

SCIENTIFIC REPORT 2017-2018

SECTION MEDICINE

Faculty of Science and Medicine

University of Fribourg

Switzerland

