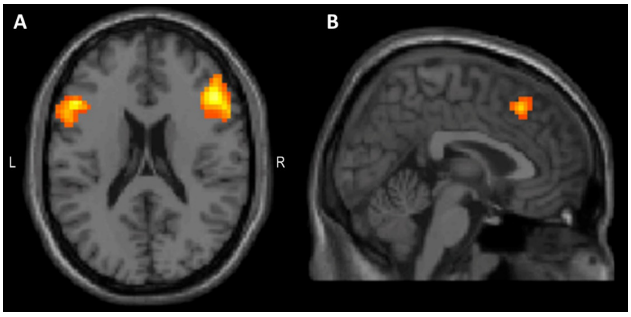


Figure 1. *Comparison of brain activation between stress and vowel processing A. Bilateral inferior frontal gyrus (IFG). B. Supplementary motor area. Image are presented in Neurological convention (L=left hemisphere, R= right hemisphere) with a statistical threshold of* p_{FWE}*<0.05.*

Selected Publications

Bathini P, Foucras S, Perna A, Berreux, JL, Doucey, MA, ***Annoni, JM****, Alberi L. (2020).*

Classifying dementia progression using microbial profiling of saliva Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. doi: 10:10002/dad2.12000.

Maria I, Pestalozzi MI, ***Annoni JM****, Müri RM, Jost LB. (2020).*

Effects of theta burst stimulation over the dorsolateral prefrontal cortex on language switching – a behavioral and ERP study Brain and Language. 205: 104775.

Jost L, Pestalozzi MI, Cazzoli D, Mouthon M, Mueri R, ***Annoni JM****. (2020).*

Effects of continuous theta burst stimulation over the left Dlpfc on mother tongue and second language production in late bilinguals. Brain Topography. 33:504–518.

Gregor Rainer

Basal forebrain neural circuit contributions to sensory processing, memory formation and regulation of behavioral state

Introduction

We are interested in characterizing neural circuits of the basal forebrain in terms of single neuron and mesoscopic network activity patterns such as local field potential oscillations particularly in the gamma band. We focus on sensory processing in the visual modality, but have recently also expanded the scope of our investigations to the auditory system. We perform comparative studies in several mammalian species, while also investigating default mode related and sleep-related activity, as it is known that the basal forebrain can influence behavioral state. We use optogenetics and electrical stimulation for causal manipulation of specific circuit elements, and use sophisticated behavioral methods to quantify how these manipulations impact performance on operant tasks as well as spontaneous behaviors. Our aim is to understand mechanisms in healthy, intact animals and apply this knowledge to disease models, with the long-term goal to contribute to translational development of interventions for sensory and central nervous system dysfunction.

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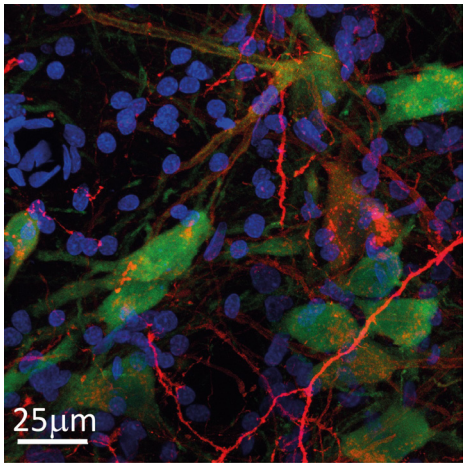
Research activity

Following up on our recent demonstration of very pronounced gamma oscillations in the basal forebrain during default mode behaviors such as quiet wakefulness, we have proceeded to perform causal neural circuit manipulations to examine a potential causal role of the basal forebrain nuclei in regulating default mode behaviors. The basal forebrain contains multiple cell types that modulate cortical as well as subcortical targets, notably including the thalamus and various brain stem nuclei. In one study, we have focused on the parvalbumin positive (PV+) population of GABAergic basal forebrain interneurons of the basal forebrain. We have focused on the MCPO nucleus, which is particularly rich in PV+ neurons, and used cell-type specific Channel rhodopsin expression to specifically upregulate activity in this set of neurons. We found, consistent with our hypothesis, that default mode behaviors were indeed upregulated following optogenetic stimulation, but there was no evidence for modulation of sensory encoding or memory formation. Electrical stimulation of basal forebrain circuits, which is not cell type specific, did however trigger modulations of memory formation in the context of a novelty preference paradigm. We complemented our findings using neurochemical mass spectrometric analyses, where we could demonstrate upregulation of specific bioactive molecules consistent with our behavioral findings. We are at present extending our investigations to a Down syndrome rat animal model together with our collaboration partner Dr. Szabo, allowing us to test hypotheses related to the importance of basal forebrain gamma oscillations in brain function.

In a second recent study, we performed recordings from auditory pathway structures to test the hypothesis that thalamic circuit modulation of the basal forebrain plays a major role mediating its effects in auditory system function. While the direct, corticopetal projections of the basal forebrain are thought to be the main mediators of neuromodulation, the role of thalamic projections are much less studied. Nevertheless, these projections are anatomically known to exist, and could provide a novel site of intervention to aid recovery or restoration in case of compromised sensory system function. We have provided several pieces of evidence using electrical stimulation of the basal forebrain that suggest that indeed the thalamic projections play a much more important role than had been appreciated. We are at present extending these findings using optogenetic activation, which permits dissociating the role of specific pathways by using axonal light illumination. These studies allow more precise characterization of effects associated with individual projections, which we are complementing using behavioral optogenetic experimentation.

Co-expression of PV+ and Channelrhodopsin in basal forebrain.



Cell bodies and processes of PV+ GABAergic neurons shown in green, cell nuclei in blue and expression of Channelrhodopsin in red, which is often localized on PV+ neurons as well as axons.

Selected Publications

Lozano-Montes L, Dimanico M, Mazloum R, Li W, Nair J, Kintscher M, Schneggenburger R, Harvey M, **Rainer G**. *(2020).*

Optogenetic stimulation of basal forebrain parvalbumin neurons activates the default mode network and associated behaviors. Cell Rep. doi: 10.1016/j.celrep.2020.108359.

Azimi H, Klaassen AL, Thomas K, Harvey MA, **Rainer G**. *(2020).*

Role of the thalamus in basal forebrain regulation of neural activity in the primary auditory cortex. Cereb Cortex. doi: 10.1093/cercor/bhaa045.

Michael Schmid

Visual system function in health and disease

Introduction

Michael Schmid has joined the University of Fribourg in 2019, via a joint appointment with Newcaslte University in UK. The research interest of Prof Schmid and his group focuses on delineating the function of the primate visual system in health and under diseased conditions.

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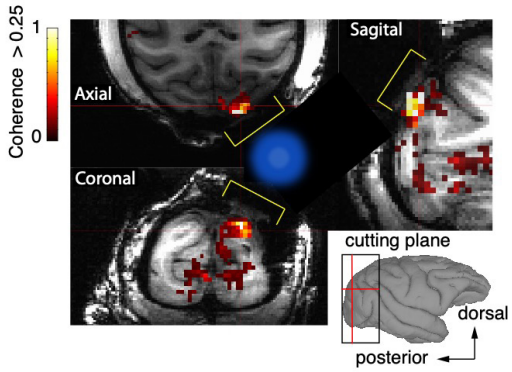
Research activity

Primate vision evolved to enable high-acuity, trichromatic vision with capacity to acquire reading as one of the hallmarks for everyday life. Reading among other visual functions is impaired under a number of different conditions, ranging from retinal disease such as age-related macular degeneration (AMD) to neurological syndromes such as developmental dyslexia. The Schmid lab aims to delineate the fundamental brain circuit operations of the primate visual system that subserve high-acuity vision and participates in various developments aimed at improving visual perception under diseased conditions.

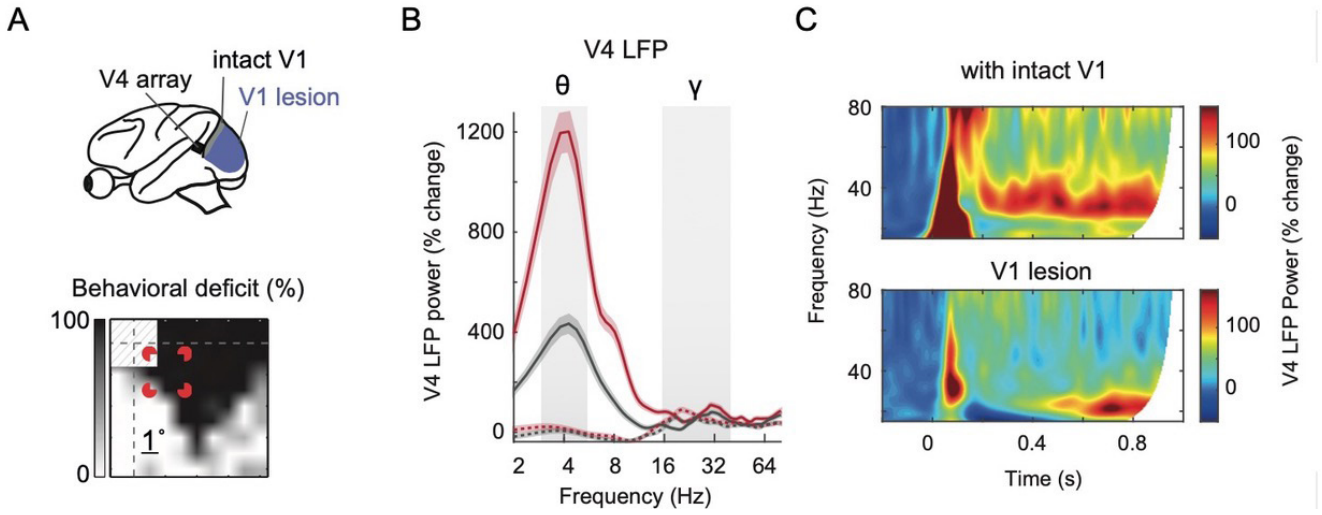
To this end the lab capitalizes on the unique opportunities of the University of Fribourg to investigate vision in non-human primates (NHP) and in parallel in humans. Experiments in NHP use state of the art neuroimaging, electrophysiology and optogenetics to delineate sensory and cognitive influences on neural processing and neural circuit function. Here current projects examine the role of rhythmic brain activity as a possible sampling mechanism in perception and the potential of optogenetic stimulation of visual cortex to artificially induce a visual percept. Outcomes from these investigations often directly motivate studies in humans where the current focus of the lab is on delineating visual and oculomotor deficits in developmental dyslexia and on identifying neural markers that predict visual recovery from hemianopia and cortical blindness.

Figure 1. Neuroimaging of optogenetic stimulation of primate primary visual cortex (V1).



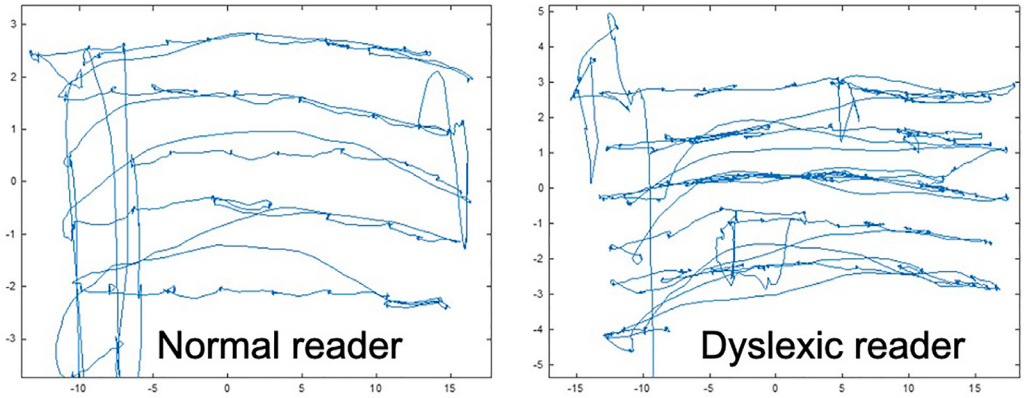
A excitatory optogenetic construct was injected into V1 and LED stimulation was performed to drive optogenetics mediated neural activity. The method of functional magnetic resonance imaging (fMRI) was used to map the location and size of the optogenetic effect in V1 and beyond. This is an important step for measuring the effectiveness of optogenetics and towards evaluating the suitability of the method to elicit artificial visual percepts as part of a visual prosthesis approach.

Figure 2. Measurement of neural oscillations in the intact visual cortex and in a primate model of cortical blindness.



***A**. Upper panel: Neural recordings were performed in visual association cortex (V4) before and after a confined lesion of primary visual cortex (V1). Lower panel: Visual stimulus overlaid on a deficit map that results from the V1 lesion. **B**. Theta (3-8 Hz) and gamma (20- 40 Hz) oscillations in intact V4 to a perceptually relevant (red solid line) vs irrelevant (gray solid line) and in V4 following V1 lesion (dashed lines). Whereas the lesion has a detrimental effect on perceptual signals in the theta range, it affects the gamma range very little. **C**. Gamma oscillations are present, but delayed in primate model of cortical blindness. This finding shows that theta, but not gamma oscillations are important markers of conscious visual perception.*

Figure 3. Comparison of eye movement patterns in normal vs dyslexic readers.



Developmental dyslexia is primarily considered a disorder of linguistic processing. Our research highlights an irregular eye movement pattern of dyslexics during reading suggesting perceptual or motor difficulties in addition. This information might be useful to identify individuals at risk to develop dyslexia early on.

Selected Publications

Kienitz R, Cox MA, Dougherty K, Saunders RC, Schmiedt JT, Leopold DA, Maier A, **Schmid MC**. *(2020).*

Theta but not gamma oscillations in area V4 depend on input from primary visual cortex, Current Biology, in press.

Tremblay S, **Schmid MC**, *Platt ML. (2020).*

An open resource for non-human primate optogenetics. Neuron, doi: 10.1016/j.neuron.2020.09.027.

Rima S, **Schmid MC**. *(2020).*

V1-bypassing thalamo-cortical visual circuits in blindsight and developmental dyslexia, Current Opinion Physiol,

https://doi.org/10.1016/j.cophys.2020.05.001.

Marco Celio

Functional role of two newly recognized brain sites: *Parvafox* and *Nucleus papilio*. Role in defensive behavior and REM-sleep

Introduction

Our research group identified the parvafox nucleus and the *Nucleus papilio* as neuronal identities in the mammalian brain which have not hitherto been described. The parvafox nucleus, located in the ventrolateral portion of the hypothalamus, harbors parvalbumin- and Foxb1-expressing neurons. The parvafox nucleus projects mainly to the dorsolateral quadrant and to the Su3 nucleus of the periaqueductal gray matter (PAG), but also to some other brain regions. Chemogenetic activation of neurons of the parvafox nucleus influences respiratory parameters in a manner that is consonant with defensive behaviors. Optogenetic activation of the axonal terminals in the dorsolateral quadrant of the PAG leads to immobilization.

The *Nucleus papilio* lodged within the dorsal paragigantocelliuliar nucles of the upper brain stem, is composed of calbindin-expressing neurons (NP^{calb}). Axons of the *Nucleus papilio* project mainly to nuclei that control the external ocular muscles (oculomotor, abducens and trochlearis). Optogenetic activation of the cell bodies of the *Nucleus papilio* or of their axonal endings in the oculomotor nuclei, selectively triggers eye movements during REM-sleep.

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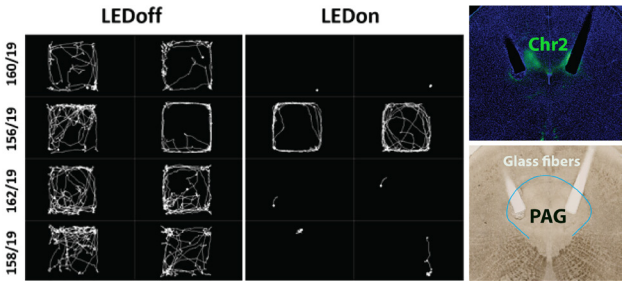
Research Activity

Morphologists have developed a panoply of useful staining techniques to reveal the structure of the brain. To quote Floyd Bloom: “the gains in the brain are mainly in the stain” (1979), thereby indicating that anatomy has been a source of inspiration for scientific inquiries. We have implemented antibodies directed against the calcium binding proteins calbindin (calb) and parvalbumin (parv) as immunologic stains. Using these tools, we have unveiled the existence of two distinct aggregates of nerve cells which are not alluded to in brain atlases. Fifteen years ago, we launched a series of investigations using various techniques spanning morphology, connectivity, phylogeny, gene expression, functional magnetic resonance (fMRI, in humans) and physiology, with a view of understanding the role of these two brain sites.

The parvafox nucleus, a longitudinal stripe in the lateral hypothalamus, is an aggregate of parvalbumin (parvafox^{parv})-, and Foxb1 (parvafox^{Foxb1}) expressing neurons, numbering 400 on each side.

Neurons of the parvafox^{parv} express various markers that typify fast-firing nerve cells and use glutamate as a neurotransmitter. Both the parvafox^{parv} and the parvafox^{Foxb1} expressing neurons project heavily to the Su3 nucleus and the parvafox^{Foxb1} also to the dorsolateral portion of the periaqueductal gray (PAG). We early postulated an involvement of this nucleus in the control of emotions. Tickling-laughter experiments in humans reveal activation of the lateral hypothalamus in fMRI. In mice, whole-body barometric plethysmography combined with chemogenetic neuromodulation disclosed modifications in respiratory patterns of the DREADD-mediated excitation of the parvafox^{Foxb1} nucleus (increases in the number of breaths / minutes, the inspiratory time, the inspiratory flow, the minute volume and the total respiratory time). All of the affected parameters and the direction in which they are affected are in accordance with physiological changes in emotion. Channelrhodopsin (ChR2)-mediated photoexcitation of the Foxb1 terminals in the dorsolateral PAG lead to immobility, the first reaction in freeze-fight-flight behavior **(Fig. 1)**. Other investigators have reported parvafox^{parv} -expressing neurons projecting to the Su3 region of the PAG to exert an analgesic effect. These observations implicate the parvafox nucleus in activities which influence the expression of positive and negative emotions.

Figure 1. Immobility after optogenetic activation of the Foxb1-terminals in the dorsolateral periaqueductal gray (PAG).

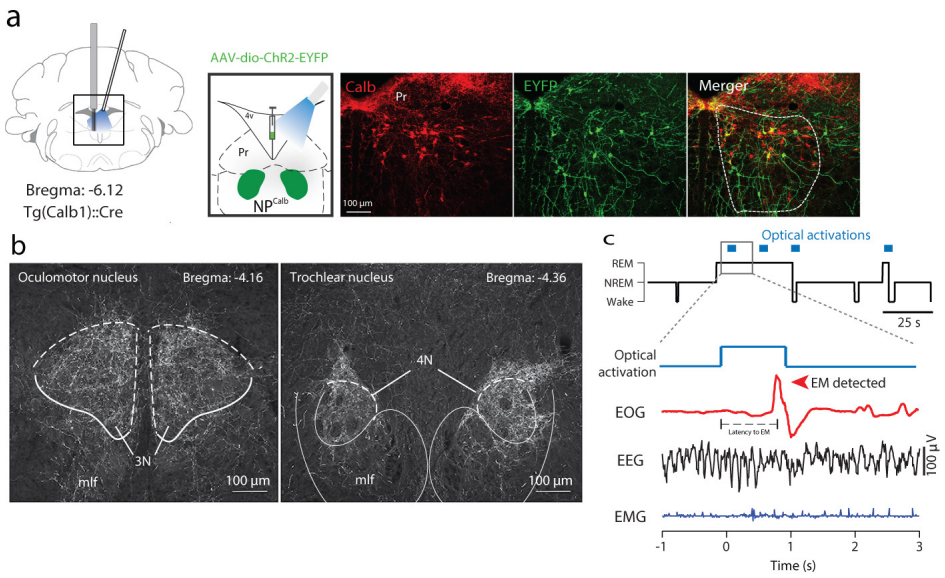


As demonstrated in these track visualizations, a stunning reduction in gross locomotor behavior was observed in 3 out of the 4 ChR2-expressing mice. The left half of the plot displays the two baseline recordings, whereas the right half displays the recordings with photoactivation of ChR2. Right image: optic fiber placement was targeted to the Chr2-expressing Foxb1+ terminals (green) in the rostral PAG.

The other symmetric cluster of bilaterally 400 calbindin-expressing neurons, the "Nucleus papilio" (NP^{Calb}), has the shape of a butterfly and is located at the dorsomedial boundaries of the dorsal paragigantocellular nucleus. It is phylogenetically conserved, and its neurons innervate the three eye-muscle nuclei. In-depth data mining revealed a subpopulation of the calbindin-neurons expressing the peptides CART (cocain and amphetamine regulated transcript) and Nesfatin. During REM- sleep, the firing activity of the opto-tagged NP^{Calb} neurons is augmented relative to that of the other cells. Importantly, the firing rate increases prior to the eye movement of REM-sleep **(Fig 2)**. Together, these data demonstrate that, during REM-sleep, the activity of NP^{Calb} neurons is time-locked to eye movements. The capacity to induce eye movements on command during REM sleep affords a powerful tool for the investigation of their functions.

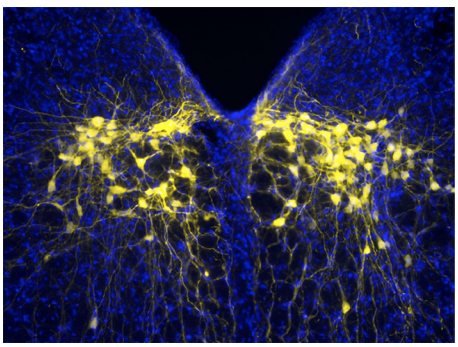
Fifteen years of research into these two anatomical units have enabled us not only to describe them in detail but also to fathom their functional roles using state-of-the-art chemo- and optogenetic techniques. These studies may serve as a model for the dissection of the functional role of aggregates of neurons.

Figure 2. Optogenetic activation of NPCalb neurons induces eye movements during REM sleep.



a) Schematic representations of the stereotactic virus injections in the brain of Calb1: Cre mice. For the optogenetics experiment, tetrodes and optical fiber were placed above the NP^{Calb}. Representative images of coronal sections show expression of ChR2-YFP and Calb in NP^{Calb} neurons. The NP^{Calb} region is delineated with white dashed lines. (b) Dense AAV-GFP expressing axon terminals of NP^{Calb} neurons were found in the oculomotor (3N) and trochlear (4N) nuclei. C) Representative hypnogram of optogenetic activation of NP^{Calb} neurons in vivo (top) together with EEG, EMG and EOG recordings. Red arrow indicates a light-evoked eye movement (EM).

Figure 3. The Nucleus papilio of the brainstem.



Immunofluorescence staining with an antiserum directed against the calcium binding proteins calbindin D-28k.

Selected Publications

Wattendorf E, Westermann B, Fiedler K, Ritz S, Redmann A, Pfannmöller J, Lotze M, **Celio MR**. *(2019).*

Laughter in the air: involvement of key nodes of the emotional motor system in the anticipation of tickling. Soc Cogn Affect Neurosci. 14:837-847.

Girard F, von Siebenthal M, Davis FP, **Celio M**. *(2020).*

Gene expression analysis in the mouse brainstem identifies Cart and Nesfatin as peptides co-expressed in the Calbindin-positive neurons of the Nucleus papilio. Sleep. https://doi.org/10.1093/sleep/zsaa085.

Lucas Spierer

Neurorehabilitation and cognitive enhancement

Introduction

Dr Spierer's Laboratory for Neurorehabilitation Science aims at establishing fundamental models of training-induced behavioral and brain plasticity in the healthy and neurological brain, and on this basis to develop and validate neurophysiologically-informed digital therapeutic interventions for the rehabilitation of clinical populations and to enhance cognition and behavior in healthy individuals.

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We focus on the capacity for cognitive functions to express experience-dependent behavioral and brain plasticity and how plasticity mechanisms can be controlled to help patients recovering after brain lesions, to enhance performance or to restore healthy behaviors in non-clinical populations.

We more specifically investigate the physiopathological and neuropsychopharmacological factors modulating the capacity of cognitive functions to express training-induced functional and structural neuroplasticity. Our modulating factors of interest notably include the effect of aging, post-lesion delays, deep- and surface- brain stimulation and pharmacological agents.

In parallel, and based on the neurocognitive models of brain plasticity we have established over the last 10 years, we develop standalone digital therapeutics rehabilitation and behavioral change software, and validate them with series of randomized controlled trials. We notably collaborate with videogame professionals to improve how our rehabilitation interventions are delivered and to make them accessible online. We also develop closed-loop technology to improve the precision and adaptability across various clinical populations of our interventions.

We are also strongly engaged in improving scientific practice and open science, as notably demonstrated by an adoption of the Registered Report publication format for most of our papers.

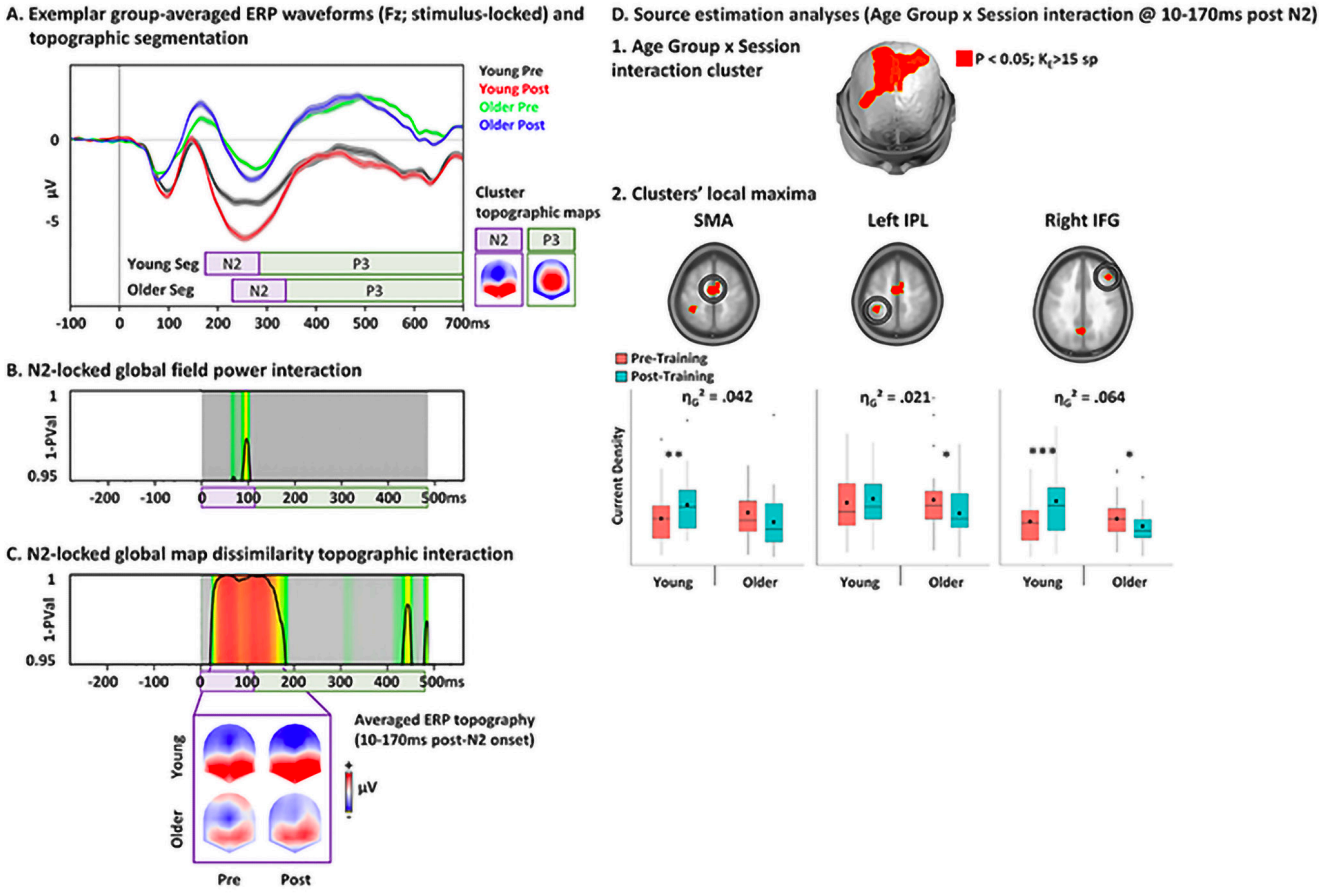

***Figure 1**. Example of Electrical Neuroimaging analyses revealing the variations in the brain responses to a 3-week executive control training intervention in older vs young populations. Age-related structural deteriorations of the frontal brain area modify how the executive control functional networks reacts to cognitive training, thereby demonstrating the state-dependency of executive control plasticity (From our study Najberg et al., 2020 Cerebral cortex).*

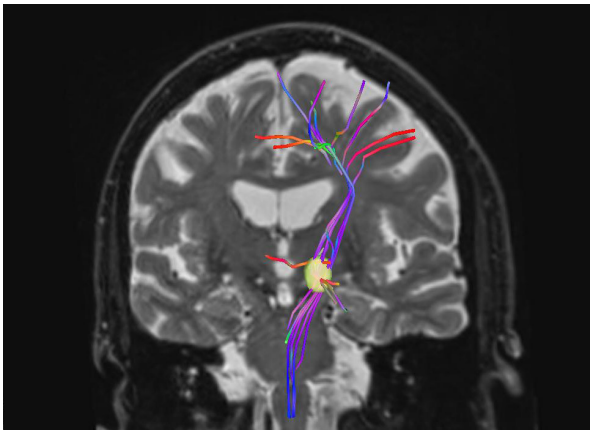

Figure 2. *Estimation of volume of tissue activated by subthalamic nucleus deep-brain stimulation (DBS) in a Parkinson patient, and a reconstruction of the stimulated fibers bundles. The main aims of the DBS projects are to better understand the role of cortico-subcortical pathways in motor control, and to predict the effects of stimulation on motor and non-motor symptoms of Parkinson's disease. We also investigate how gait can be improved with rhythmic auditory stimulations in these patients.*

Selected Publications

Ribordy Lambert F, Wicht CA, Mouthon M, **Spierer L**. *(2020).*

Acute alcohol intoxication and expectations reshape the spatiotemporal functional architecture of executive control, Neuroimage. doi: 10.1016/j.neuroimage.2020.116811.

Najberg A, Wachtl L, Anziano M, Mouthon M, **Spierer L**. *(2020).*

Aging modulates prefrontal plasticity induced by executive control training Cerebral Cortex. https://doi.org/10.1093/cercor/bhaa259.

Mario Prsa

Neuronal mechanisms of upper limb somatosensation and motor control

Introduction

Movements are at the center of all our behavior and accurate movements allow us to properly interact with the world. Loss of movement accuracy occurs in many diseases such as multiple sclerosis, Parkinson's and most often post-stroke, but can also result from autoimmune responses to viral infections and physiological aging. The impairments often have devastating consequences on human experience as they interfere with even the simplest every day activities. To identify the aetiology and gain insight into the pathophysiology of the associated neurological diseases, a fundamental understanding of the underlying neural circuitry is necessary.

The group of Prof. Mario Prsa, who joined the University of Fribourg in 2019, uses state of the art genetic, optical and microscopy tools to study brain mechanisms involved in goal-directed movement control. The main focus of the research is on the adaptation and proprioceptive sensation of voluntary forelimb movements; two physiological processes crucial for maintaining movement accuracy.

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Sensorimotor adaptation

How does the brain ensure that our movements consistently arrive at their intended targets given an almost infinite number of motor contexts, each requiring its own specific pattern of muscle contractions? Despite decades of research, the answer to this basic question remains largely incomplete.

The group of Prof. Prsa aims to identify the neural mechanism in the mouse cerebellum underlying the adaptation of voluntary movements. For this purpose, mice are trained to voluntarily displace a robotic manipulandum with their upper limb and adapt their movements to unexpected force field perturbations. Simultaneously, the activity of genetically labeled neural populations in the cerebellum (climbing fibers, Purkinje cells and deep cerebellar nuclei) are imaged with two-photon microscopy. Once identified, the underlying cerebellar plasticity mechanisms are gated and/or mimicked with real-time optogenetic manipulations to artificially induce and/or suppress learning in a behaving animal.

Proprioceptive sensory system

Most of proprioception is non-conscious as it takes the form of reflex loops between muscles and neurons in the spinal cord allowing us to stand and walk straight. These low-level pathways are well described, but are only one part of the overall connectivity. Proprioceptive sensory neurons, whose cell bodies lie in the dorsal root ganglia also project to segments of the spinal cord that relay the information via ascending pathways through the medulla and thalamus to the somatosensory cortex. This conscious access to proprioceptive information is indispensable for accurately executing planned movements. Despite its importance, the cortical representation of proprioception is very poorly understood. This is a remarkable gap in knowledge given that comparable neuroscientific studies of other sensory modalities (e.g. vision) began some 80 years ago.

The group of Prof. Prsa is developing novel behavioral methods based on robotic control to characterize the neuronal code of conscious proprioception in the mouse somatosensory cortex. In addition to optical imaging of neural populations, the group is developing an innovative approach for selective optogenetic tagging and anatomical dissection of proprioceptors in the mouse forelimb (Golgi tendon organs, muscle spindles and joint mechanoreceptors) using rare earth up-conversion nanoparticles.

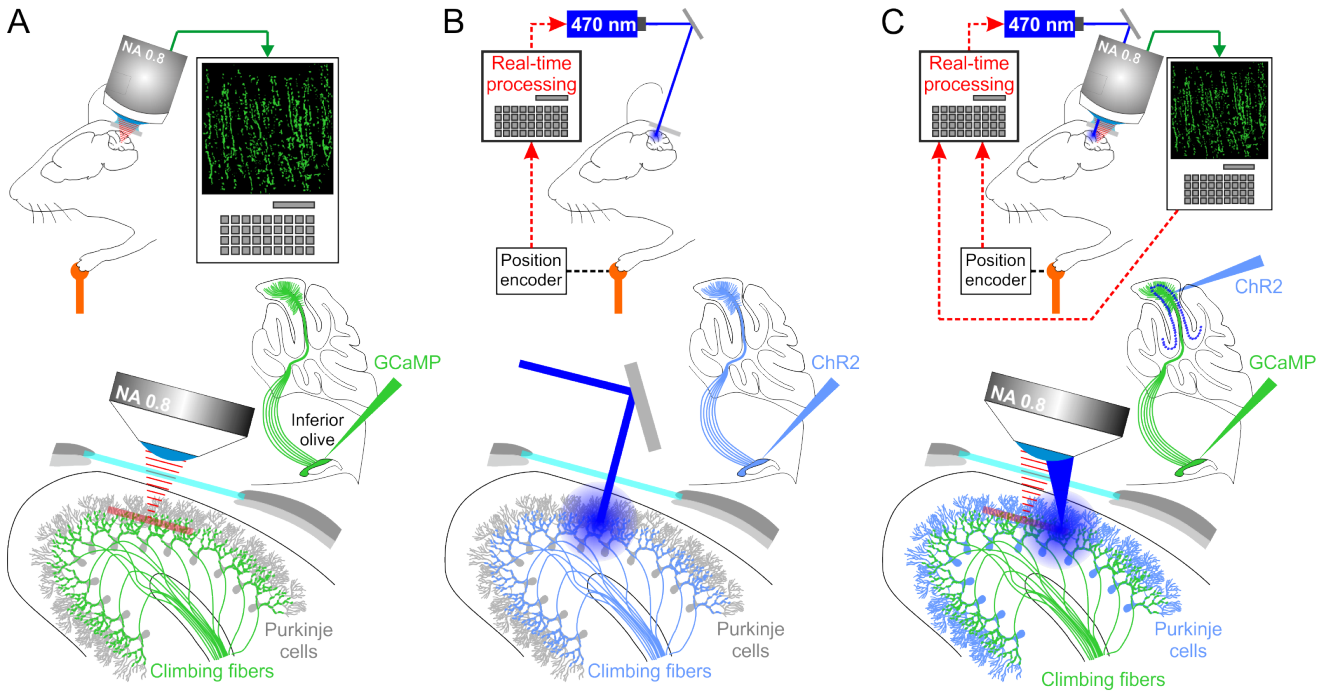


Figure 1. *Population imaging and real-time manipulation of cerebellar activity during upper limb movement adaptation. A: Two-photon imaging of climbing fiber population signals in the cerebellar cortex after transfection of GCaMP in the inferior olive. B: Optogenetic stimulation of climbing fibers controlled in real-time by online analysis of forelimb position after transfection of ChR2 in the inferior olive. C: Real-time gating of climbing fiber-Purkinje cell (PC) plasticity after GCaMP expression in climbing fibers and selective ChR2 transfection in PCs. Online analysis of two-photon images of climbing fiber activity and forelimb position triggers activity dependent optogenetic stimulation of PCs.*

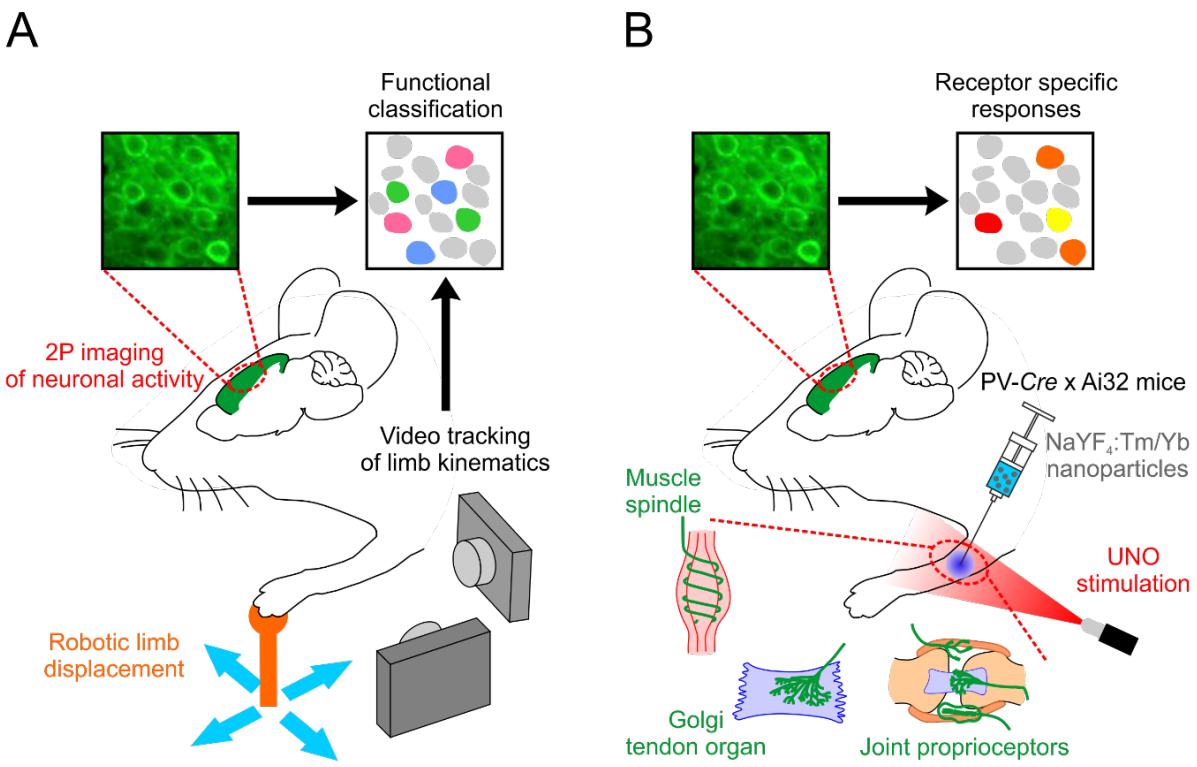


Figure 2. *Functional and receptor specific mapping of proprioceptive responses in the somatosensory cortex. A: Robotic displacement of the forelimb paired with video tracking and two-photon imaging of cortical neural activity with single cell resolution. B: Microinjections of up-conversion nanoparticles in the muscle, tendon or joint capsule allow for a selective optogenetic activation of proprioceptive classes and their subsequent mapping in cortical responses.*

Selected Publication

Prsa M, *Morandell K, Cuenu G and Huber D. (2019).*

Feature selective encoding of substrate vibrations in the forelimb somatosensory cortex. Nature. 567:384-388.

Cancer, Microbiology and Immunology

Curzio Rüegg

Tumor-host interactions in cancer progression and metastasis

Patrice Nordmann

Emerging antibiotic resistance in bacteria

Jens Stein

Exploring tissue-specific $CD8^+$ T cell biology during adaptive immune responses

Csaba Szabo

Biological and pathophysiological roles of labile, diffusible small molecules

Michael Walch

Pierre-Yves Mantel

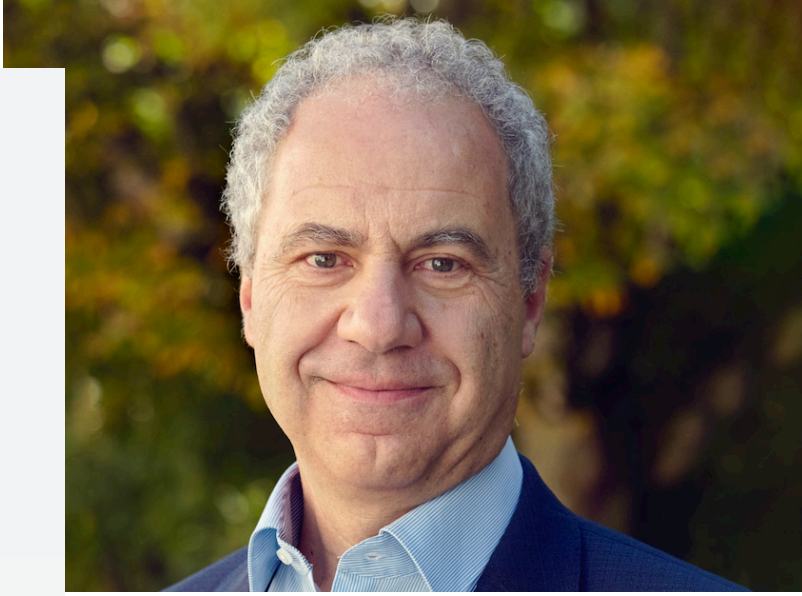
Host-pathogen interactions in the context of bacterial infections and malaria

Luis Filgueira

Clinical anatomy, cell biology and medical education

Curzio Rüegg

Tumor-host interactions in cancer progression and metastasis



INTRODUCTION

Cancer is a genetic disease. Genomic alterations activate tumor promoting genes (a.k.a. oncogenes), such as RAS or PI3K, and/or inactivate tumor-suppressor genes, such as P53 or APC resulting in uncontrolled cell growth and survival. Most of these alterations are the result of intrinsic errors of DNA replication. They can be exacerbated by extrinsic, such as ionizing radiations or chemicals, or intrinsic events, such as chronic infections (e.g. *H. Pilory*), inflammation (e.g. *colitis ulcerosa*), diabetes and obesity. However, in order to generate clinically-relevant tumors progressing toward metastasis, cancer cells have to establish complex heterotypic multi-cellular interactions with its surroundings, the tumor microenvironment (TME). The TME contains many distinct cell types, such as endothelial cells, pericytes, fibroblasts, leucocytes, lymphocytes, and monocytes/macrophages. These cells generate a state of chronic inflammation promoting cancer progression. Genetic tumor cell heterogeneity and TME events cooperate to facilitate cancer cell dissemination to distant organs. Once disseminated, cancer cells adapt to the novel microenvironment through a combination of newly acquired genetic traits and complementary cues provided by the local tissue. Because of this systemic tumor-host crosstalk, cancer should be considered as a systemic disease since its inception. This organism-wide crosstalk opens new diagnostic and therapeutic opportunities.

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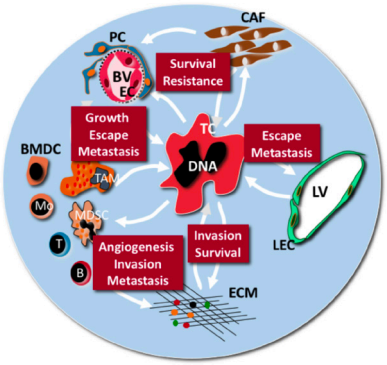
Research

Our research investigates mechanisms of metastasis to devise new therapeutic strategies in breast and colorectal cancer. In addition, we are pursuing novel approaches for blood-based cancer detection. Experimental results are complemented and validated by clinical investigations. Here some highlights of recent results from our projects.

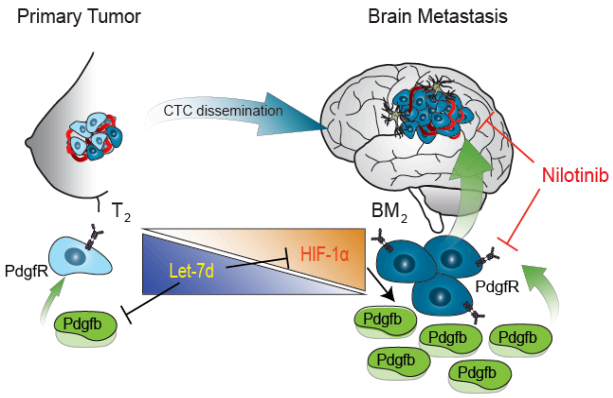
Breast cancer metastasis to the brain. Brain metastasis is a late complication of metastatic breast cancer. Treatments for brain metastases show limited efficacy calling for new therapies. Current models of brain metastasis are based on intraarterial injection of cancer cells and do not recapitulate the initial steps of the metastatic cascade in the primary tumor. We have established the first model of spontaneous breast cancer metastasis to the brain in immunocompetent mice from the primary tumor and demonstrated that the colonization step in the brain is the rate limiting event in brain metastasis. We identified FAK and PDGFR as key molecular mediators. As their inhibition halted progression of already established metastases, their testing in patients presenting brain metastases is warranted *(Wyss et al. 2020; Lorusso et al. 2020)*.

Obesity-induced breast cancer relapses. Obesity promotes ER+ breast cancer incidence in post-menopausal women, and metastatic progression of all breast cancer subsets. The mechanisms involved in the latter effect remain elusive. We developed mouse models of obesity-promoted breast cancer metastasis, and demonstrated that in ER+ breast cancer, obesity does so by promoting the expansion of metastasis-initiating cells through hypoxia and recruitment of inflammatory cells *(Bousquenaud et al. 2019)*. Specifically, we have identified a novel population of inflammatory cells promoting metastasis in obese mice that can be pharmacologically targeted. These results open new opportunities for adjuvant therapy for obese breast cancer patients *(Bousquenaud et al, submitted)*.

Figure 1. The tumor microenvironment.



Tumor cells attract and activate a multitude of stromal cells, including endothelial cells (EC), carcinoma associated fibroblast (CAF), bone marrow-derived cells, (BMDC) and immune/inflammatory cells, and modify the extracellular matrix (ECM). Most of these stromal modifications start early during tumor progression and contribute to determine cancer outcome: growth, dormancy, invasion, metastasis and resistance to therapy. Abbreviations: B, B lymphocyte; BV, blood vessel; Gr, granulocyte; LEC, lymphatic endothelial cell; LV, lymphatic vessel; Mo, monocyte; PC, pericyte; T, T lymphocyte; TAM, tumor associated monocyte/macrophage; TC, tumor cell.



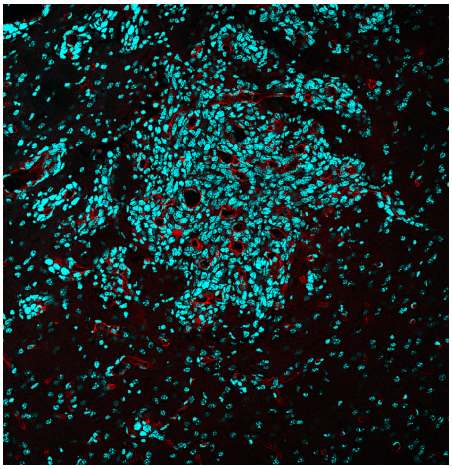


Figure 2 (left). Figure 3 (right). Mechanisms of brain metastasis.

Figure 2, schematic summary of the role of HIF-1 and PDGF in brain metastasis. Loss of let-7d upregulates HIF-1 activity leading to increased PDGFA/B secretion promoting brain metastasis growth. Treatment with a TKI PDGFR inhibitor halts brain metastasis progression.

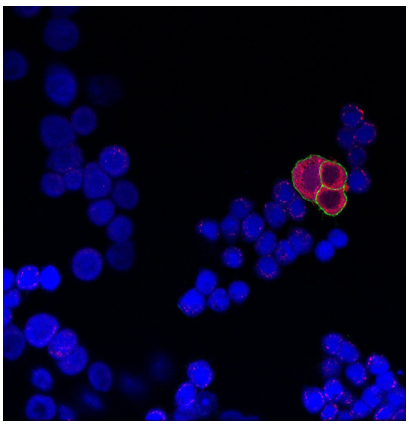
Figure 3, brain metastatic 4T1-BM2 cells showed as a DAPI-positive cluster (blue) in the brain parenchyma, and infiltrated by angiogenic endothelial cells (CD31 staining, red).

MAGI1 as breast cancer tumor suppressor. Nonsteroidal anti-inflammatory drugs (NSAIDs) have chemo-preventive but also anti-tumor activities. We have previously identified MAGI1 as a NSAIDs-induced tumor suppressor in colorectal cancer. Recently we showed that MAGI1 is tumor suppressive in ER+HER2- breast cancer. Loss of MAGI1 expression in this subtype correlates with worse prognosis. MAGI1 loss impairs ER signaling, activate PI3K signaling and generates a more aggressive phenotype. MAGI1 is downregulated by PGE_2 and upregulated by COXIB. We are now dissecting the link between inflammation, MAGI1 loss, inhibited ESR1 signaling and activation of the PI3K pathway that may contribute to resistance to hormonal therapy *(Alday-Parejo et al. 2020)*.

NOX1 inhibition blocks tumor growth and enhances checkpoint inhibitor activity. NADPH oxidases (NOX) catalyze the production of ROS in physio/pathological processes. NOX1 is highly expressed in colon cancer and promotes tumor growth. We observed that pharmacological or genetic NOX1 inhibition reduced tumor growth, angiogenesis and stimulated the recruitment or cytotoxic lymphocytes in the TME. Importantly, the NOX1 inhibitor GKT771 enhanced anti-tumor activity of anti-PD1 antibody (a checkpoint inhibitor) on colon carcinoma. Based on these results, we propose blocking of NOX1 by GKT771 as a potential novel strategy to treat colorectal cancer in combination with checkpoint inhibition *(Stalin et al., 2019)*.

Detection of circulating tumor cells (CTC). Detection of CTC is being investigate as a non-invasive way to detect and monitor cancer including breast cancer. We used a DNA hybridization chain reaction (HCR) approach consisting of DNA oligonucleotide hairpins activated by an initiator oligonucleotide that switches structure and self-assemble into amplification polymers to detect HER2+ CTC. HCR is activated by targeting the initiator oligonucleotide to HER2+ CTC with anti-HER2 antibody. We obtained a highly specific signal amplification signal on cancer cells mixed with peripheral blood leukocytes *(Rafiee et al., 2020)*. We are currently considering improving the sensitivity of this approach using plasmonic resonance-based detection. We are developing an alternative CTC detection method based on fibrin polymerization driven by thrombin-loaded gold nanoparticles targeted to HER2+ cancer cells by anti-HER2 antibody *(Reis et al., in preparation)*.

Figure 4. Detection of circulating Cancer Cells.



$HER2^{pos}$ breast cancer cells detected with fluorescent Gold nanoparticles (green) that induced the polymerization of fibrinogen into fibrin (red). $HER2^{neg}$ cells are not stained. Nuclei are stained by DAPI (blue).

Selected Publications

Wyss CB, Duffey N, Barras D, Martinez Usatorre A, Coquoz O, Romero P, Delorenzi M. Lorusso G, **Rüegg C.** (2020).

Gain of HIF-1 activity and loss of miRNA let-7d orchestrate breast cancer metastasis to the brain via PDGF/PDGFR axis. Cancer Res. doi: 10.1158/0008-5472. CAN-19-3560.

Alday-Parejo B, Richard F, Wörthmüller J, Desmedt C, Santamaria-Martinez A, **Rüegg C.** (2020).

MAGI1 is a new potential tumor suppressor gene in estrogen receptor positive breast cancer, Cancers (Basel). doi: 10.3390/cancers12010223.

Rafiee S, Kocabey S, Mayer M, List J, **Rüegg C.** (2020).

Detection of individual HER2+ breast cancer cell using DNA-based signal amplification, Chem Med Chem. doi: 10.1002/cmdc.201900697.

Patrice Nordmann

Emerging Antibiotic Resistance in Bacteria

Introduction

Emerging antibiotic resistance in multidrug resistance (MDR) Gram-negative is currently dominated by the emergence of resistance to expanded- ß-lactams such as cephalosporins and carbapenems, to polymyxins, and to fosfomycin and to novel antibiotics. Resistance to expanded-spectrum cephalosporins and carbapenems through production of acquired extended-spectrum ß-lactamases and carbapenemases, respectively, are dominating this scene. Currently broad-spectrum cephalosporins such as ceftazidime, cefotaxime and even cefepime may be already considered as “old” antibiotics. As a result of this problematic situation, other drugs such as polymyxins (colistin) and fosfomycin have recently showed renew of interest. Therefore, a special attention is now also given to acquired resistance to those last-resort molecules. MDR bacteria that are the most clinically relevant in human medicine are *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. A One-Health concept of resistance has emerged with possible transfer of resistance genes from or to human or veterinary medicine. Spread of resistance can predominately be explained by spread of resistance genes in clinically-significant organisms and of MDR clones. Those resistance genes may be transferred vertically or horizontally. The key elements to control the emergence of antibiotic resistance at the worldwide scale are as follows; (i) rapid detection of emerging antibiotic genes and surveying their spread (ii) improving hygiene in particular in hospital settings to prevent its spread (iii) decrease antibiotic consumption, and (iv) development of novel antibiotic molecules. Most of our research activities have been conducted in association with the reference center of emergence of antibiotic for Switzerland (NARA) and with Swiss laboratory of the National Institute for Health and Medical Research (INSERM), we established recently at the University of Fribourg.

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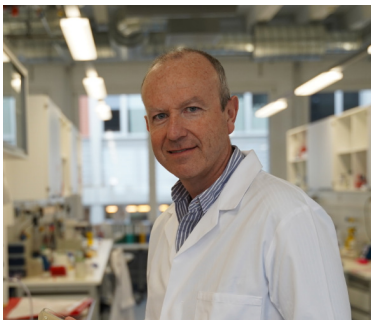

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Research activities

The overall aim of our research is to identify early antibiotic resistance traits emerging worldwide, to characterize their biochemistry, their genetics and their spread in the most clinically-relevant antibiotic-resistant Gram-negative bacteria. In addition, their natural reservoirs has been identified in several instances. More recently, we have developed approaches to the development of rapid tests for identification of emerging resistance traits and we have contributed to propose therapeutic solutions.

Deciphering antibiotic resistance genes and their spread

Resistance to expanded-spectrum ß-lactams. We have contributed to unravel several genetic mechanisms as the source of spread of emerging resistance to carbapenems that are considered among antibiotics of last resort. Ongoing dissemination of the genes coding for the carbapenemase OXA-244 and NDM-5 has been identified in Switzerland as well as its cross border spread in Germany **(Fig. 1)**. Their dissemination is quite silent mostly occurring in limited number of clones of community-acquired *E. coli.*

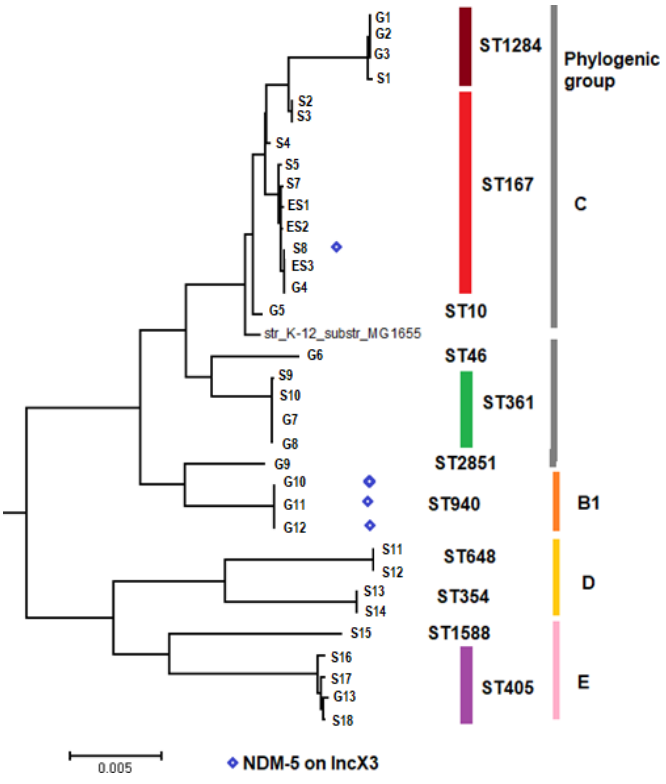


Figure 1. *Phylogenomic clustering of NDM-5 producing E. coli isolates with the respective ST types and phylogenic group indicated in Switzerland (S and ES) and Germany (G). Spread of NDM-5 gene on same plasmid (IncX3) is also indicated.*

We have identified the molecular mechanisms as a source of acquired resistance to novel combinations of ß-lactamase/ß-lactame inhibitor in Enterobacterales of clinical settings. This was the case of *K. pneumoniae* isolates being resistant to the ceftazidime/avibactam and of *E. coli* isolates being resistant to aztreonam/avibactam. Spread of those novel resistance mechanisms will contribute to limit the efficacy of novel antibiotics. An extended-spectrum ß-lactamase (CTX-M-33) has been also characterized that signals the possible evolution of enzymes from features of ESBL to those of carbapenemases.

Resistance to fosfomycin, fluoroquinolones and polymyxins. Several novel mechanisms of resistance to fosfomycin have been identified in *E. coli*. They may be clinically significant since they are transferable and confer resistance to one of the most prescribed antibiotics, fosfomycin, for treating urinary tract infections. Pathogenicity islands have been identified as associated to the novel fluoroquinolone resistance determinants CrpP in *P. aeruginosa*. Several chromosome and plasmid-mediated resistance mechanisms to polymyxins have been characterized in Enterobacterales, including identification of their reservoir and the genetic bases of their mobility. More specifically, a functional characterization of a miniature inverted transposable element at the origin of *mcr-5* gene acquisition in *E. coli* has been performed as well as the first inducible MCR gene, *mcr-9*, in *E. coli*.

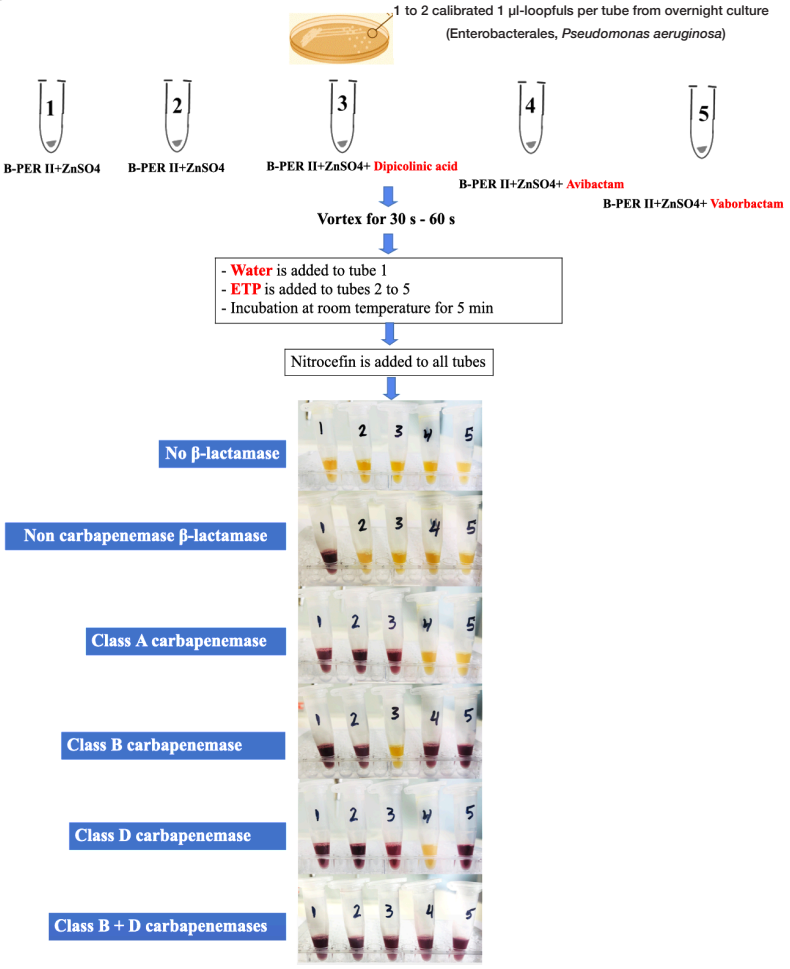
One-health concept of spread of multidrug resistance. Spread of clinically significant antibiotic resistance determinants in humans have being identified in animals such as the ESBL CTX-M-15 and the polymyxin resistance determinants MCR-1 in pigs, MCR-3 in crickets sold as food and ESBL and carbapenemase genes in gull feces. Spread of known resistance determinants and totally novel carbapenemase genes have been identified in the environment in remotely areas such as in Pakistan and Nigeria. Those reports further support the spread of several resistance determinant sfrom soil, animal and human isolates and vice versa. Collaborations have been established worldwide (France, Germany, Italy, Portugal, Nigeria, Pakistan, Turkey) to evidence this One-Health concept.

Rapid diagnostic tests, screening media for multidrug resistance and novel therapeutic strategies

We have developed rapid techniques for identification of emerging antibiotic resistance based on biochemical and rapid culture techniques. Those tests were aimed for a rapid detection of fosfomycin resistance in *E. coli*, of polymyxin resistance in *P. aeruginosa*, and *A. baumannii*. The NitroSpeed Carba NP test is the latest test we developed that identifies carbapenemases and their types in Enterobacterales and *P. aeruginosa* ***(Fig. 2)*** The developed tests have high sensibility and specificity that meet the criteria of clinical use, with results obtained with a turn around time from 30 min to 3 h. Screening media for multidrug resistance have been also developped for screening linezolid resistance in Gram-positive bacteria and ceftazidime-avibactam resistance as well a specific antibiotic-containing culture media for improving the identification of MDR bacteria from stools (carriage stage). Several of those tests and media are or will be commercially available.

Novel therapeutic strategies we developped include the use of phages for successful decontamination of MDR bacteria from the gut flora and the demonstration of the *in-vitro* and *in-vivo* efficacy of dual carbapenem treatment for treating infections due to carbapenem-resistant *A. baumannii*. A zinc chelator (dimercapto succinic acid) used for treating lead poisining was shown to be a promising strategy for inhibiting the activity of some carbapenemases that belong to the metallo-enzyme group (NDM, VIM, IMP), as demonstrated in an animal model of infection.

Figure 2. NitroCarba NP test.



Selected Publications

Sadek M, Juhas M, Poirel L, **Nordmann P.** (2020).

Genetic features leading to reduced susceptibility to aztreonam-avibactam among metallo-ß-lactamase-produing Escherichia coli isolates. Antimicrob. Agents Chemother. doi: 10.1128/ AAC.01659-20.

Nordmann P., *Sadek M, Demord A, Poirel L.* (2020).

NitroSpeed-CarbaNP test for rapid detection and differentiation between different classes of carbapenemases in Enterobacterales. J Clin Microbiol. doi: 10.1128/JCM.00965-20.

Cheminet G, De Lastours V, Poirel L, Chau F, Peoc'h K, Massias L, Fantin B, **Nordmann P.** (2020).

Dimercapto succinic acid in combination with carbapenems against isogenic strains of Escherichia coli producing or not producing a metallo-ß-lactamase in vitro and in murine peritonitis. J Antimicrob Chemother doi: 10.1093/ jac/dkaa347.

Jens Stein

Exploring tissue-specific CD8+ T cell biology during adaptive immune responses

Introduction

The adaptive immune system protects us from harmful microbial infections and cancer, while providing life-long immunity after vaccination. To accomplish this extraordinary feat, cellular components of the immune system, T and B cells, continuously interact with antigen-presenting cells (APCs) in lymphoid organs. A well-studied example are naïve $CD8^+$ T cells interactions with dendritic cells (DCs), the most powerful APCs for this subset. This leads to $CD8^+$ T cell activation, differentiation to cytotoxic effector cells and invasion of infected organs. This process contributes decisively to elimination of intracellular pathogens such as viruses, as well as tumor cells. After clearing of a pathogen, memory $CD8^+$ T cells patrol the body to protect from reinfection. While the general principle of such adaptive immune responses is well established, little is known on how this dynamic process unfolds on a single cell level in the context of tissue-derived environmental cues.

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Our laboratory is combining multiple platforms including multicolor flow cytometry, functional in vitro assays and high-end microscopy to "shed light" on the molecular and cellular processes that govern adaptive immune responses mediated by cytotoxic CD8+ T cells. We follow three lines of investigation:

- We are examining the role of key regulators of T cell activation by using genetically modified CD8+ T cells. Our technical platforms include flow cytometry, RNA sequencing, viral infection models, immunofluorescent analysis and twophoton microscopy (2PM) of lymphoid tissue. Using software-based analysis of key parameters, we determine the critical decision-making steps at the onset of immune responses.
- We follow CD8+ T cells at their effector sites, for example in exocrine glands, skin and other non-lymphoid organs and observe how these cells contribute to host protection. A special focus is on tissue-resident memory T cells that provide a first line of defense against reinfection.
- We are applying large-scale imaging techniques, Optical Projection Tomography (OPT) and Selective Plane Illumination Microscopy (SPIM) for a quantitative analysis of adaptive immune responses by visualizing the entire 3D structure of lymph nodes and other organs during inflammation.

The combination of these approaches permits to obtain unprecedented insight into the dynamic nature of the adaptive immune system on a single cell level.

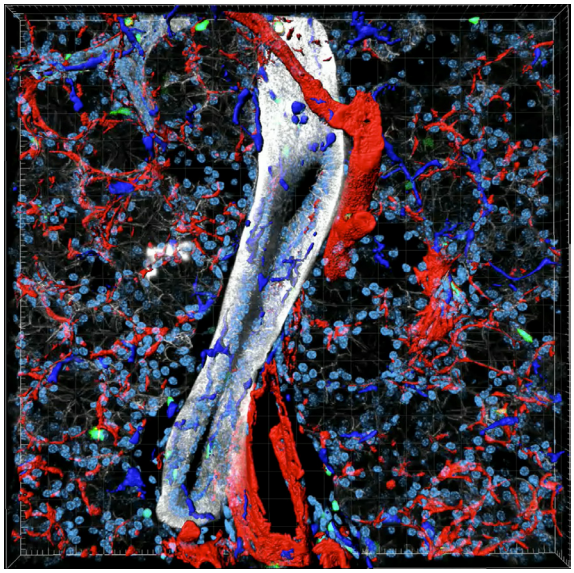

Figure 1. *Confocal image of memory CD8+ T cells (green) patrolling salivary glands. EpCAM+ epithelial cells are labeled white, while smooth muscle cell actin+ pericytes and myofibroblasts are labeled red. CD11c+ tissue macrophages (CD11c), while nuclei are light blue (DAPI).*

Selected Publications

Ficht X, Ruef N, Stolp B, Samson GPB, Moalli F, Page N, Merkler D, Nichols BJ, Diz-Muñoz A, Legler DF, Niggli V, **Stein JV.** *(2019).*

In vivo function of the lipid raft protein Flotillin 1 during CD8+ T cell-mediated host surveillance. J Immunol. doi: 10.4049/jimmunol.1900075.

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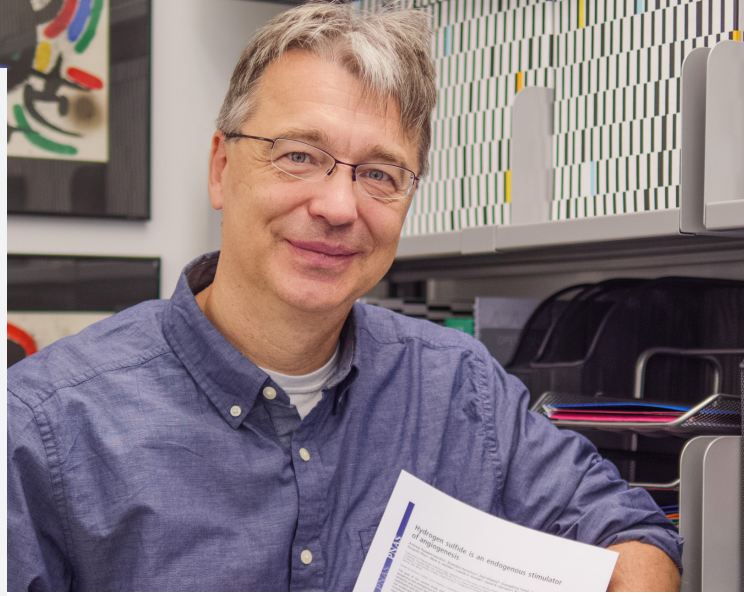
Regulation of global CD8+ T-cell positioning by the actomyosin cytoskeleton. Immunol Rev. doi: 10.1111/imr.12759.

Stolp B, Thelen F, Ficht X, Altenburger LM, Ruef N, Inavalli VVGK, Germann P, Page N, Moalli F, Raimondi A, Keyser KA, Jafari SMS, Barone F, Dettmer MS, Merkler D, Iannacone M, Sharpe J, Schlapbach C, Fackler OT, Nägerl UV, **Stein JV**. *(2020).*

Salivary gland macrophages and tissue-resident CD8+ T cells cooperate for homeostatic organ surveillance. Sci Immunol. doi: 10.1126/sciimmunol.aaz4371.

Csaba Szabo

Biological and pathophysiological roles of labile, diffusible small molecules



INTRODUCTION

The research interest of Pr. Szabo and his group focuses on the biological and pathophysiological roles of various labile, diffusible small molecules.

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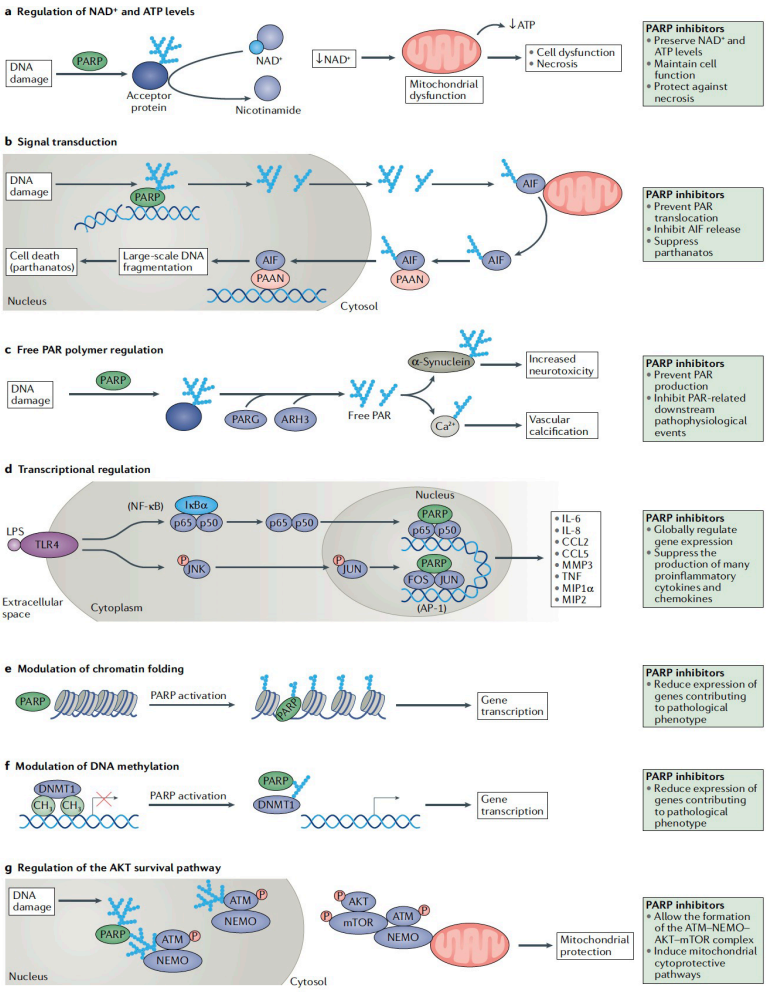
One special class of labile, diffusible small molecules is free radicals. These species (for example superoxide, or nitric oxide) are produced in various cells during biological and pathophysiological processes and are involved in various processes ranging from cell death to inflammatory responses. Free radicals can induce cellular injury through damage to proteins, lipids or nucleic acids. One of the consequences of free radical mediated cellular injury involves the activation of an enzyme called poly(ADP-ribose) polymerase (PARP). Pr. Szabo has been working on the role of PARP in various pathophysiological processes (vascular injury, circulatory shock, inflammation) for many years, and is now involved in efforts seeking to repurpose clinically used (for cancer) PARP inhibitors for the experimental therapy of various non-oncological diseases.

Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) represent a particular class of labile biological mediators called gasotransmitters. These molecules travel easily through cell membranes and mediate multiple processes in the vascular, immune and nervous system through acting on multiple interrelated receptors and effectors. For the last decade, Pr. Szabo has been active in the field of H_2S biology, where he studies the pathophysiology, pharmacology and experimental therapy of various diseases (vascular, metabolic, cancer) in the context of alterations in H_2S homeostasis. Much of his current work focuses on the role of H_2S in metabolic disease, cancer and Down syndrome.

Figure 1. Molecular mechanisms of the anti-inflammatory and cytoprotective effects of inhibition of the PARP pathway.



In various disease conditions (inflammation, reperfusion injury, sepsis, ARDS), the constitutive enzyme poly(ADP-ribose) polymerase (PARP) becomes pathologically overactivated. This triggers cellular bioenergetic dysfunction and maladaptive inflammatory and immune responses. Using pharmacological inhibitors of PARP (including recently clinically approved drugs that are used in cancer therapy, such as olaparib), therapeutic repurposing is possible for various non-oncological disease states. Figure from: Curtin N and Szabo C, Nature Reviews Drug Discovery 19: 711, 2020.

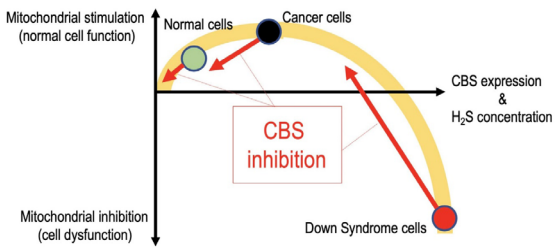


Figure 2. Role of the H_2S pathway in Down syndrome.

In several diseases, H_2S levels are increased. In some conditions (e.g. in various cancers), the cancer cells utilize these elevated levels to drive their metabolic and proliferative processes. In other conditions (e.g. Down syndrome), H_2S levels are so high that that it can exert adverse effects through inhibition of mitochondrial ATP generation. In these conditions, pharmacological inhibitors of the H_2S-producing enzyme CBS can exert beneficial effects. Figure from: Szabo C, FEBS Journal 287: 3150, 2020.

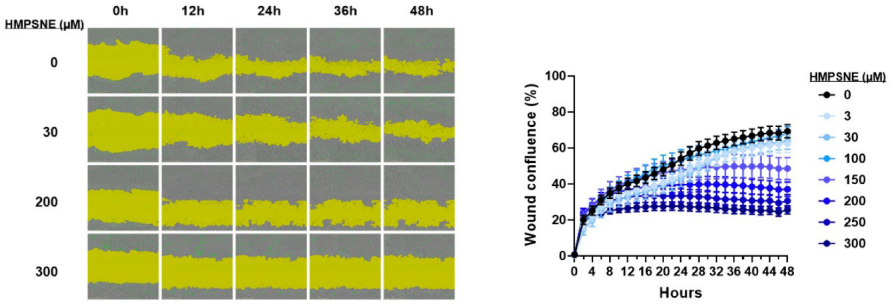


Figure 3. 3-MST, one of the key H_2S-producing enzymes, supports cancer cell proliferation.

Pharmacological inhibition of 3-MST using the small molecule HMPSNE reduces cancer cell proliferation in an in vitro wound healing assay. Figure from: Augsburger F, Randi EB, Jendly M, Ascencao K, Dilek N, Szabo C. Biomolecules 10: 447, 2020.

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Selected Publications

Panagaki T, Randi EB, Augsburger F, **Szabo C.** (2019).

Overproduction of H_2S, generated by CBS, inhibits mitochondrial Complex IV and suppresses oxidative phosphorylation in Down syndrome. Proc Natl Acad Sci U S A. 116:18769-18771.

Ahmad A, Vieira JC, de Mello AH, de Lima TM, Ariga SK, Barbeiro DF, Barbeiro HV, Szczesny B, Törö G, Druzhyna N, Randi EB, Marcatti M, Toliver-Kinsky T, Kiss A, Liaudet L, Salomao R, Soriano FG, **Szabo C.** (2019).

The PARP inhibitor olaparib exerts beneficial effects in mice subjected to cecal ligature and puncture and in cells subjected to oxidative stress without impairing DNA integrity: A potential opportunity for repurposing a clinically used oncological drug for the experimental therapy of sepsis. Pharmacol Res. 145:104263.

Augsburger F, **Szabo C.** (2020).

Potential role of the 3-mercaptopyruvate sulfurtransferase (3-MST)-hydrogen sulfide (H_2S) pathway in cancer cells. Pharmacol Res. 154:104083.

Michael Walch
Pierre-Yves Mantel

Host-pathogen interactions in the context of bacterial infections and malaria

INTRODUCTION

Pathogenic bacteria and parasitic diseases, such as malaria, are a global major health threat that is alarmingly aggravated by the drastic increase in antimicrobial resistance in recent years. Therefore, an in-depth analysis of efficient immunologic effector mechanisms against microbial pathogens, including the dissection of evolutionary conserved host-pathogen interactions, is of pressing importance. We recently discovered that the immune serine proteases of cytotoxic lymphocytes, the granzymes, when delivered into the pathogens by pore forming proteins, exhibit potent antimicrobial activity by cleaving multiple vital protein substrates triggering rapid pathogen death. We, thus, defined a novel immunological paradigm suggesting a crucial role of cytotoxic effector proteases in antimicrobial immune defense. Over the past few years, we found that the lymphocytic granzymes were not only delivered into pathogenic bacteria to induce their death (Walch et al. 2014) but also into certain unicellular parasites, such as Trypanosoma spp. (Dotiwala et al. 2016) and Plasmodium spp. (Hernandez-Castaneda et al. 2020). In addition, we found that the granzymes efficiently degrade secreted key virulence proteins in our main model bacterial pathogen *Listeria monocytogenes* (Lopez Leon et al. 2020). This recent findings clearly indicate that the granzymes evolutionarily learned to target and destroy vital bacterial metabolic pathways that are involved in the infectious growth.

In addition, we revealed a novel form of cellular communication in malaria that allows the parasites to survive in a hostile environment (Mantel et al. *Cell Host Microbe*, 2013; Mantel et al. *Nature Communication*, 2016). We found that the parasites release small vesicles containing signaling cargoes that synchronize the parasites to optimize the transmission to the mosquito. Furthermore, the EVs have potent immune regulatory properties. Altogether, EVs might be essential for the success of the infection.

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A. Cytotoxic effector proteases in antibacterial immunity – specific attack on bacterial virulence (PI Walch)

Comprehensive proteomics analysis of bacterial granzyme B substrates in the model pathogen Listeria monocytogenes revealed a highly targeted attack on protein networks that are up-regulated during infectious growth in vivo. This finding suggested an unexpected immune mechanism that specifically targets bacterial proteins directly related to virulence and pathogenicity. Our study, published in iScience, mainly conducted by the PhD student Diego López León, explored this novel immune strategy in clinically relevant pathogenic bacteria and revealed a highly targeted attack on bacterial virulence that acts as an innate immune barrier. These data provided an evolutionary insight of how to effectively kill bacterial pathogens and restrict infections. In complementary work, mainly performed by the master student Oluwadamilola Adenuga, we found that also the intracellular death inducing effector proteases, the caspases, such as caspase 3 and 7, efficiently inhibit virulent behavior and survival of intracellular pathogenic bacteria. These data revealed an unexpected, yet critical role of the intracellular death proteases in antibacterial defense.

B. Understanding cytotoxic lymphocyte responses against blood-stage human malaria (PIs Walch and Mantel)

Plasmodium spp., the cause of malaria, have a complex life cycle. However, the exponential growth of the parasites in the blood is responsible for almost all the clinical symptoms of malaria and the associated morbidity and mortality. Therefore, to prevent malaria pathogenesis and progression toward severe disease, tight control of parasitemia is essential.

In collaboration with Dr. Pierre-Yves Mantel, the expert in blood-stage Malaria and host-pathogen interactions at the University of Fribourg, we characterized the cytotoxic lymphocyte populations capable to restrict the growth of Plasmodium in red blood cells (RBC). The work, published in The Journal of Immunology, mainly performed by our SNSF-funded PhD student, Maria Hernández-Castañeda, demonstrated that the particular lymphocyte subset of gd T cells in a granzyme-dependent mechanism contributes crucially to the observed Plasmodium growth restriction during the blood phase. In follow-up work, we already identified several parasite proteins, involved in virulent growth and pathogenicity that were efficiently destroyed by granzyme B. The next step is the unbiased and comprehensive characterization of the molecular targets of the immune proteases in stage-specific proteomics screens (collaboration with Prof. Jörn Dengjel). These data will potentially identify novel essential proteins for virulence and growth of RBC-residing Plasmodium that could be used for future anti-Malaria drugs selection.

C. Cellular communication in malaria (PI Mantel)

Plasmodium falciparum has to develop strategies to survive in hostile environments. We have described that Plasmodium falciparum infected RBCs secrete small vesicles that mediate communication between parasites and between parasites and hosts. However, the signaling cargoes present inside EVs remained unknown. In collaboration with Prof. Ionita Ghiran (Harvard Medical School), we have demonstrated that the parasites release RNAs through EVs. We found that although most of the RNAs derived from the human host, approximately 10% came from plasmodium. In addition, we found that EVs have potent immune-regulatory properties and target a wide range of host immune cells. In collaboration, with the laboratory of Prof. Rickard Sandberg (Karolinska Institutet), we have established a single cell RNA-Seq protocol to address cellular communication at the single cell level. In collaboration with Prof. Daniel Irimia (Harvard Medical School), we use microfluidics to investigate neutrophil function.

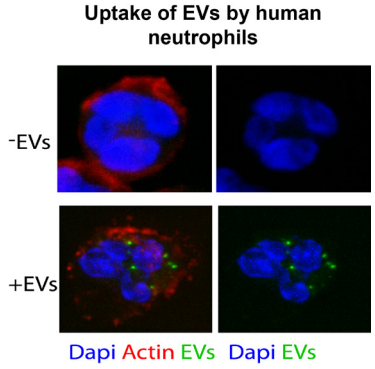

Figure 1. *Human primary neutrophils were incubated for 1 hour with Extracellular Vesicles (green) isolated from Plasmodium falciparum cultures. The confocal microscopy images demonstrate the rapid uptake of EVs.*

Selected Publications

Lopez Leon D, Matthey P, Fellay I, Blanchard M, Martinvalet D, **Mantel PY**, *Filgueira L,* **Walch M.** *(2020).*

Granzyme B attenuates bacterial virulence by targeting secreted factors. iScience. 23: 100932.

Hernández-Castañeda M, Happ K, Cattalani F, Wallimann A, Blanchard M, Fellay I, Scolari M, Kharoubi Hess S, Felly B, Filgueira L, **Mantel P.Y**., and **Walch M**. (2020).

γδ T Cells kill Plasmodium falciparum in a granzyme- and granulysin-dependent mechanism during the late blood stage. J Immunol. 204:1798-1809.

Luis Filgueira

Clinical Anatomy, Cell Biology and Medical Educatiom

Introduction

The areas of research interest of Luis Filgueira has been cell biology, immunology, clinical anatomy and educational research, addressing various topics. The following report shall focus on 3 research topics that have been addressed during the reporting period.

The first topic covers clinical anatomy. Supported my Dr Yotovski and Dr Larionov, various projects are ongoing in collaboration with orthopaedic surgeons, including Prof Tannast (HFR). Most importantly, numerous clinical courses for further education in various medical professions have also been hosted.

The second topic covers infectious immunology, where various models are applied, including Japanese encephalitis virus and microglia (Dr Lannes), various bacterial models (collaboration with Prof Walch) and Malaria (collaboration with Prof Walch and Dr Mantel).

The third topic covers educational research, done in collaboration Dr E. Eppler (University of Bern) focussing on medical and biomedical curricula and especially on anatomy teaching.

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Topic 1, clinical anatomy by A. Larionov et al.:

The innervation of the deltoid muscle is clinically relevant in the context of trauma and surgery of the shoulder. A new study identified that in about 80% of cases, the clavicular portion of the deltoid muscle is innervated by the lateral pectoral nerve, which has not been described before. Other similar projects are ongoing, including the clinical anatomy of the piriformis muscle (A. Larionov) and the arterial blood supply of the knee (F. Ramadani).

Topic 2, infectious immunology and cell biology by S. Mbagwu and A. Larionov:

The mechanisms behind cerebral malaria are not well understood, where the microcirculation of the brain and the blood-brain barrier plays a major role. This project focuses on the endothelial cells of the brain, indicating that various regions display biologically relevant differences in the make-up of the endothelial cells.

Topic 3, educational research:

This project investigates new approaches of how to enhance anatomy education in the medical curriculum. On one hand, ultrasound and clinical investigation has been combined with traditional anatomy teaching. Study evaluation indicates that this combination improves applied anatomy knowledge.

Selected Publications

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CX_3CR1-CX_3CL1-dependent cell-to-cell Japanese encephalitis virus transmission by human microglial cells. Sci Rep. doi: 10.1038/s41598-019-41302-1.

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Mbagwu SI, **Filgueira L.** *(2020).*

Differential expression of CD31 and Von Willebrand factor on endothelial cells in different regions of the human brain: potential implications for cerebral Malaria pathogenesis. Brain Sci. doi: 10.3390/brainsci10010031

Public Health

Arnaud Chiolero

Population health, life course epidemiology, and public health surveillance

Gregor Hasler

Discovering biomarkers and developing novel therapeutic options for severe psychiatric disorders (depression, psychosis)

Martina King

Medical humanities

Johannes Wildhaber

Petra Zimmermann

The maternal and infant microbiome and its association with health outcomes in children

Arnaud Chiolero

Population health, life course epidemiology, and public health surveillance

Introduction

The Population Health Laboratory (#PopHealthLab), created in November 2019 by Prof Arnaud Chiolero MD PhD, develops research activities aiming to inform public health surveillance & monitoring to help citizens, health stakeholders, clinicians, and policy makers take data-informed and evidence-based decisions.

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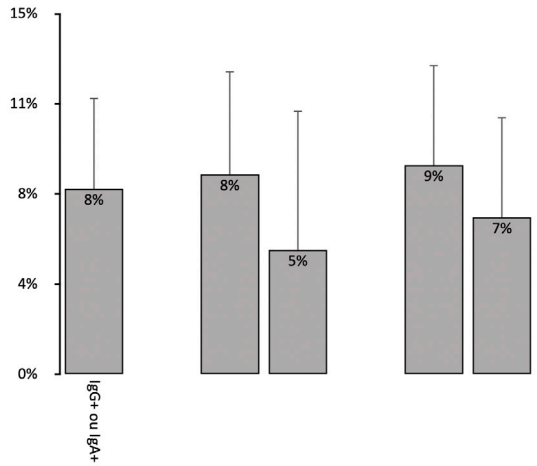
Research areas are the epidemiology of population health in a life course and consequential perspective and the study of health services activities and quality of care in an evidence-based public health framework. The #PopHealthLab has skills for the handling and analyses of complex data from multiples sources. The #PopHealthLab frames research along three main areas: 1) life course epidemiology (i.e., early life determinants, social epidemiology, and primordial prevention) 2) consequential epidemiology (i.e., public health implication, effect size, causality), and 3) evidence-based public health (i.e., public health surveillance, data-informed healthcare decisions, quality of care monitoring)

Proportion of the adult population of Fribourg with antibodies (IgG or IgA) against the SARS-CoV-2 virus, by age and sex, after the 1st wave of the pandemic. *Source: Anker et al. Corona Immunitas Fribourg 2020, in press*



Selected Publications

Chiolero A, *Buckeridge D. (2020).*

Glossary of public health surveillance in the age of data science. J Epidemiol Community Health.74:612-616.

West EA, Anker D, Amati R, Richard A, Wisniak A, Butty A, Albanese E, Bochud M, **Chiolero A**, *Crivelli L, Cullati S, d'Acremont V, Epure AM, Fehr J, Flahault A, Fornerod L, Frank I, Frei A, Michel G, Gonseth S, Guessous I, Imboden M, Kahlert CR, Kaufmann L, Kohler P, Mösli N, Paris D, Probst-Hensch N, Rodondi N, Stringhini S, Vermes T, Vollrath F, Puhan MA, Corona Immunitas Research Group. (2020).*

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Epure A, Rios-Leyvaraz M, Anker D, Di Bernardo S, **Chiolero A**, *Sekarski N. (2020).*

First 1,000 days risk factors for carotid intima-media thickness in infants, children, and adolescents: a systematic review with meta-analyses. Plos Med, in press.

Gregor Hasler

Discovering biomarkers and developing novel therapeutic options for severe psychiatric disorders (depression, psychosis)

Introduction

Our research group investigates how biological factors, most prominently the central glutamate and GABA systems, contribute to specific aspects of psychopathology. Based on this knowledge, we investigate the therapeutic potential of novel pharmacological agents that alter central glutamate activity. To this end, we combine experimental psychopharmacology with a wide variety of neuroimaging methods and diagnostic instruments.

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Samir Suker

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Tashi Voskamp, UniFr
Ladina Meier-Ruge, UniBE
Moritz Huber, UniFr

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Dr. Funda Akkus, Klinik Wil, SG
PD Dr. Valerie Treyer, PET Center, University of Zurich (PET)
Prof. Dr. Simon Ametamey, ETH Zurich (PET tracer)

COLLABORATOR WHO LEFT THE TAB
Dr. Sabrina Müller

For years, our research group has been at the forefront of investigating the implication of metabotropic glutamate receptors subtype 5 (mGluR5) in psychiatric disorders. We have been studying mGluR5 *in vivo* using positron emission tomography (PET) in collaboration with our partners at the University Hospital of Zürich (USZ) and the Swiss Federal Institute of Technology in Zürich (ETH Zürich). Our research has advanced the knowledge of mGluR5 in smoking, alcohol addiction, depression, obsessive-compulsive disorder, and schizophrenia. In the period 2019-2020, we built on our previous findings, to conduct the following research projects:

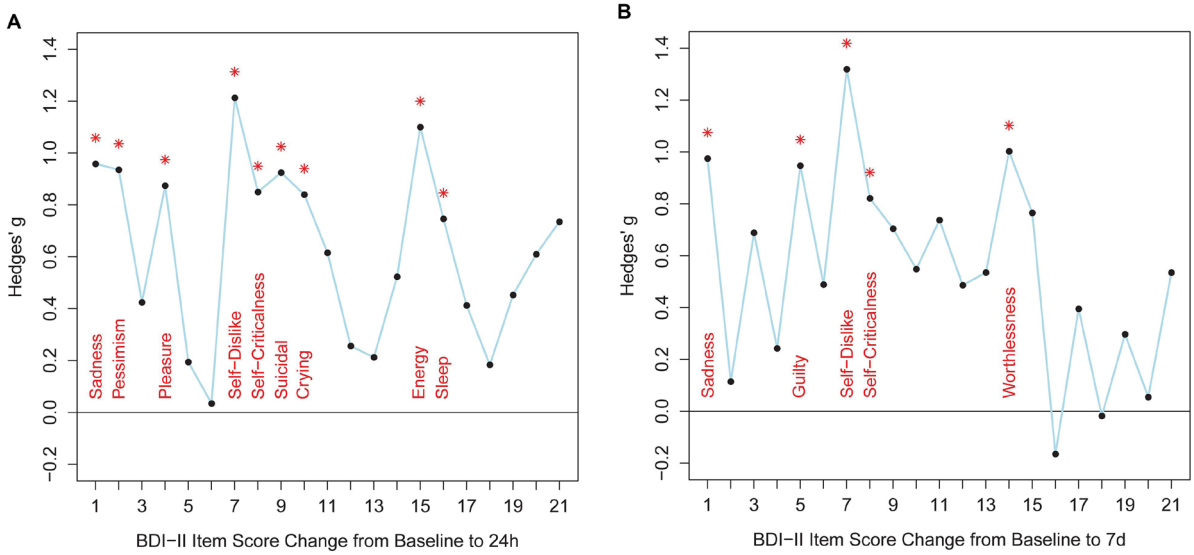
- We published the first longitudinal and long-term *in vivo* study of the effects of chronic nicotine exposure on mGluR5 in rats (Müller-Herde et al., 2019).
- We published the first *in vivo* investigation of mGluR5 in women with bulimia nervosa (Mihov et al., 2020).
- We are currently employing multimodal imaging to study the interplay between mGluR5, glutamate concentration, and brain activity in subjects with bipolar disorder and at clinical high risk for schizophrenia (ongoing project).

Based on our knowledge of the central glutamate system, we investigated the effects of ketamine in treatment-resistant depression. Our results supported a recent surge in evidence for the potential of ketamine to rapidly improve depressive symptoms (Hasler et al., 2020). Furthermore, we investigated factors that help predict whether patients would profit from ketamine ("responders") or not ("non-responders") (Hasler et al., 2020). Importantly, we showed a specific symptom profile of clinical improvement after ketamine treatment, suggesting that ketamine has a stronger effect on some symptom domains than on others (Hasler et al., 2020). In this way, we contributed to the development of evidence-based precision medicine, delivering individually tailored treatment to patients.

Over the years, our research group has gained international recognition for employing magnetic resonance spectroscopy (MRS) to investigate GABA, glutamate, and glutamine in psychiatric disorders. In the period 2019-2020, we continued this tradition by publishing a report, from our Zürich cohort study, on the relation between brain concentration of GABA glutamate, and glutamine and neuroticism, a personality trait strongly related to psychiatric disorders (Hasler et al., 2020).

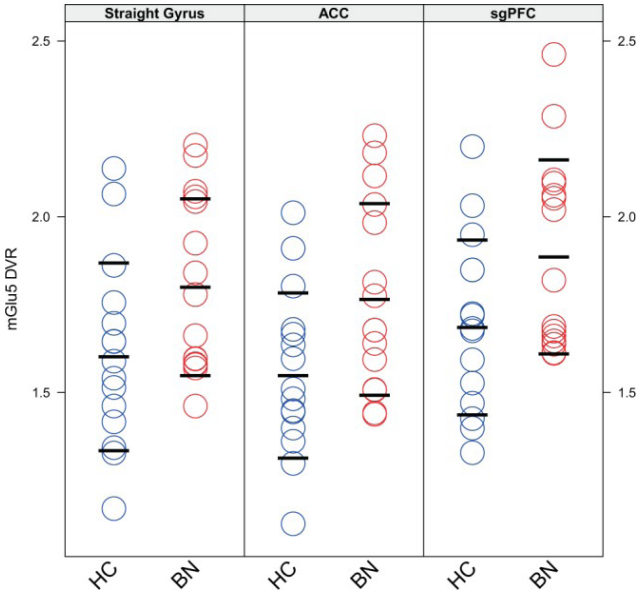
In the past, our group has conducted a series of studies on the biological factors influencing economic decision-making and competition in psychiatric disorders and in healthy persons. In the period 2019-2020, we participated in a large international endeavor to study the influence of genetic markers on risk tolerance and risky behaviors. The results of this large-scale study were published in the prestigious journal Nature Genetics (Karlsson Linner et al., 2020). Moreover, in collaboration with our partners in Denmark, we investigated competition behavior in a unique sample of monozygotic twins (ongoing project).

Figure 1. Frontiers in Neuroscience, 2020.



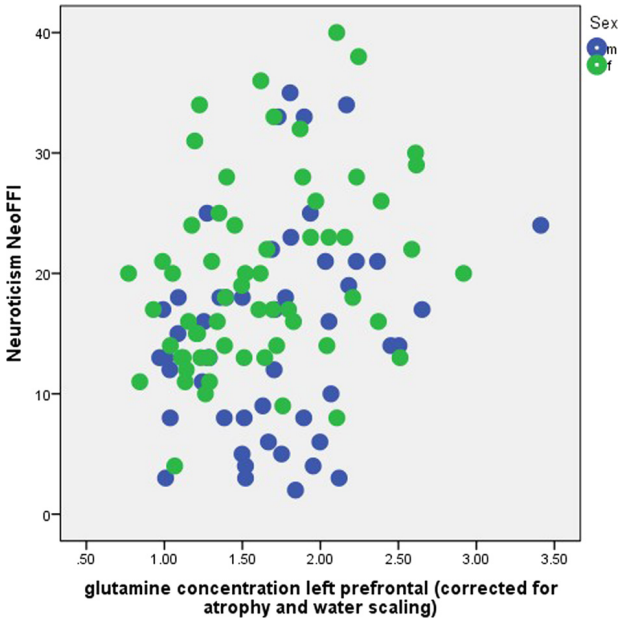
Patients with treatment-resistant depression received a ketamine infusion. We observed a strong variance in symptom improvement after ketamine treatment, with some patients displaying a rapid and pronounced remission of symptoms, visible after 24 hours and sustained over 7 days (responders), and others not improving after ketamine (non-responders). Importantly, responders improved in specific symptom domains, such as Sadness, Self-Dislike, and Self-Criticalness.

Figure 2. Scientific Reports, 2020.



Using positron emission tomography, we found the first evidence for an aberrant distribution volume ratio of the metabotropic glutamate receptor subtype 5 (mGluR5 DVR) in women with bulimia nervosa (BN, red circles), as compared to healthy controls (HC, blue circles). ACC, anterior cingulate cortex; sgPFC, subgenual prefrontal corte.

Figure 3. Translational Psychiatry, 2019.



We combined magnetic resonance spectroscopy with a dimensional approach to psychopathology. Our investigation revealed that higher glutamine concentration in the left prefrontal cortex corresponds to higher neuroticism, and may be associated with a higher risk for mood and anxiety disorders.

Selected Publications

Hasler G, *Buchmann A, Haynes M, Müller ST, Ghisleni C, Brechbühl S, Tuura R. (2019).*

Association between prefrontal glutamine levels and neuroticism determined using proton magnetic resonance spectroscopy. Transl Psychiatry. 9:170.

Hasler G, *Suker S, Schoretsanitis G, Mihov Y. (2020).*

Sustained improvement of negative self-schema after a single ketamine infusion: an Open-label study. Front Neurosci. 14: 687.

Mihov Y, Treyer V, Akkus F, Toman E, Milos G, Ametamey SM, Johayem A, **Hasler G**. *(2020).*

Metabotropic glutamate receptor 5 in bulimia nervosa. Sci Rep. 10:6374.

Martina King

Medical Humanities

Introduction

Medical Humanities is not a single discipline; rather a cluster of disciplines within the humanities that make a serious contribution to the analysis and improvement of medicine. Medical Humanities include philosophy, literary and cultural studies, history of medicine, medical sociology and medical anthropology, which altogether offer a complementary perspective on medicine; in the sense that they promote critical role reflection, historical understanding and ethical consciousness. Medical Humanities have originally developed in the USA and UK as a didactic tool in order to improve medical education – and this implies strong normative claims. Now if Medical Humanities are basically a teaching programme, how about research? This is much less clear and varies strongly in the international scene of Medical Humanities.

In Fribourg, we think that a strict distinction should be made between teaching and research in Medical Humanities. As scholars, we work in an analytical and descriptive, non-normative way; our research is located at the intersection of medical history, medical theory, media theory and literary studies, and it explores various, historical and systematic aspects of medicine and culture. Research subjects range from biological concepts of self-regulation in the 19th century and the 'making of sick child' in the mass media around 1850 to the cultural history of German bacteriology and to written clinical communication in our present. The central focus of all these projects is how medical knowledge and medical practice are intimately linked to their textual and media representations. Being fundamentally hermeneutic, our research contributes to a richer, broader, more-encompassing picture of medicine as a historically grown social and scientific system.

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SECRETARY
Margrit Walthert

POST-DOC ASSISTANTS
Dr. Dr. Felix Rietmann
PD Dr. Benjamin Specht (since April 2020)

DOCTORAL ASSISTANT
Lea Bühlmann

DOCTORAL CANDIDATE
Zeno jr. Bampi (funded by DFG)

Project 1 (Martina King): The cultural history of German bacteriology.

After Robert Koch's famous discoveries of the germs that caused Anthrax, Tbc and Cholera (1876, 1882, 1884), microbes became sensationally famous in German culture: they appeared everywhere – in mass media, in popular textbooks, in medical debates and in everyday life. The project explores the dimensions of this 'microbe entertainment' in fin de siècle and avantgarde German culture: microbe entertainment infiltrated womens' magazines and popular shows as well as fictional prose, poetry and art. Microbes served – within modernist movements such as biological monism or aesthetic dadaism – as ambivalent symbols for both death, decay, killing and life, movement, reproduction, even absolute art. The project shows that the outreach of this fundamentally scientific discourse went far beyond medicine and science. Bacteriology shaped, as entertaining sensation, political ideology, artistic stimulus and medical practice, the contours of the whole epoch; and Robert Koch was declared the prototypical German hero within expanding colonialism. The project finished in 2020; the monograph is about to appear *https://www.degruyter.com/view/title/524949*).

'Germ hoover', Fa. Nissen, in: The bacteriology of everyday life (popular textbook, Hamburg 1906).

Advertising poster of Laboratoires Anios (Lille), lithograph ca. 1910 (Wellcome collection).

Project 2 (Martina King): The history and epistemology of the medical report

The project explores – for the first time – the expert genre 'medical report' from a narratological point of view. Firstly, the history of this core medium of medical communication is investigated, drawing on sources from the *Insel Archiv Bern*. Preliminary results indicate that the medical report developed in the 1940ies and became an integral part of the patient file around 1960. Secondly, the project investigates possible epistemological functions of the contemporary medical report, claiming that it serves as a cognitive frame for physicians. The event-sequencing in medical reports has become remarkably selective, reductive and fundamentally linear over time, has lost all eventfulness and subjectivity and it can be assumed that this kind of 'mechanically objective' storytelling helps to create order and causal links, helps to understand the pathophysiology of the individual course of illness.

Project 3 (Lea Bühlmann): Self-regulation and feedback. A genealogy of ecological thinking

The project is dedicated to the genealogy of ecological thinking: It focuses on six concepts of the life sciences between the late 18th and early 20th centuries that mark central moments in this development. Around 1800, the concepts of the *surrounding Milieux* by French naturalist Jean-Baptiste de Lamarck and of *excitability* by Scottish physician John Brown initiate the idea that livings things depend on their environment; the latter is pursued by the German physician Andreas Röschlaub and thereafter by Friedrich Schelling. Around 1850, the French physiologist Claude Bernard develops the idea of a *milieu intérieur* which is, at the beginning of the 20th century, followed by the concept of *homeostasis* by the American physiologist Walter B. Cannon and the concept *Umwelt* from the German biologist Jakob von Uexküll. The thesis was submitted to the Philosophical Faculty on 30th November 2020 (see below).

Project 4 (Felix Rietmann): Audiovisual Technologies and the Rise of Infant Mental Health

The project explores epistemic, social, and cultural dimensions of audiovisual technologies in infant psychology and psychiatry in the USA and Western Europe from the mid-twentieth to the present. It investigates how scientific and medical practitioners employed cinematography, video, computational assessment methods, and digital interfaces to analyze the psychology of young children, diagnose normal and pathological development in infants, and treat relationship problems within families. The study engages with the increasing presence of old and new media in laboratories and clinics, and asks about both the limits these media pose and the opportunities they offer to science and medicine. It investigates the emergence of the recent sub-specialty of infant mental health, asking how this multi-disciplinary field shaped and was shaped by audiovisual technologies, how the discipline and the technologies have contributed to the ways we conceptualize, treat, and educate families and children today.

Selected Publications

Martina King *(2019)*

'Herzensergießungen kunstliebender Ärzte'. Praktische Heilkunde und Literatur um 1800, Alexander Honold, Grit Schwarzkopf (Eds.): Themenheft 'Medizin', in: Non-Fiktion. Arsenal der anderen Gattungen, 13. Jahrgang (2018), 1/2, Hannover 2019, p. 27-65.

Martina King *(2020)*

Hypersthenische Erkenntnis: Novalis' Beitrag zum Schwindsucht-Topos, in: Blütenstaub – Jahrbuch für Frühromantik Jg.5/ 2019, Würzburg 2020, p. 87-105.

Martina King *(2020)*

«Nach Aufnahme arterielle Hypotonie»: Personenkonzept und Kommunikationsformen in der Experten-Medizin. Gesnerus. doi: 10.24894/Gesn-de.2020.77015

Johannes Wildhaber
Petra Zimmermann

The maternal and infant microbiome and its association with health outcomes in children

Introduction

Prof Wildhaber and Dr Zimmermann and their group investigate the effect of antibiotics, during birth and infancy, on the maternal and infant microbiomes and whether changes in their composition are associated with differences in health outcomes.

GROUP LEADERS

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Prof Nigel Curtis, Department of Paediatrics, The University of Melbourne, Parkville, Australia

Valentin Scherz, Institute of Microbiology, Lausanne University Hospital and University of Lausanne, CH

Stefan Pfister, Microbiology Laboratory, Hospital HFR, CH

Diana Bandeira, Microbiology Laboratory, Fribourg Hospital HFR, CH

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Prof Anna Lauber-Biason, Faculty of Science and Medicine, University of Fribourg, CH

Jakob William, Microbiology Laboratory, Fribourg Hospital HFR, CH

Research activity

In a prospective cohort study (ABERRANT study), we use metagenomic sequencing to determine the effect of (i) intrapartum antibiotics on the composition of the breast milk, and the infant oral and intestinal microbiome (including the development and persistence of antibiotic resistance); (ii) antibiotic exposure in the first year of life on the composition of the infant oral and intestinal microbiome (including the development and persistence of antibiotic resistance); and (iii) disruption of the infant oral and intestinal microbiome on health outcomes. (iv) We also determine the compositional overlap between the maternal intestinal microbiome, the breast milk microbiome and the infant oral and intestinal microbiome.

Trial registration number: The U.S. National Institutes of Health NCT04091282.

https://clinicaltrials.gov/ct2/show/NCT04091282

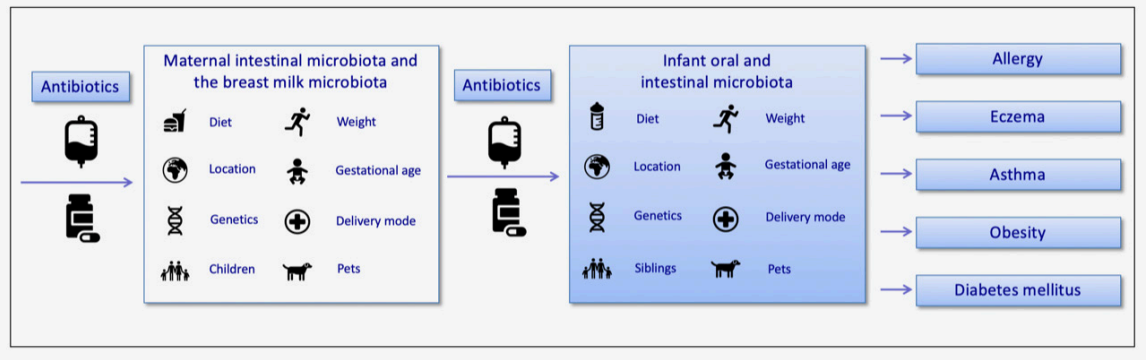

Figure 1. *Summary of factors that might influence the composition of the maternal intestinal and breast milk microbiome, and the infant oral and intestinal microbiome together with possible associated adverse health outcomes.*

MIRACLE
Microbiota and Children Laboratory Fribourg

Figure 2*. Logo of the Miracle Laboratory – Microbiota and Children Laboratory Fribourg.*

ABERRANT
Antibiotics-induced disruption of the maternal and infant microbiota

Figure 3. *Logo of the Aberrant study - Antibiotic-induced Disruption of the Maternal and Infant Microbiota and Adverse Health Outcomes.*

Selected Publications

Volery M, Scherz V, Jakob W, Bandeira D, Deggim-Messmer V, Lauber-Biason A, **Wildhaber J**, *Falquet L, Curtis N,* **Zimmermann P.** *(2020).*

Study protocol for the ABERRANT study: antibiotic-induced disruption of the maternal and infant microbiome and adverse health outcomes – a prospective cohort study among children born at term. BMJ Open. doi: 10.1136/bmjopen-2019-036275.

Zimmermann P, *Curtis N. (2020).*

Breast milk microbiota: a review of the factors that influence composition. J Infect. 81:17-47.

Zimmermann P, *Curtis N. (2020).*

Coronavirus Infections in children including COVID-19: an overview of the epidemiology clinical features diagnosis treatment and prevention options in children. Pediatr Infect Dis J. doi: 10.1097/INF.0000000000002660.

Medico-Surgical Disciplines

Moritz Tannast

Clinical research in orthopaedic surgery and traumatology

Bernhard Egger

Surgical research unit

Daniel Betticher

Medical oncology, clinical research in solid tumours, lymphomas and leukaemias

Harriet Thoeny

Imaging and data processing in urogenital radiology

Moritz Tannast

Clinical Research in Orthopaedic Surgery and Traumatology

Introduction

The research group of Prof. Tannast focuses on clinical research in the field of orthopaedic surgery and traumatology.

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Joseph M Schwab, Medical College of Wisconsin, USA

Johannes Dominik Bastian, University of Bern, CH

Michael K Ryan, American Sports Medicine Institute, Birmingham, AL, USA

Research activity

Our research covers all aspects in orthopaedic surgery and traumatology including two and three-dimensional imaging, intraoperative data acquisition, biomechanical modelling, anatomical considerations (e.g. blood supply), clinical evaluation of postoperative results, and development and evaluation of novel surgical techniques. In addition, we focus on translational medicine novel cartilage therapies in an experimental sheep model.

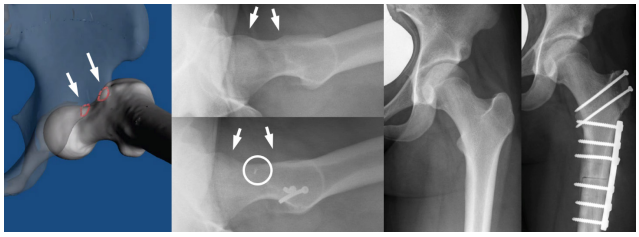


Figure 1. *The three-dimensional simulation of hip motion shows a contact between the femur and the acetabular socket due to a rotational error of the femur shaft. This has been corrected by a subtrochanteric osteotomy.*

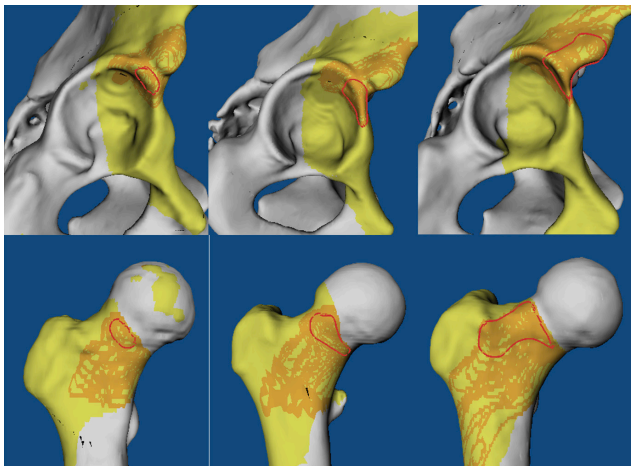


Figure 2. *The different contact zones of the three-dimensional simulation of the patient in Figure 1 are shown.*

Selected Publications

Zurmühle C, Schmaranzer F, Nuss K, Wolfer N, Ryan MK, Zheng G, von Rechenberg B, **Tannast M**. *(2019).*

Proof of concept: hip joint damage occurs at the zone of femoroacetabular impingement (FAI) in an experimental FAI sheep model. Osteoarthritis Cartilage. 7:1075-1083.

Lerch TD, Boschung A, Todorski IAS, Steppacher SD, Schmaranzer F, Zheng G, Ryan MK, Siebenrock KA, **Tannast M**. *(2019).*

Femoroacetabular impingement patients with decreased femoral version have different impingement locations and intra- and extraarticular anterior subspine FAI on 3D-CT-based impingement simulation: implications for hip arthroscopy. Am J Sports Med. 47:3120-3132.

Lerch TD, Siegfried M, Schmaranzer F, Leibold CS, Zurmühle CA, Hanke MS, Ryna MK, Steppacher SD, Siebenrock KA, **Tannast M.** *(2020).*

Location of intra- and extra-articular hip impingement is different in patients with pincer-type and mixed-type femoroacetabular impingement due to acetabular retroversion or protrusio acetabuli on 3D CT-based impingement simulation. Am J Sports Med. 48:661-672.

Bernhard Egger

Surgical Research Unit

Introduction

Our research group is aiming to develop translational and clinical research.

For the translational research, we are focusing on two main topics:

i) Liver regeneration, we are investigating the mechanisms that initiate the process of liver regeneration after injury or resection by using in vitro and small animal models. We have established a collaboration with the ETHZ (Zurich Federal Institute of Technology) and the Kings College University Hospital in London. We are testing peptides released by activated platelets that interact with liver sinusoidal endothelial cells initiating the regeneration process.

ii) Cell xenotransplantation, we aim to develop cell therapies to replace or support pancreatic or liver functions using cell encapsulation. We have ongoing collaborations with the EPFL (Lausanne Federal Institute of Technology) to develop new polymers for the cell encapsulation.

For the clinical research, we have launched protocols focusing on (i) the early detection, (ii) the pre-operative management and (iii) the treatment of patients with pancreatic adenocarcinoma.

For the detection of early pancreatic cancer, we have a collaboration with the primary care institute of the Faculty of Medicine, Geneva University. For the pre-operative management, we are collaborating with the Departments of Radiology and Surgery of the Geneva University Hospital.

GROUP LEADER
Bernhard Egger

COLLABORATORS
Léo Bühler
Carmen Gonelle-Gispert
Ana Maria Quintela Pousa
Marlène Sanchez

Translational research

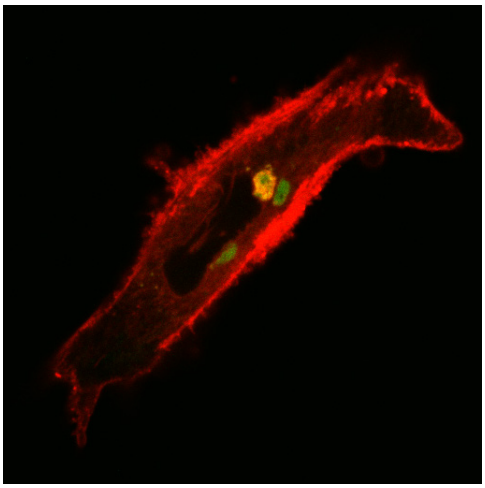
Acute liver failure due to toxic, viral or surgical resection is a dramatic clinical situation with high mortality. To find new treatments for patients with severe and life-threatening diseases of the liver, a better understanding of the molecular events regulating liver regeneration is essential. Our hypothesis is that the release of molecules by platelets, directly or indirectly, induces hepatocyte proliferation. We are using in vitro models of isolated and purified primary liver cells, as well as mouse in vivo models to elucidate the regeneration process and understand the interaction between platelets and liver cells. This study has the potential to develop new approaches for supporting liver regeneration by liposomal delivery of growth factors. This project is supported by a SPARK grant of the Swiss National Research Foundation.

To further support patients with liver or pancreatic failure, we aim to develop cell therapies to replace or support liver and pancreatic functions using cell encapsulation. We have ongoing collaborations with the EPFL (Lausanne Federal Institute of Technology) to develop new polymers for the cell encapsulation of porcine cells that we transplant into rodents with liver or pancreatic failure. Xenotransplantation, i.e. the use of animal sources for transplantation into humans could resolve the severe shortage of human organ donors.

Clinical research

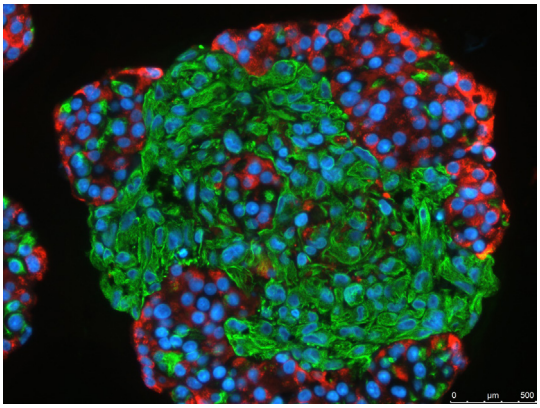
Pancreatic adenocarcinoma is one of the most aggressive cancers and overall survival of patients suffering of this disease has not made significant progress over the last two decades. We aim to improve the prognosis for patients with pancreatic cancer by improving early detection. As new onset diabetes is one early symptom of this disease, we aim to screen patients with recent diabetes by biological and radiological signs for pancreatic cancer. For patients with established diagnosis, we aim to improve the pre-operative management by using 3D printing of the tumor to allow better localization and predict surgical resectability of the tumors. Finally, we will test new molecules inhibiting the IL6 pathway for treatment of patients with metastatic pancreatic adenocarcinoma.

Bernhard Egger group



Platelet - LSEC.

Confocal microscopical view of a mouse sinusoidal liver endothelial cell (in red) with internalization of activated platelets (in green). These early interactions are initiating the liver regeneration process.



Overlay ilot msc 40x.

Immunofluorescence of aggregated human beta cells (in red) and human mesenchymal stroma cells (in green), nuclei are stained in blue. Mesenchymal stroma cells are supporting viability and function for transplanted beta cells.

Selected Publications

Balaphas A, Meyer J, Sadoul K, Fontana P, More Pl, Gonelle-Gispert C, Buhler LH. (2019).

Platelets and platelet-derived extracellular vesicles in liver physiology and disease. Hepatol Commun. 3:855-866.

Balaphas A, Meyer J, Perozzo R, Zeisser-Labouebe M, Berndt S, Turzi, P A. Fontana P, Scapozza L, Gonelle-Gispert C, Buhler LH. (2020).

Platelet transforming growth factor-beta1 induces liver sinusoidal endothelial cells to secrete interleukin-6. Cells, 10.3390/cells9051311.

Montanari E, Szabó L, Balaphas A, Meyer J, Perriraz-Mayer N, Pimenta J, Giraud MN, **Egger B**, *Gerber-Lemaire S, Bühler L, Gonelle-Gispert C. (2020).*

Multipotent mesenchymal stromal cells derived from porcine exocrine pancreas improve insulin secretion from juvenile porcine islet cell clusters. Xenotransplantation, in press.

Daniel Betticher

Medical oncology, clinical research in solid tumours, lymphomas and leukaemias

Introduction

The department of medical oncology of the HFR / UniFr is a member of the Swiss Group for Clinical Cancer Research (SAKK). Research protocols for solid tumours are activated nationally and internationally, so that:

- Our patients have access to the new, not yet approved drugs.
- Can participate in clinical research and so that the Fribourg centre is one of the oncology centres in Switzerland allowing our hospital to participate in the development of new drugs and better therapeutic strategies.

GROUP LEADER
Prof. Daniel Betticher
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DEVELOPMENT OF THE CLINICAL TRIAL UNIT
Natacha Szüts
responsible for the research unit
Dr. Adrienne Bettini

CTC
Mireille Maître
Nicole Neuhaus
Jessica Lutz
Lucille Folly
Karine Genoud

In order to increase our research activity in medical oncology and haematology, we have modified the structure of our Cinical trial unit for haemato-oncology allowing thereby patients to receive their treatments in the peripheral sites of the HFR (Riaz, Tafers, Meyriez and Payerne). Numerous changes were necessary to ensure that our research protocols could be activated transversely at all sites in the canton of Fribourg (quality assurance, ethic's approval, electronic exchange of patient documents and others). **(see Fig. 1)**.

Our activated research protocols cover in particular breast, lung and prostate cancer. Examples of running protocols:

- *Lung cancer:* Patients with lung cancer and hilary / mediastinal lymph node involvement, but without distant metastases (stage II-III), after radical surgery and adjuvant chemotherapy are randomised in our trial to immunotherapy or placebo. This highly interesting study will allow us to define the importance of supporting the immune system (immunotherapy) to eradicate the micro-metastases. We hope that this new therapeutic strategy will enhance the chance of cure. Several patients have been able to participate in this study this year. The immunotherapy drug was very well tolerated. Whether it will also achieve the goal of a better cure will only be demonstrated in the next few years.
- *Breast cancer*: Research protocols after complete resection of the breast carcinoma have investigated the importance of intensive physical activity. In fact, it has been shown that physical activity reduces the risk of breast cancer recurrence, thereby improving overall survival. A high number of patients has been included in this SAKK trial.

Other internal protocols have been developed in our centre. They examine the needs of patients with cancer:

- *Survivorship program for cancer patients at the HFR* (M. Küng, M. Bana, N. Szüts, D. Betticher), project in collaboration with the Haute École de Santé (HEDS).
- *Advanced care planning - Implementing the "SENS" structure in the daily practice of a medical oncologist* (F. Gallot Lavallée, N. Szuets, A. Ebneter, V. Dougoud, S. Eychmueller, D. Betticher), project in collaboratin with the Palliative care unit of the university of Bern.

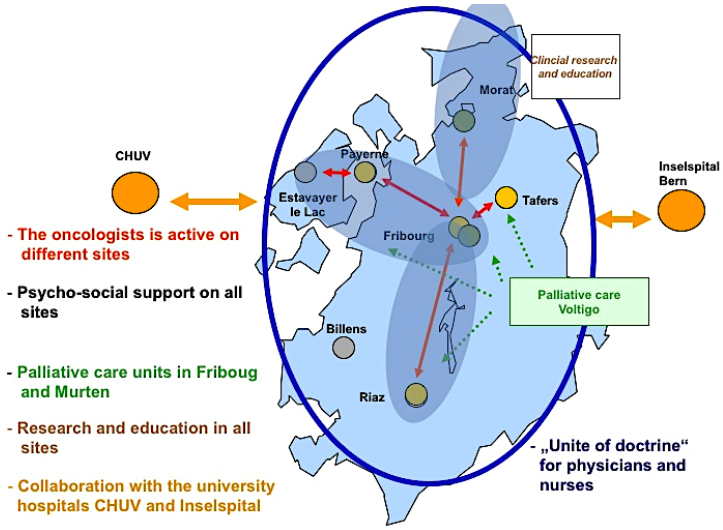

Figure 1. *The development of the HFR/UniFr centre for medical oncology/haematolgoy research. The collaboration of the different HFR sites have been just established, thus covering a large population (300'000 inhabitants).*

Selected Publications

Sood R, Mancinetti M, **Betticher D**, *Cantin B, Ebneter A. (2019).*

Management of bleeding in palliative care patients in the general internal medicine ward: a systematic review. Ann Med Surg. 50:14-23.

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Harriet Thoeny

Imaging and Data Processing in Urogenital Radiology

Introduction

Functional imaging techniques are increasingly gaining importance in clinical practice. These include methods such as diffusion-weighted magnetic resonance imaging (DW-MRI), blood oxygen level dependent (BOLD) imaging, and dual-energy computed tomography (CT). The research interest of Prof. Thoeny and her group focuses on the investigation of novel functional imaging techniques and the quantitative parameters extracted from them for the diagnosis, active surveillance and treatment monitoring of urogenital diseases with the long-term goal of integrating them into the clinical routine.

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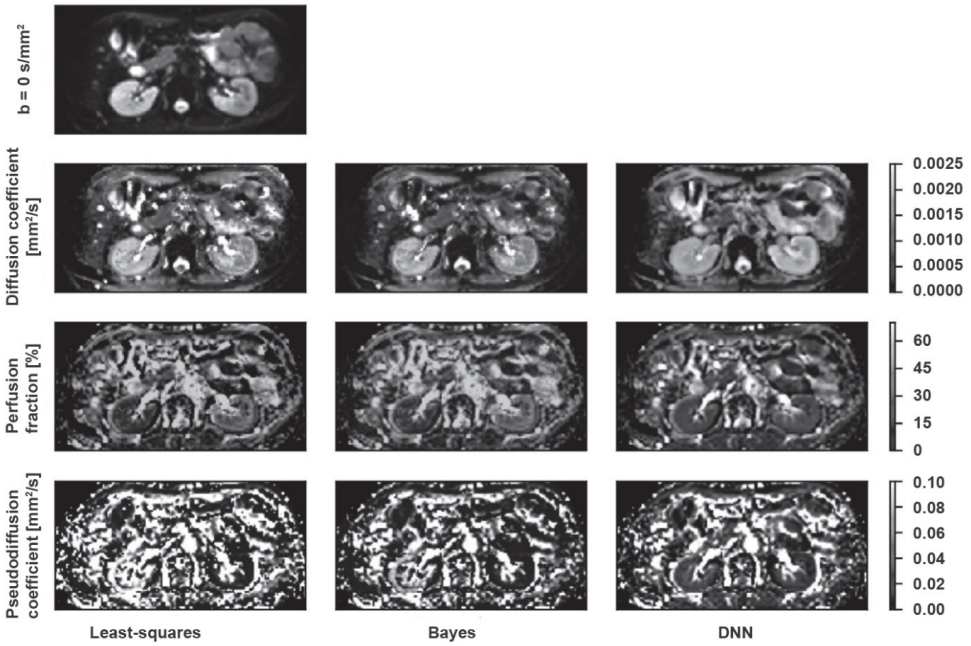
As part of a research grant awarded by the Swiss National Science Foundation, the group currently focuses on evaluating whether quantitative parameters derived from functional imaging techniques may be used as biomarkers to improve detection of clinically significant prostate cancer and to monitor disease progression in patients undergoing active surveillance with the aim of postponing or avoiding biopsy in selected cases. To achieve this goal, a main research interest is the incorporation of machine learning methods and in particular deep learning algorithms.

One prominent functional imaging technique is DW-MRI, which is sensitive to changes on the cellular level that precede pathological alterations that are visible on morphological images. Quantitative parameters may be computed from DW-MRI using the so-called intravoxel incoherent motion (IVIM) model but applicability is hampered by the limited reproducibility of the results. The group could recently show that both accuracy and precision may be increased by using deep neural networks (DNNs) for model fitting **(see Figure 1)**. Alternatively, DNNs may be utilized directly to detect and classify prostate cancer lesions and/or to extract quantitative parameters in an automated manner to improve risk assessment and help in decision-making between active surveillance and radical or focal treatment in the clinical routine. Furthermore, by increasing the detection accuracy of clinically significant prostate cancer, unnecessary biopsies may be avoided or postponed in selected future patients. However, applicability of DNNs in this context is impaired by the limited availability of high-quality medical data which are needed for training and validation of DNNs. To address this issue, a novel approach has been developed under the leadership of Prof. Cudré-Mauroux's group (eXascale Infolab, University of Fribourg, Fribourg, Switzerland) that combines layer freezing and fine-tuning steps alternatively to train DNNs over multiple and diverse datasets for cancer detection **(see Figure 2)**. In the next step, the approach will be applied to patient cohorts from the Cantonal Hospital Fribourg (Department of Radiology, Cantonal Hospital Fribourg, Fribourg, Switzerland) and the University Hospital Bern (Department of Urology, Bern University Hospital, Bern, Switzerland).

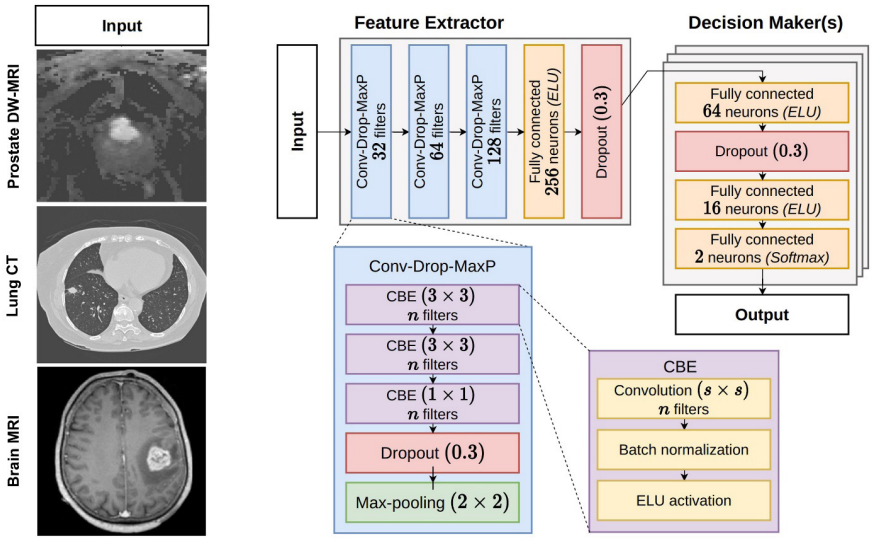
An additional research field applying functional imaging in urogenital radiology includes the assessment of imaging biomarkers in chronic kidney disease with main focus on renal DW-MRI and BOLD as part of an international COST project as well as a project funded by the Swiss National Science Foundation together with the radiology department of the University of Geneva.

Figure 1. Improving accuracy and precision of quantitative parameters derived from DWI using DNN



Axial sample image of the upper abdomen of a healthy 38 year-old volunteer with corresponding parametric maps derived using the IVIM model. In the parametric maps computed by the DNN, the outer contours of the kidneys are delineated better, and the renal parenchyma is more homogeneous compared with a least-squares fit and the Bayesian method. Furthermore, parameter values computed by the DNN are similar in the right and the left kidney, as expected in a healthy volunteer (adapted from Barbieri S et al. Magn Reson Med. 2020; 83(1): 312-321).

Figure 2. Improving cancer detection by a novel framework that enables training a DNN on multiple and diverse datasets.



The neural network architecture is split into a feature extractor and multiple independent decision makers. In this manner, generic features that are common across several datasets (here prostate DW-MRIs, lung CTs, and brain MRIs) may be learned which leads to improvements in accuracy for cancer detection (adapted from Cuccu Get al. IEEE Big Data 2020: SP03204).

COLLABORATIONS

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Zimmermann P*, Curtis N. (2020).*
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Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review. Arch Dis Child. 105:201-208.

Zimmermann P*, Ritz N, Curtis N, Tebruegge M. (2020).*
In reference to the management of nontuberculous mycobacterial cervicofacial lympha denitis: a view beyond surgery. Laryngoscope. doi: 10.1002/lary.28608.

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Prophylactic antibiotics after operative vaginal delivery. Lancet. doi: 10.1016/S0140-6736(19)32632-7.

INVITED LECTURES AND SEMINARS GIVEN BY DEPARTEMENT MEMBERS

Group Jean-Marie Annoni

J.M. Annoni. Third Conference on Interdisciplinarity in Translation and Interpreting, SISU.
Shanghai (China), November 2019

Group Daniel Betticher

D. Betticher Presentation on lung cancer in Geneva
Activity within the Swiss Academy of Multidisciplinary Academy
(https://www.samo-workshop.ch)
Geneva, 2019

Group Marco Celio

M.R. Celio. Symposium, Karolinska Institute. Neuronal substrate of eye movement during REM-sleep.
Stockholm (Sweden) April 2019

M.R. Celio. Symposium, Karolinska Institute. The gains in the brain are mainly in the stain.
Stockholm (Sweden) April 2019

Group Arnaud Chiolero

A. Chiolero. Centre de Recherche du Centre Médical de l'université de Montréal (CHUM). Hypertension in Children: from Screening to Primordial Prevention.
Montreal (Canada), January 2019

S. Cullati. Workshop of the NCCR LIVES. Educational reserve and health.
University of Geneva, April 2020

Group Stéphane Cook

Marie-Noëlle Giraud

L. Dumas. LS2 annual congress. Role of fitness in a myocardial infarction event.
Zürich, February 2019

M.N. Giraud. European Society of cardiology Congress 2020 - The digital experience. As a biopatch, fibrin and bone marrow-derived cells modulate macrophage polarization and cardiomyoblasts proliferation.
August 2020

MN. Giraud. Printemps de la Cardiologie – Digital. Extracellular matrix for heart regeneration.
Fribourg, October 2020

Group Bernhard Egger

L. Bühler. Congress of the International Xenotransplantation Association. Xenotransplantation of encapsulated liver cells for the treatment of liver failure.
Münich, October 2019

Group Gregor Hasler

G. Hasler. Neuroscience Distinguished Lectureship Series. Psychotherapy, Psychedelics, and Neuroplasticity.
Toronto (Canada) February 2020

Group David Hoogewijs

D. Hoogewijs. 8th Research Day in Medicine. Oxygen binding and sensing: beyond hemoglobin and myoglobin.
Fribourg, March 2019

A. Keppner. Annual Swiss Physiology Meeting. Genetic ablation of the newly identified androglobin leads to multiple phenotypes.
Bern, September 2019

D. Maric. Annual Swiss Physiology Meeting. Novel erythropoietin regulating transcription factors.
Bern, September 2019

D. Maric. 98th Annual Meeting of the German Physiological Society DPG. Novel erythropoietin regulating transcription factors.
Ulm (Germany), October 2019

D. Hoogewijs. Mini-symposium future perspectives of biomedical science studies. The beauty and the beast of an academic path.
Fribourg, October 2019

A. Keppner. Annual Swiss Physiology Meeting. Genetic ablation of the newly identified androglobin leads to multiple phenotypes.
Fribourg, September 2020

T. Koay. Annual Swiss Physiology Meeting. Unraveling the cryptic transcriptional landscape of the androglobin gene.
Fribourg, September 2020

M. Correia. Annual Swiss Physiology Meeting. Absence of androglobin leads to male infertility.
Fribourg, September 2020

Group Martina King

M. King. Invited lecture at SFB 1288 Midterm-conference «Vergleichen - Interdisziplinär». Zentrum für interdisziplinäre Forschung der Universität Bielefeld. Tasthaare, Gesteinsschichten, Damenmoden: Epistemologie des Vergleichens zwischen Natur und Kultur – um und nach 1800.
Bielefeld, (Germany) March 2019

F. Rietmann. History of Science Society Annual Meeting. Raising a Well-Grown Child: Medial and Material Cultures of Child Health in the Early 19th Century.
Utrecht, (The Netherlands) July 2019

Z. Bampi. Vortrag gehalten auf der Kasseler Jahrestagung der Arbeitsgemeinschaft Literarischer Gesellschaften und Gedenkstätten e. V. Bewegte Dichtung in bewegter Zeit. Die Reisefeuilletons des Jungen Deutschland.
September 2019

F. Rietmann. Séminaire de formation et recherche, GHU Paris Psychiatrie et Neuroscience. Visualiser l'esprit de l'enfant: vers une épistémologie historique de l'observation de la petite enfance.
Paris (France), January 2020

F. Rietmann. HSSuisse, EPFL. Towards a Media History of Child Health: Problems and Perspectives. Lausanne, March 2020

F. Rietmann. Forschungskolloquium at the Center for Medical Humanities. Narrating Infant Experiences: Audiovisual Tools in the Clinic and around the Globe.
Zürich, March 2020

B. Specht. Conference, organized by Michael Gamper and Uta Böhme (SFB 1688 Ästhetische Eigenzeiten): Physiker lesen, Physiker schreiben. Die Literatur der Physik. FU Berlin. Alles Vergängliche / Ist nur ein Gleichnis? Hermann von Helmholtz liest Johann Wolfgang von Goethe.
Berlin (Germany), March 2020

Group Anna Lauber-Biason

A. Lauber-Biason. Kinderspital Kolloquium (Zürich). The Secret Life of Flies and the Power of Stem Cells: New Perspectives for Human Sex Development and its Defects.
Zürich, March 2019

A. Lauber-Biason. Ginecologia e Genetica. Disturbi della pubertà e presa a carico della giovane paziente.
Lugano, December 2019

A. Lauber- Biason DSD and exome sequencing.
UniGE Geneva, October 2019
Die Herausforderung pädiatrischen Labormedizin.
St.Gallen, February 2020

A. Lauber- Biason UniSpital Basel Weiterbildung. The Secret Life of Flies and the Power of Stem Cells: New Perspectives for Human Sex Development and its Defects.
Basel, June 2020

Group Patrice Nordmann

P. Nordmann. Symposium: Rapid Antibiotic Susceptibility Testing. Emerging Antibiotic Resistance in Gram negatives and their rapid diagnostic.
Uppsala University (Sweden) 2019

P. Nordmann. Microbiology and Infectious Diseases, (ECCMID). Overview of rapid diagnostics: current and potential future role. Futur Outlook on Gram-Negative Resistance: From Shifting Epidemiology to Improving the Paradigm of Care.
Amsterdam (The Netherlands), April 2019

P. Nordmann. Club Pathologie Infectieuse - Society for Antimicrobial Chemotherapy. Emerging Antibiotic Résistance phenotype / genotype in Switzerland.
Bern, February 2019

P. Nordmann. Association des responsables de laboratoire de la Suisse Romande. Résistance aux Antibiotiques Emergentes et leur diagnostic rapide en 2019.
Yverdon-les-Bains, March 2019

P. Nordmann. Glaxo Smith Kline Beecham. Emerging Resistance to Antibiotics in 2019; novel antibiotics.
Bruxelles (Belgique), September 2019

P Nordmann. Séminaire bioMérieux. Résistances Emergentes aux Antibiotiques chez les bacilles à Gram négatif.
Genève, May 2019

P. Nordmann Symposium: Congrès de la Société Suisse de Microbiologie. Diagnostic challenges of Gram negative multidrug resistant organisms.
Zürich, September 2019

P. Nordmann. Basel Life 2019. Emerging antibiotic resistance in Gram negatives and their rapid diagnostic.
Basel, September 2019

P. Nordmann. Merani Symposium. Carbapenemases producers in Switzerland in 2020.
Bern, January 2020

P. Nordmann. World antibioic Awareness week. Interdisciplinary biotechnology univt, Faculty of Life Sciences. Aligarh Muslim University (AMU)
Aligarh (India), November 2020
WebEx ID:574 751 292

L. Poirel. International Conference on One-Health Antimicrobial Resistance (ICOHAR). Emergence of acquired polymyxin resistance in Gram negatives; perfect example of a One-Health issue.
Utrecht Rthe Netherlands), April 2019

L. Poirel. ESCMID Postgraduate Technical Workshop Diagnostic Microbiology: MALDI-TOF, bacterial genomics, metagenomics, automation and molecular microbiology. Carbapenemases: how to detect them?
Lausanne, September 2019

L. Poirel. 7èmes Journées Suisses des Vétérinaires. Emergence of acquired polymyxin resistance in Gram negatives; perfect example of a One-Health issue.
Fribourg, May 2019

L. Poirel. ESCMID Postgraduate Education Course “Phenotypic and Molecular approaches for Detection and Control of Carbapenem- and Colistin-resistant Gram-negatives”. “Resistance genes / phenotypes pf carbapenem- and colistin-resistant Enterobacterales” and “Resistance genes / phenotypes of ESBL-producing Enterobacterales”.
Volos (Greece), May 2019

L. Poirel. International Congress of CiiEM “Health, Well-Being and Ageing in the XXI century. Resistance to last-resort antibiotics in Gram negatives; mechanisms, epidemiology, and detection strategies.
Lisbon (Portugal), June 2019

L. Poirel. 3rd International Caparica Congress in Antibiotic Resistance. Acquired resistance to polymyxin antibiotics in Gram negatives; mechanisms, epidemiology, and detection strategies.
Caparica (Portugal). June 2019

L. Poirel. 12th International Symposium on the Biology of Acinetobacter. Role of rapid diagnostics in prevention and control of multidrug-resistant Acinetobacter.
Frankfurt (Germany), September 2019

L. Poirel Colloque Résistance aux Antibiotiques, Centre Hospitalier Général de Troyes, France. Résistances aux antibiotiques ; pourquoi c’est si compliqué?
Troyes (France), January 2020

L. Poirel. Institut Hospitalo-Universitaire (IHU). Marseille, France. Gènes de résistance acquis aux antibiotiques ; “silence, on tourne !
Marseille (France), January 2020.

Group Mario Prsa

M. Prsa. Neurobiology seminar, University of Fribourg. A roadmap for artificial sensory feedback.
Fribourg, November 2019.

M. Prsa. Day of Cognition 2020, University of Fribourg. Tuned to vibrations: selective neuronal and perceptual encoding of forelimb pallesthesia.
Fribourg, October 2020.

Group Curzio Rüegg

S. Cattin. 2nd Swiss Cytometry Meeting. Unsupervised analysis of flow cytometry clinical data: How to deal with algorithms as lambda researcher.
Lausanne, February 2020

C. Rüegg. Journées en recherche et imagerie de la santé (RITS). Cancer cell detection through a bio-inspired amplification approach.
Tours (France), May 2019

Group Michael Schmid

Ernst Strüngmann. Symposium, Frankfurt (Germany), 2019

Group Beat Schwaller

B. Schwaller. 8th Research day in Medicine, UniFR and HFR. Parvalbumin neurons as a hub in autism spectrum disorder (ASD).
Fribourg, March 2019

Group Jens Stein

J. Stein. Invited seminar. Kyushu University (Japan). Mechanisms of CD8 T cell surveillance in vivo.
Kyushu (Japan), May 2019

J. Stein. European Chemokine and Cell Migration Conference. Chemokine-controlled host protection by CD8 T cells.
Salamanca (Spain), June 2019

J. Stein. 50 year symposium Dept. Immunology, University of Zurich. Actomyosin cytoskeleton during CD8 T cell activation.
Zürich, July 2019

J. Barreto de Albuquerque. 18th International Congress of Mucosal Immunology. Oral infection triggers systemic CD8 T cell immunity.
Brisbane (Australia), July 2019

J. Stein. Cancer Immunology Ph. D. course. Mechanisms of CD8 T cell surveillance in vivo.
Lausanne, August 2019

J. Stein. Brazilian Congres of Immunology. Chemokine-controlled host protection by CD8 T cells.
Florianopolis (Brazil), October 2019

J. Stein. Immunology research seminar series. Actomyosin cytoskeleton during CD8 T cell activation.
Cambridge (UK), October 2019

J. Stein. Online seminar for Ph.D. course, San Raffaele. Mechanisms of CD8 T cell surveillance in vivo.
Milan (Italy), October 2020

Group Csaba Szabo

C. Szabo. Gordon Conference. The pathophysiology of H2S/NO interactions
Ventura, CA (USA), February 2019

C. Szabo. International Union of Biochemistry and Molecular Biology (IUBMB) Keynote Lecture, FEBS Meeting. H2S: an endogenous gasotransmitter with diverse roles ranging from cardiovascular disease to cancer.
Krakow (Poland), July 2019

C. Szabo. Greek Academy of Sciences. The World According to PARP: Poly(ADP-ribose) polymerase, a multifunctional enzyme with roles in neuroinjury, vascular disease, critical illness and cancer - from basic science to pharmacological modulation and clinical translation.
Athens (Greece), October 2019

C. Szabo. Annual Meeting of the European Shock Society. Effects of the PARP inhibitor olaparib in sepsis and pancreatitis.
Chania, Crete (Greece), October 2019

C. Szabo. Department of Pharmacology, University of Lausanne. PARP: a multifunctional enzyme with roles in cancer and non-oncological diseases.
Lausanne, November 2019

C. Szabo. Institute of Genetics and Molecular and Cellular Biology. Regulation of cellular metabolism by H2S.
Strasbourg (France) January 2020

C. Szabo. Redox 2020 Meeting. H2S in cancer.
Paris (France), October 2020

C. Szabo. World Mitochondria Society Meeting. The role of the CBS/H2S system in Down Syndrome.
Berlin (Germany), October 2020

Group Harriet Thoeny

H.C. Thoeny. European Congress of Radiology (ECR). Functional imaging of the kidneys - Chairperson’s introduction.
Vienna (Austria), 2019

H.C. Thoeny. European Congress of Radiology (ECR). Prostate MRI: the accreditation issue - Towards a certified radiologist.
Vienna (Austria), 2019

H.C. Thoeny. European Congress of Radiology (ECR). Renal, adrenal and urinary tract pathologies. A. Renal pathologies.
Vienna (Austria), 2019

H.C. Thoeny. International Diagnostic Course Davos (IDKD). Differential Diagnosis of Focal Renal Masses.
Davos, 2019

H.C. Thoeny. Visiting Professor, Medical University of South Carolina (MUSC) - From NSF to Brain Hyperintensities - Update on Gadolinium-based Contrast Agents: grand rounds, differential diagnosis of focal renal masses: teaching for resident - Interactive teaching course: focal renal masses.
Charleston (USA), April 2019

H.C. Thoeny. Workshop. European School of Radiology (ESOR). Imaging of metastatic lymph nodes: focus on DWI - Asklepios Course.
St Petersburg (Russia), May 2019

H.C. Thoeny. European Society of Urogenital Radiology (ESUR). Prostate Cancer: local staging.
Rome (Italy), May 2019

H.C. Thoeny. European School of Radiology (ESOR). GALEN Advanced Course on Oncologic Imaging: Imaging from Head to Toe. Update of Prostate Cancer Imaging.

H.C. Thoeny. Workshop on Prostate Cancer Imaging. European Society of Urogenital Radiology (ESUR).
Dublin (Ireland), September 2019

H.C. Thoeny. MRI in Oncology. Diagnosis and management of renal lesions.
Novara (Italy), September 2019

H.C. Thoeny. Workshop-Prostate Imaging-Reporting and Data System (PI-RADS) for All: Prostate Cases. International Cancer Imaging Society (ICIS).
Verona (Italy), November 2019

H.C. Thoeny. European Multidisciplinary Congress on Urological Cancers (EMUC). Prostate cancer screening by MRI: Will it ever happen?
Vienna (Austria), November 2019

H.C. Thoeny. Financial Outlook of Radiology from International Perspective. Radiological Society of North America (RSNA).
Chicago (USA), November-December 2019

H.C. Thoeny. European Congress of Radiology (ECR). Online Highlights Session - European Diploma Prep. Session: Prostate Imaging.
Vienna (Austria), August 2020

H.C. Thoeny. European Multidisciplinary Congress on Urological Cancers (EMUC), Online Congress.
- Oligometastatic disease in genito-urinary cancers
- Take home messages and closing remarks

Athens (Greece), November 2020

Group Johannes Wildhaber

Petra Zimmermann

P. Zimmermann. Annual Meeting European Society for Paediatric Infectious Diseases (ESPID). Factors influencing antibody responses to routine immunisations during the first year of life.
Ljubljana (Slovenia), May 2019

P. Zimmermann. Westschweizer Repetitorium Pädiatrie. Updates Infectiologie pédiatrique.
Fribourg, February 2019

THIRD PARTY FUNDINGS TO GROUP LEADERS

Group Jean-Marie Annoni

S. Schwaab and JM Annoni. Linguistic, cognitive, and neural predictors in the ability to detect and learn L2 stress: The impact of L1, musical aptitude, phonological awareness, auditory working memory and brain activation.
Pool de recherche project from UNIFR 35'000 CHF.

L. Alberi. (and Pr. Draganski, Annoni, and Demonet). "BrainFit4Life Symposium Series" within the program "TFV – Networking Events Series" (Innosuisse).
115'940 CHF. 2021-2024

Group Daniel Betticher

These funds allow the support of clinical trial coordinators and study nurses for the conduct of clinical research trials (budget: 220'000.- / year). Founds:
- SAKK: 188'946 CHF
- Pharmaceutical companies (Novartis, Novocure TTS): 43'897 CHF

Group Arnaud Chiolero

A. Chiolero (PI). Swiss National Science Foundation (SNSF). Personalized preventive care and life expectancy among older multimorbid adults.
495'000 CHF. 2020-2022

A. Chiolero & S. Cullati (CO-PI). Swiss School of Pubic Health (SSPH+). Corona-Immunitas: Research program to determine the SARS-CoV-2 immunity of the Swiss population.
330'000 CHF. 2020-2021

A. Chiolero (CO-PI). Ligue contre le Cancer. Examining Cancers and Labor Indicators to assess the Burden (ExCaLIBur).
226'800 CHF. 2019-2022

A. Chiolero (CO-POI). Microsoft Swiss Joint Research Centre. Monitoring, modeling, and modifying dietary habits and nutrition based on large-scale digital traces.
285'000 CHF. 2019-2021

S. Cullati (PI). Swiss National Science Foundation (SNSF). Social inequalities in the gut microbiome: individual participants meta-analyse of population-level data.
79'642 CHF. 2020.

Group Bernhard Egger

C. Gonelle-Gispert SPARK (PI). Swiss National Science Foundation (SNSF). Intra-portal TGF-ß delivery by liposomes to stimulate liver regeneration.
99'977 CHF. 2020-2021

Group Gregor Hasler

G. Hasler (PI). Swiss National Science Foundation. A combined PET-MRS investigation of the metabotropic glutamate receptor 5 in first-episode psychosis and clinical high risk for psychosis.
588'000 CHF.

G. Hasler (PI). Vontobel Foundation, Zurich, DEBOTA - Botulinum Toxin A as a new treatment option for depression.
53'537 CHF.

Group David Hoogewijs

D. Hoogewijs Human clinical cooperative project (PI). National Centre of Competence in Research (NCCR) Kidney. Novel Epo regulating factors.
60'000 CHF. 2019-2021

A. Keppner Junior Grant (PI). National Centre of Competence in Research (NCCR) Kidney.CH. Renal role of androglobin.
180'000 CHF. 2020-2023

D. Hoogewijs R'Equip (CO-PI). Swiss National Science Foundation (SNSF). Multichannel confocal microscope.
402'000 CHF.

Group Martina King

F. Rietmann (PI). Raising a well grown child: media and material cultures of child health in the early nineteenth century (SNSF Ambizione Grant No: PZ00P1_193557 / 1). Research project Ambizione. duration
864'687 CHF. 2021-2025.

Group Anna Lauber-Biason

A. Lauber-Biason (PI). Swiss National Science Foundation. Grant n° 320030_184807. Understanding human sex development and its defects: novel approaches.
538'606 CHF. 2019-2023.

A. Lauber-Biason (PI). Research Pool University of Fribourg. High glucose-sensitive nanocarriers for diabetes treatment.
12'600 CHF. 2019-2020

Group Patrice Nordmann

Ministry of Health, Bern. National Reference Center for Emerging Antibiotic Resistance (NARA). P. Nordmann (PI)
1'277'100 CHF. 2019-2021

P. Nordmann (PI). National Research Program Swiss National Science Fundation (SNSF) Emerging Antibiotic Resistance in Gram-negative bacilli: deciphering acquired resistance mechanisms to ß-lactam/ß-lactamase inhibitor combinations and to.
474'000 CHF 2020-2022

Group Mario Prsa

M. Prsa. Eccellenza Professorial Fellowship (PI). Swiss National Science Foundation (SNSF). Dissecting Neural Mechanims of Motor Learning in the Cerebellum with Optical Techniques.
1'800'000 CHF. 2019-2024

M. Prsa. Catalyst fund (PI) Fondation Bertarelli. Feel the vibe: expand the range of perceptible vibrations for the hearing impaired.
142'000 CHF. 2020-2022

Group Gregor Rainer

SNF Project 182504.
724'286 CHF. 2019-2023

Group Curzio Rüegg

C. Rüegg, B. Rothen-Ruthishauser. NCCR Bioinspired Material (CO-PI). Swiss National Science Foundation (SNSF). Development of a tumor cells/immune organoid model.
367'500. CHF. 2019-2022

C. Rüegg (PI). ISREC Foundation. Single cell transcriptomic and phenotypic profiling of blood circulating leukocytes in early breast cancer and breast cancer relapse.
314'520 CHF. 2020-2022

C. Rüegg (PI). Innosuisse. Immuno-diagnostic blood test for breast cancer monitoring.
269'298 CHF. 2020-2022

M. Bousquenaud (PI). Pool de Recherche University of Fribourg. Characterizing the role of CCN1 in obesity-mediated colorectal cancer.
23'700 CHF. 2019-2020

J. Stalin. SPARK (PI). Swiss National Science Foundation (SNSF). Unravelling the role of NOX1 and NOX4 in metastatic breast cancer progression and metastatic dissemination.
100'000 CHF. 2020-2021

S. Kocabey, and G. Acuna (CO-PI). NCCR Bioinspired Material. Detection of Circulating Tumor Cells (CTCs) by Surface Enhanced Raman Scattering (SERS) using DNA based systems as signal amplifier.
200'000 CHF. 2020-2022

S. Kocabey. MSCA-IF. EU Horizon 2020 (PI). miRNA assay system based on self-assembled nanoscale DNA arrays.
203'000 EUR. 2021- 2023

Group Michael Schmid

EU international PhD training network grant In2primateBrains

Group Lucas Spierer

M. De Pretto. Swiss Parkinson Foundation. Boosting rhythmic auditory stimulation therapy with swing to improve gait in Parkinson's disease.
60'000 CHF. 2019-2020

M. De Pretto. (PI) SNF Sparks. Can swing enhance auditory stimulation therapy for gait disturbance in Parkinson's disease?
88'000 CHF. 2020

L. Spierer. (PI) UNIFR Research Pool. SwissMedics notification of rehabilitation software as Medical Device.
50'000 CHF. 2019-2020

Group Jens Stein

J. Stein. Forschungspool UNIF(PI). Photoconversion for immune surveillance.
25'000 CHF. 2020

J. Stein (with B. Egger, F. Meyenhofer, S. Sprecher, A. Jazwinska, D. Hoogewijs, M. Geisler, P.-Y. Mantel). SNF R'equip grant (CO-PI). Multichannel confocal microscope with fluorescence lifetime imaging for life science samples.
401'028 CHF. 2019-2020

J. Stein. SNF SPARK project grant (PI). Using super-resolution shadow imaging (SUSHI) to quantify the extracellular space structure in tissue sections.
96'400 CHF. 2019 – 2020

J. Abe. Vorbereitung von Projekten (PI). Forschungspool der Universität Freiburg. Establishing a platform to exploit CRISPR/Cas9 for optimal cytotoxic immune responses against tumors.
33'000 CHF. 2019-2020

J. Abe. Förderung für Forschungsnachwuchs (Project No. 1154) (PI). Jubiläumsstiftung der Schweizerischen Lebensversicherungs- und Rentenanstalt für Volks- gesundheit und medizinische Forschung. Mechanismen der organ-spezifischen Wanderung von CD8+ T-Zellen für optimale anti-mikrobielle und anti-tumorale Wirkung.
20'000 CHF. 2019-2020

J. Abe. Starthilfe für den wissenschaftlichen Nachwuchs (PI) Werner und Hedy Berger-Janser Stiftung zur Erforschung der Krebskrankheiten. Establishing a platform to exploit CRISPR/Cas9 for optimal cytotoxic immune responses against tumors.
45'000 CHF. 2019

Group Csaba Szabo

C. Szabo (PI). Swiss Krebsliga. Role of CBS and H2S in colon cancer. To characterize the role of the CBS system in colon cancer cells.
350'000 CHF. 2019-2022

C. Szabo (PI). LeJenue Foundation (Paris, France). CBS-derived H2S overproduction in Down Syndrome. To characterize the functional role of the CBS/H2S system in Down Syndrome. 450'000 CHF. 2019-2021

C. Szabo (PI). Swiss National Foundation. Repurposing of a clinically used PARP inhibitor for the experimental therapy of ARDS. To evaluate the cytoprotective and potential therapeutic potential of clinically approved PARP inhibitors.
700'000 CHF.2020-2023

C. Szabo (PI). Leading House. PARP inhibition for the experimental therapy of sepsis. To collaborate with the University of Sao Paulo to evaluate the efficacy of PARP inhibition in critical illness.
25'000 CHF. 2020-2021

Group Moritz Tannast

C. Heinen-Vees (PI). Research Grant Swiss Orthopaedics. Biomechanical analysis of transversal locking by Kirschner wires and temporary arthrodesis by plating in unstable Lisfranc injuries.
20'000 CHF. 2019

T. Martinho (Principal investigator). Research Grant Swiss Orthopaedics. Presence and topographical distribution of mechanoreceptors in the ligamentum capitis femoris – a multicenter immunohistological study.
20'000 CHF. 2019

V. Stetzelberger (Principal investigator). Research Grant Swiss Orthopaedics. The Fossa-Foveolar-Mismatch: Biomechanical 3D-based Evaluation of the Foveolar Tracking in the Acetabular Fossa in Hips with Femoral Malversion.
20'000 CHF. 2020

Group Harriet Thoeny

HC Thoeny Project funding in biology and medicine. n° 32003B_176229. (PI). Swiss National Science Foundation (SNSF). Personalized imaging for active surveillance of prostate cancer patients.
632'000 CHF. 2019-2022

Group Michael Walch
Pierre-Yves Mantel

M. Walch. Kurt-und-Senta Herrmann Stiftung project grant (PI). The role of caspases in the control of intracellular bacteria.
2020-2021

M. Walch. Research Pool UNIFR project grant (PI). Caspase death proteases in the control of intracellular bacterial infections.
2020-2021

M. Walch. Vontobel Foundation project grant (PI). A comprehensive analysis of granzyme substrates in pathogenic bacteria as a guideline to novel targets for antibiotic therapy.
2020-2022

M. Walch. Novartis Foundation project grant (PI). Identify immune protease substrates in pathogenic bacteria that are important for infectious growth.
2020-2021

P-Y. Mantel. Kurt-und-Senta Herrmann Stiftung. Characterization of extracellular vesicles in malaria patients.
2020-2021

P-Y. Mantel. Research Pool University of Fribourg. Cell engineered vehicles for drug delivery to SARS-CoV-2 infected cells.
2021

P-Y. Mantel. SNSF project grant (PI). Investigating the role of cellular communication to promote bacterial infections during malaria.
2019-2023

Group Johannes Wildhaber
Petra Zimmermann

P. Zimmermann. Forschungspool Universität Fribourg. Pilot project for antibiotic-induced disruption of the maternal and infant microbiome and adverse health outcomes.
38'200 CHF. 2020-2021

P. Zimmermann. Swiss Society of Paediatrics. SPSU study on SARS-CoV-2.
5'000 CHF. 2020

P. Zimmermann. Pediatric Infectious Disease Group of Switzerland, SPSU study on SARS-CoV-2.
2'000 CHF. 2020

FUTHER ACHIEVEMENTS

Group Jean-Marie Annoni

Networking

Jean Marie Annoni: Vice President of Ethic Research Committee, hospital Fribourg 2019.

Public outreach activities: radio, TV, press

Café Scientifique, University of Fribourg : éthique et médecine, octobre 2020.

Group Marco Celio

Creation of novel structures

Human embryology web-site accessible with handy and tablets (www.embryology.ch) (2019-2020).

Awards

In the *"Lifetime Citation Rankings"* (PLOSBiology, 2019) M Celio was listed as the third most highly cited investigator at the University of Fribourg.

Scientific committee

Opponent in the doctoral thesis committee of Paul Williams, Karolinska Institute, Stockholm (April 6, 2019).

President of the committee in charge of hiring a new Histology professor, University of Barcelona (January 2020).

Group Stéphane Cook

Marie-Noëlle Giraud

Member of the Center for Applied Biotechnology and Molecular Medicine (CABMM) Zurich.

Ordinary nucleus member of the ESC Working Group on Cardiovascular Regenerative and Reparative Medicine.

President of the cardiovascular biology working group associated with Life Science Swiss and the Swiss Society of Cardiology.

Scientific consultant for the magazine FaireFace of the Association Suisse des Paralysés ASPr-SVG | Polio.ch.

Group Gregor Hasler

Scientific committee

G. Hasler has been elected to the program committee of the International Society for Bipolar Disorder Annual meeting.

G. Hasler has been elected Secretary of the Section on Pharmacopsychiatry of the World Psychiatry Association (WPA).

Networking

G. Hasler is president of the Swiss Society of Bipolar Disorders.

G. Hasler is president of the Swiss Society of Pharmacovigilance in Psychiatry.

Public outreach activities: radio, TV, press

G. Hasler has been several times on radio and television to talk about topics related to psychiatry and psychotherapy (*10 vor 10*, *Puls* etc.).

He published a updated version of his best-selling book *"The Gut-Brain-Connection"* and published a new book *"Pharmakotherapie, Wirkung, Nutzen, Grenzen"* in Beobachter-Verlag.

Group David Hoogewijs

Awards

Young Investigator award 2020 of the *Stiftung für Physiologie*, Swiss Physiological Society (Anna Keppner).

Young Investigator award 2019 of the *Stiftung für Physiologie*, Swiss Physiological Society (Anna Keppner).

DPG award 2019, German Physiological Society (Teng Wei Koay).

Scientific committee

Board member of the Swiss Physiological Society (D. Hoogewijs).

Group Martina King

Scientific committee

Martina King: external committee member for Habilitation Dr. Sonja Klimek (Modern German literature and comparative literature), 26.11.2019, Philosophical faculty, Fribourg University.

Martina King: external committee member for PhD Linda Ratschiller (History), 6.6.2020, Philosophical faculty, Fribourg University.

Martina King: committee member for the Henry-E.-Sigerist-Prize in the history of medicine and science (Swiss Society for the History of Medicine and Science).

Martina King: Co-editor (with Vincent Barras, Mariacarla Gadebusch-Bondio, Susanne Michl) of new book series *"Medical Humanities"*, Verlag Schwabe, Basel.

Felix Rietmann: secretary and member of steering committee of the Swiss Society for the History of Medicine and Sciences.

Felix Rietmann: Expert for Swiss national competition Science et Jeunesse, expert for «L'influence de l'éthique sur les décisions médicales relatives à la prématurité» by Luisa Miranda Oliveira.

Benjamin Specht: Co-editor (with Juliane Blank, Bernard Dieterle, Manfred Engel, Monika Ritzer): KulturPoetik. Zeitschrift für kulturgeschichtliche Literaturwissenschaft Journal for Cultural Poetics.

Public outreach activities: radio, TV, press

Martina King: *SRF* television programme *"Sternstunde Religion",* 19.4.2020, visible on srf play
https://www.srf.ch/play/tv/sternstunde-religion/video/corona-verschwoerungsmythen-und-andere-seuchen?urn=urn:srf:video:94608f5a-830b-4673-861d-b31a2589c129

Martina King: "Seuchen bieten Erzählungen realen Grauens» Samstagsinterview Bieler Tagblatt, 14.3.2020
https://www.bielertagblatt.ch/nachrichten/fokus/seuchen-bieten-erzaehlungen-realen-grauens

Group Anna Lauber-Biason

Networking

Swiss Representation and active participation in international consortia, e.g. COST Action DSDnet of the European Community *(http://www.dsdnet.eu/general-information-in-english.html)*

Member of the Scientific Committee of the International Foundation on study on Congenital Adrenal Hyperplasia (IFCAH). Several Collaborations with colleagues inland and abroad (see also publication list).

Public relations and communication

Significant contribution in communicating advances in DSD research and understanding to the community *(most recent Horizons https://issuu.com/snsf/docs/hoizons_107-en-issue?e=1883535/31585077; Tages Anzeiger 02.03.2016, page 58).*

Group Patrice Nordmann

Creation of novel structures

2020: European Institute for Emerging Antibiotic Resistance (France, Germany, Italy, Switzerland).

Awards

2019 and 2020. Thomson Reuters ISI Awards 2017 to 1% most cited scientifics worldwide (all scientific fields: 4100 nominees worldwide, 100 for Switzerland, 120 for France). Ranking of P. Nordmann and L. Poirel in Pharmacology and P. Nordmann in addition in Microbiology/Immunology and in France.

Award Universtiy of Fribourg, Outstanding Ph Thesis 2020; N. Kieffer.

Patents and Industrial development

Dimercaptsuccinic acid as ß-lactamase inhibitor. 2019. University of Fribourg. Patent obtained in the USA and in Europe (Nordmann P, Poirel L, Girlich D).

Method for detecting the presence of expanded-spectrum ß-lactamase-producing bacteria in a sample. 2020. INSERM. Patent obtained in the USA (Nordmann P, Poirel L, Dortet L).

Kit and Methods for the Rapid Detection of the Absence or Presence of a ß-Lactamase in

Samples of Body Fluids. 2020. University of Fribourg. Patent obtained in the USA (Nordmann P, Poirel L, Kieffer K).

Rapid detection of polymyxin-resistant in *Acinetobacter baumannii* (Rapid ResaAcinetobacter Polymyxin NP test) European market by Nov 2020 (LiofilChem, Italy).

Rapid detection of ESBL producers in *Enterobacteriaceae* (Rapid ESBL NP) test European market by Nov 2020 (LiofilChem, Italy).

Public outreach activities: radio, TV, press (P. Nordmann)

Winter 2019: le magazine de la Fondation pour la Recherche Médicale R&S N° 157, *Antibiorésistance: la lutte continue ou les antibiotiques: une ressource à protéger.*

11.02.2019: Ecole Moser, Genève : Présentation du centre NARA et des recherches résistances aux antibiotiques.

11.03.2019: Online-Magazins für Wissen *higgs.ch*, conversation téléphonique: Résistance aux antibiotiques.

03.04.2020 La Liberté N°155 149e année « Désamorcer la bombe – Covid 19 ».

30.10.2019 La recherche@unifr (*//www3.unifr.ch/research/fr/*) News - Une petite victoire contre les bactéries résistantes aux antibiotiques _ Service Promotion Recherche, _ Université de Fribourg.

18.11.2020 Newsletter PNR 72 - La résistance aux antimicrobiens - Programme national de recherche «*La résistance aux antibiotiques est plus difficile à contrôler*».

Group Curzio Rüegg

Creation of novel structures

Cell Analytics Facility (CAF). CAF was created on the initiative of Pathology with contribution from Pharmacology and AMI and has now become an official core service of the University of Fribourg (*https://www3.unifr.ch/scimed/de/cellanalytics).*
CAF covers needs for flow cytometry analysis and cell sorting and soon single cell sequencing. It includes 3 analyzers (MACSQuant, Millteny; LSF Fortessa and FACS Canto II, BD) and a BSL2 sorter (FACSAria Fusion, BD). It provides access to the instrumentation, technical expertise and training to perform experiments including cell sorting service and is well connected with sister facilities at UNIL and EPFL. CAF is managed by a fully trained scientist, Sarah Cattin, who also contributes to teaching to BMS3 and EBR students and organizes seminars and training courses. It is available for HFR for clinical research projects of and MasterMed students. CAF is currently financed by Pathology, the Section of medicine and users' fees.

Awards

S. Kocabey. Marie Sklodowska Curie Award (Personal Fellowshiop). EU Horizon 2020.

Industrial development: patent, license

C. Rüegg et al., (co applicant) Biomarker for colorectal neoplasia. 2019 (19171645.5 – 1111).

C. Rüegg, S. Cattin (co-applicants) Biomarkers for breast cancer detection and monitoring. 2020 (pending).

Group Michael Schmid

Scientific committee

President Interfaculty Center for Cognition, University of Fribourg.

Guest editor elife

Board member Kommission für Tierversuchsethik, Schweizerische Akademie der Medizinischen Wissenschaften.

Group Jens Stein

Creation of novel structures

Leica Stellaris confocal microscope workstation (with B. Egger, F. Meyenhofer, S. Sprecher, A. Jazwinska, D. Hoogewijs, M. Geisler, P.-Y. Mantel).

TrimScope twophoton microscopy workstation.

Lonza Nucleofection device.

Group Csaba Szabo

Awards

In 2019, C. Szabo was listed as one of the most highly cited investigators in the field of pharmacology (Thomson Reuters), one of 5 such individuals at the University of Fribourg.

He gave a plenary Lecture at the 2019 Gordon Conference (USA).

He gave a Keynote Lecture at the 2019 FEBS Meeting and received their annual IUMB Award.

The Swiss Pharmacological Society has elected C. Szabo to be their representative for EPHAR (European Pharmacological Society).

Scientific committee

C. Szabo was invited to be a Section Editor in the journal *"Biomolecules"*. I continue to act as an Editor of *"British Journal of Pharmacology"*. Ihe continues to act as a Section Editor of *"Pharmacological Research"*. He also continue sto serve as Contributing Editor for *"Molecular Medicine"* (USA), and Editor for the journal *"SHOCK"* (USA).

Networking

Continue to work as a Council member of the Swiss Pharmacological Society and started to work as a representative of Switzerland for the European Pharmacological Society.

Public outreach activities: radio, TV, press

C. Szabo have conducted an interview in conjunction with my Keynote Lecture at the 2019 FEBS Meeting and received their annual IUMB Award.: *https://network.febs.org/posts/43559-febs2019-iubmb-lecturer-csaba-szabo.*

He have co-signed a declaration related to the need to continue research in the area of Down Syndrome:

- *https://www.kcl.ac.uk/news/looking-for-down-syndrome-treatment-an-inspiring-scientific-project-which-deserves-eus-political-will.*
- *https://www.lalibre.be/debats/opinions/trouver-un-traitement-pour-la-trisomie-21-un-projet-scientifique-enthousiasmant-meritant-une-volonte-politique-de-l-union-europeenne-5e74e742d8ad582f31c4c05a*
- *https://www.lefigaro.fr/vox/culture/l-ue-doit-faire-davantage-pour-la-recherche-d-un-traitement-de-la-trisomie-21-20200321*

His work related to the role of the CBS pathway in Down Syndrome was covered in UniFR magazines (e.g. Universitas). It also received national and international attention and was covered in various national and international news releases and articles. The Swiss TV has also made a segment, but it was never aired because of the COVID epidemic arrived and it became priority for their scientific programming. Some examples of the articles are below:

- *https://www.unifr.ch/news/en/21878*
- *https://www3.unifr.ch/universitas/fr/editions/2019-2020/spielen/trisomie-21-quand-les-cellules-sauto-empoisonnent.html*
- *https://www.swissinfo.ch/fre/un-pas-vers-un-traitement-des-effets-délétères-de-la-trisomie/45208272*
- *http://www.laliberte.ch/info-regionale/sciences/decouverte-importante-sur-la-trisomie-21-realisee-a-fribourg-532485*
- *https://www.tagblatt.ch/kultur/die-idee-zum-ersten-trisomie-21-medikament-ld.1149395*
- *https://www.bluewin.ch/de/news/wissen-technik/forscher-entdecken-stoffwechsel-mechanismus-beim-down-syndrom-295548.html*
- *https://www.ieb-eib.org/fr/actualite/maladies-et-handicaps/trisomie-21/trisomie-21-des-chercheurs-appellent-l-ue-a-financer-la-recherche-sur-des-traitements-prometteurs-1772.html*
- *https://www.science-et-vie.com/corps-et-sante/genetique-trisomie-21-l-origine-du-deficit-cognitif-se-dessine-52037*
- *https://www.freiburger-nachrichten.ch/grossfreiburg/mogliche-behandlung-fur-das-downsyndrom*
- *https://www.lesalonbeige.fr/trisomie-21-3-questions-au-professeur-csaba-szabo/*
- *https://www.famillechretienne.fr/politique-societe/bioethique/trisomie-21-une-etude-recente-suscite-de-nouveaux-espoirs-265703*
- *https://www.t21.ch/2019/09/actualites/trisomie-21-une-avancee-scientifique-qui-nourrit-de-nouveaux-espoirs-therapeutiques/*

The Foundation which supports his laboratory's work in the area of Down syndrome has also made several interviews and news releases. Some examples are below:

- *https://www.fondationlejeune.org/cbs-et-trisomie-21-une-avancee-scientifique-importante/*
- *https://www.fondationlejeune.org/percee-scientifique-pour-la-trisomie-21-3-questions-au-professeur-csaba-szabo/*
- *https://www.institutlejeune.org/recherche-sur-la-trisomie-21.html*

Group Moritz Tannast

Awards

Best Poster Award on '*Legg-Calvé-Perthes Disease Can Lead To Acetabular Retroversion'*, European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Lisbon, Portugal, June 5-7, 2019.

Venel Prize for the best clinical paper of a Swiss Orthopaedic Institution in 2019 on Prevalence of Femoral and Acetabular Version Abnormalities in Patients With Symptomatic Hip Disease. Swiss Society for Orthopaedic Surgery (SGO), Baden, Switzerland, June 26-28, 2019. CHF 8'000.-

Venel prize for the best basic research paper of a Swiss Orthopaedic Institution in 2020 on Proof of concept: hip joint damage occurs at the zone of femoroacetabular impingement (FAI) in an experimental FAI sheep model. Swiss Society for Orthopaedic Surgery (SGO), Basel, Switzerland, June 26-28, 2019. CHF 8'000.-

Group Harriet Thoeny

Scientific committee

European Multidisciplinary Congress on Urological Cancers (EMUC): Scientific Committee Member.

Swiss Society of Radiology (SGR/ SSR): Scientific Committee Member.

International Cancer Imaging Society (ICIS): Executive Board Member, Trustee and Honorary Secretary.

European Organization for Research and Treatment of Cancer (EORTC): Imaging Group Member.

European Society of Urogenital Radiology (ESUR): Co-opted Board Member.

Radiological Society of North America (RSNA):

- Chairperson, Regional Committee for Europe
- International Advisory Board Member
- Margulis Award, Scientific Committee Member

Radiology; Editorial Board: Associate Editor

Impact of multiparametric MRI on the staging and management of patients with suspected or confirmed ovarian cancer. Short title: MR in Ovarian Cancer (MROC study). Trial Steering Committee Member

Prostate Imaging-Reporting and Data System (PI-RADS): Steering Committee Member until 2019

Research network: see above §12-13.

Public outreach activities: radio, TV, press

Radio Fribourg, Prof. Harriet Thoeny & Lucien Widmer, interviewed by Lukas Siegfried. 07.28.2020.

Group Michael Walch

Pierre-Yves Mantel

Scientific committee

M. Walch, founding member and vice-president of the Liechtenstein Academia of Sciences, October 2019 (president: Prof. Dr. Thomas Meier, Imperial College, London)

M. Walch, guest associate editor for *Frontiers in Immunology* Research Topic *"The role of reactive oxygen species in protective immunity"*, 2020-2021

P-Y. Mantel, grant reviewer: ERC Starting Grants, Welcome Trust

Industrial development: patent, license

P-Y. Mantel, patent: Diagnosis of infection by detecting RNA in sample. EP17209859.2

Networking

P-Y. Mantel, editor Journal of Circulating Biomarkers.

Group Johannes Wildhaber

Petra Zimmermann

Public outreach activities: radio, TV, press

Media releases for Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology Clinical Features Diagnosis Treatment and Prevention Options in Children. Pediatr Infect Dis J, 2020, 39:355-368: *https://wolterskluwer.altmetric.com/details/77441072/news*

Media releases for COVID-19 in Children Pregnancy and Neonates: A Review of Epidemiological and Clinical Features. Pediatr Infect Dis J, 2020. DOI: 10.1097/INF.0000000000002700. *https://wolterskluwer.altmetric.com/details/82335261/news*

MEETINGS ORGANIZED BY DEPARTMENT MEMBERS

Group Jean-Marie Annoni

SNF supported collaboration and internal collaborative Workshop collaboration with Iran on bilingualism Dr. Narges Radman
July 2020

Group Daniel Betticher

High school students: presentation of the physician profession, university of Fribourg. January 22, 2020

SAMO Workshop on combined therapy: chemo-, radio- immunotherapy
January 31 – February 1, 2020

SAMO Virtual Meeting on Evidence based treatment options during the coronavirus pandemic
May 7, 2020

SAMO Masterclass I + II: Med. Oncology, preparation for the FMH exam, Organizer and Chairman of both days (presentation of "systemic therapy in advanced lung cancer")
August 28, September 4, 2020.

SAMO Workshop: Brain tumours
October 2-3, 2020

Sharing clinical experiences, presentaton on lung cancer, targeted therapies
Genève, September 2, 2020.

Meetings Medecine Interne Hospital Fribourg (2019-220), n=31

Group Arnaud Chiolero

40 years of the Research Committee Sociology of health and medicine of the Swiss Sociological Association
S. Cullati
Lausanne, October 2, 2020
(with Prof Raphaël Hammer, HESAV Lausanne)

Groupe Stéphane Cook

Marie-Noëlle Giraud

LS2 cardiovascular section annual conference
Fribourg, March 14-15, 2019

Group Gregor Hasler

Annual Meeting of the Swiss Society of Bipolar Disorders
Lausanne

Annual Meeting of the Swiss Society of Pharmacovigilance in Psychiatry

Group Martina King

Kolloquium zur Medizingeschichte in der Schweiz
Fribourg, May 2019
(with Vincent Barras, Lausanne, Flurin Condrau, Zürich, Hubert Steinke, Bern, Andrea Carlino, Genève)

Séminaire Romande sur l'histoire de la médicine : Conetta Pennuto (Tours) : « Owsei Temkin et l'histoire humaniste de la médicine »,
Fribourg, October 2019

Honorary lecture Paul Weindling (Oxford, Brookes): "Survivor Narratives of Nazi Human Experiments"
Fribourg, November 2019

Group Patrice Nordmann

39 ème Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI). P. Nordmann Co-organizer. Paris, December 2019

40 ème Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI). P. Nordmann Co-organizer. Paris, December 2020

Group Michael Schmid

Day of Cognition 2020
Fribourg

Group Jens Stein

Cytomeet 2019,
Bern, January 2019
(with Prof. Legler, BITg Kreuzlingen and Prof. Engelhardt, University of Bern)

Cytomeet 2020,
Bern (Switzerland), February 2020 (with Prof. Legler, BITg Kreuzlingen and Prof. Engelhardt, University of Bern)

Group Moritz Tannast

Round Table "Instabilität in der Hüftprothetik"
M. Tannast
Zürich, January 24, 2019

Wetlab DePuy Synthes Anterior Total Hip Arthroplasty
M. Tannast
Zuchwil, March 29, 2019

Joints University – Einstieg Hüfte und Knie, DePuy Synthes
M. Tannast
Zuchwil, June 6-7, 2019

AO Peer course "Principles of Clinical Research"
M. Maniglio, M. Tannast
Fribourg, October 25-26, 2019

Bern Hip Symposium
K.A. Siebenrock, M. Tannast.

University of Bern, February 27-29, 2020, Including separate pre-course for residents
Wetlab DePuy Synthes Anterior Total Hip Arthroplasty
M. Tannast,
Zuchwil, October 9, 2020

Workshop Department of Orthopaedic Surgery "How to write a research grant"
M. Tannast
Fribourg University, HFR

Workshop (videoconference),
Neo round table
G. Maestretti, Chairman International 05.06.2020, 09.06.2020, 23.06.2020, 30.06.2020, 08.10.2020

SEMS, module 7, Genève, e-congress, Degenerative knee disorders and sport and Overuse injuries in the knee joint,
D. Petek, Médecine sportive, 2020

Virtual EFORT Congress: Knee surgical treatment for degenerative changes
D. Petek, 2020

Swiss Orthopaedics e-congress: Main subject II: Sport and Orthopaedics
D. Petek, Chairman, 2020

Group Harriet Thoeny

European Society of Urogenital Radiology (ESUR). 10th Prostate MRI course planned for May 2020 in Fribourg and postponed due to Covid-19 to June 2021 in Lausanne (CHUV)

Group Michael Walch

Pierre-Yves Mantel

EMBO workshop, Cell death in immunity and inflammation
M. Walch,
Crete, Greece 2019

15th World Immune Regulation Meeting (WIRM)
P-Y. Mantel
Davos, 2020

Group Johannes Wildhaber

Petra Zimmermann

Annual Meeting of the Swiss Society of Paediatrics (SGP)
Fribourg, June 2020

DISSERTATIONS

Group Jean-Marie Annoni

PhD THESIS
Maria Pestalozzi

MASTER MED THESIS
Irene Seiler, Unil

MASTER BIOMED THESIS
Ece Eldem

Group Daniel Betticher

MD THESIS
Dr Peisl
Dr Bettini

Group Marco Celio

MASTER MED THESIS
Lars Lämmler

MASTER BIOMED THESIS
Luca Varra

MASTER SCIENCES THESIS
Ebba Thunstrom
Reto Cola

Groupe Stéphane Cook

Marie-Noëlle Giraud

MASTER MED THESIS
Jeremy Egger

MASTER EBR THESIS
Loïc Dumas

Group Bernhard Egger

MASTER MED THESIS
Christelle De Vico
Naomi Koehler
François Sudan
Benjamin Schneebeli

BACHELOR BIOMED SCIENCES
Léa Schlunke
Matilde Strozzi

Group Luis Filgueira

PhD THESIS
Dr Smart Mbagwu

Group Gregor Hasler

PhD THESIS
Yoan Mihov

MASTER MED THESIS
Tashi Voskamp
Ladina Meier-Ruge
Moritz Huber

Group David Hoogewijs

PhD THESIS
María Suárez Alonso

Group Martina King

PhD THESIS
Lea Bühlmann

Group Anna Lauber-Biason

PhD THESIS
Patrick Sproll
Leila Bouazzi

MASTER MED THESIS
Mira Stürmlin
Tabea Breckwoldt

Group Patrice Nordmann

PhD THESIS
Nicolas Kieffer
Amandine Masseron
José Manuel Ortiz de la Rosa

Groupe Curzio Rüegg

PhD THESIS
Praveen Bathini
Flavia Fico
Sarah Rafiee
Matteo Rossi
Gianluca D'Agostino

MASTER BIOMED THESIS
Manon Bulliard
Stien De Coninck

MASTER MED THESIS
Simona Disler

MASTER SCIENCES THESIS
Jeremy Kessler

Group Michael Schmid

PhD THESIS
Ricardo Kienitz (University of Darmstadt, DE)

Group Beat Schwaller

PhD THESIS
Emanuel Lauber

Group Lucas Spierer

MASTER MED THESIS
Julie Poisson

MASTER SCIENCES THESIS
Yoshi Walter
Michael Romet
Stephan Schneider
Spriani Giona
Marta Koc
Lauriane Grob
Lauriane Ecabert

Group Jens Stein

MASTER BIOMED THESIS
Laura Yerly

Group Csaba Szabo

MASTER BIOMED THESIS
Simona Jacquemai
Emilia Compagnon

Group Moritz Tannast

PhD THESIS
G. Zeng

MD THESIS
S. Vuilleumier
R. Helfenstein
C. Fontanellaz-Castiglione
M. Siegfried

Group Harriet Thoeny

PhD THESIS
Maria Firsova
Timmy Cancelli

Group Johannes Wildhaber

Petra Zimmermann

PhD THESIS
Tess Bonato

MD THESIS
Maryse Volery
Lorena Salomon
Anita Uka

MASTER MED THESIS
Quynh Duong
Michèle Keller
Salome Hertli

ACKNOWLEDGMENTS

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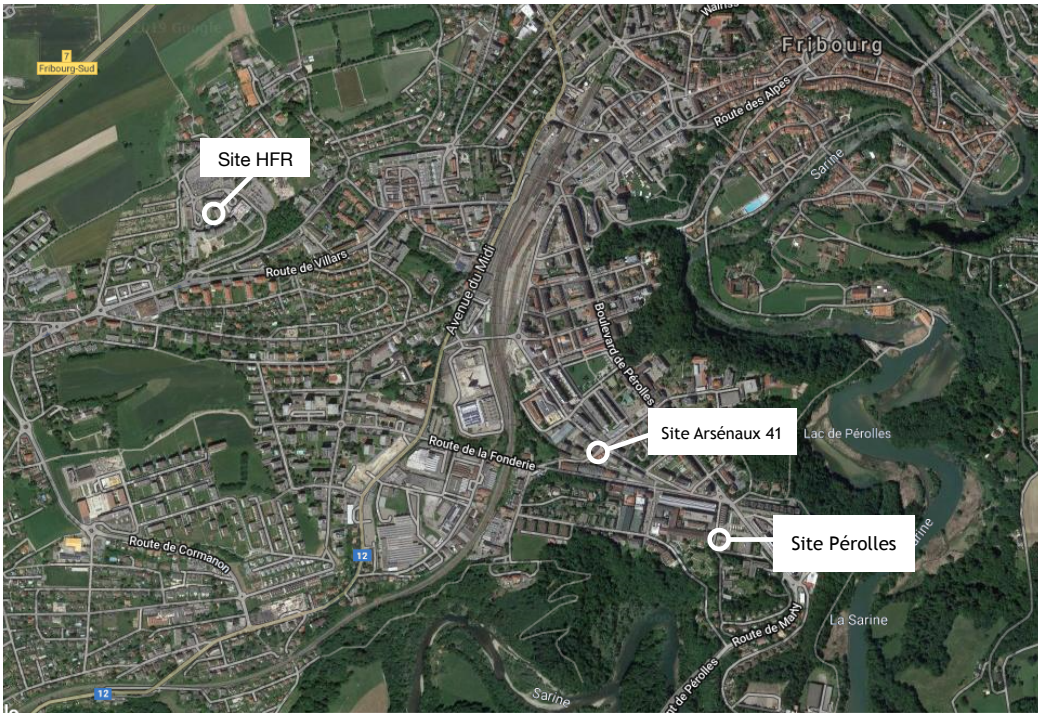

FRIBOURG

Site Pérolles

Anatomie
Cardiologie
Endocrinologie
Histologie I et II
Immunologie
Médecine et société
Métabolisme
Microbiologie
Neurologie
Neurophysiologie I et II
Neuroréhabilitation
Neurosciences
Pathologie
Pharmacologie
Physiologie
Physiologie systématique I et II
Psychiatrie
Santé publique
Science du sport et du mouvement I et II

Site Arsénaux

Médecine de famille
Pédagogie médicale
Pédiatrie

Site HFR (Hôpital Cantonal)

Chirurgie générale
Chirurgie orthopédique
Gériatrie
Gynécologie et obstétrique
Médecine d'urgence
Médecine interne générale
Médecine interne spécialisée
Psychiatrie

SCIENTIFIC REPORT 2019/2020

SECTION OF MEDICINE

Faculty of Science and Medicine
University of Fribourg
Switzerland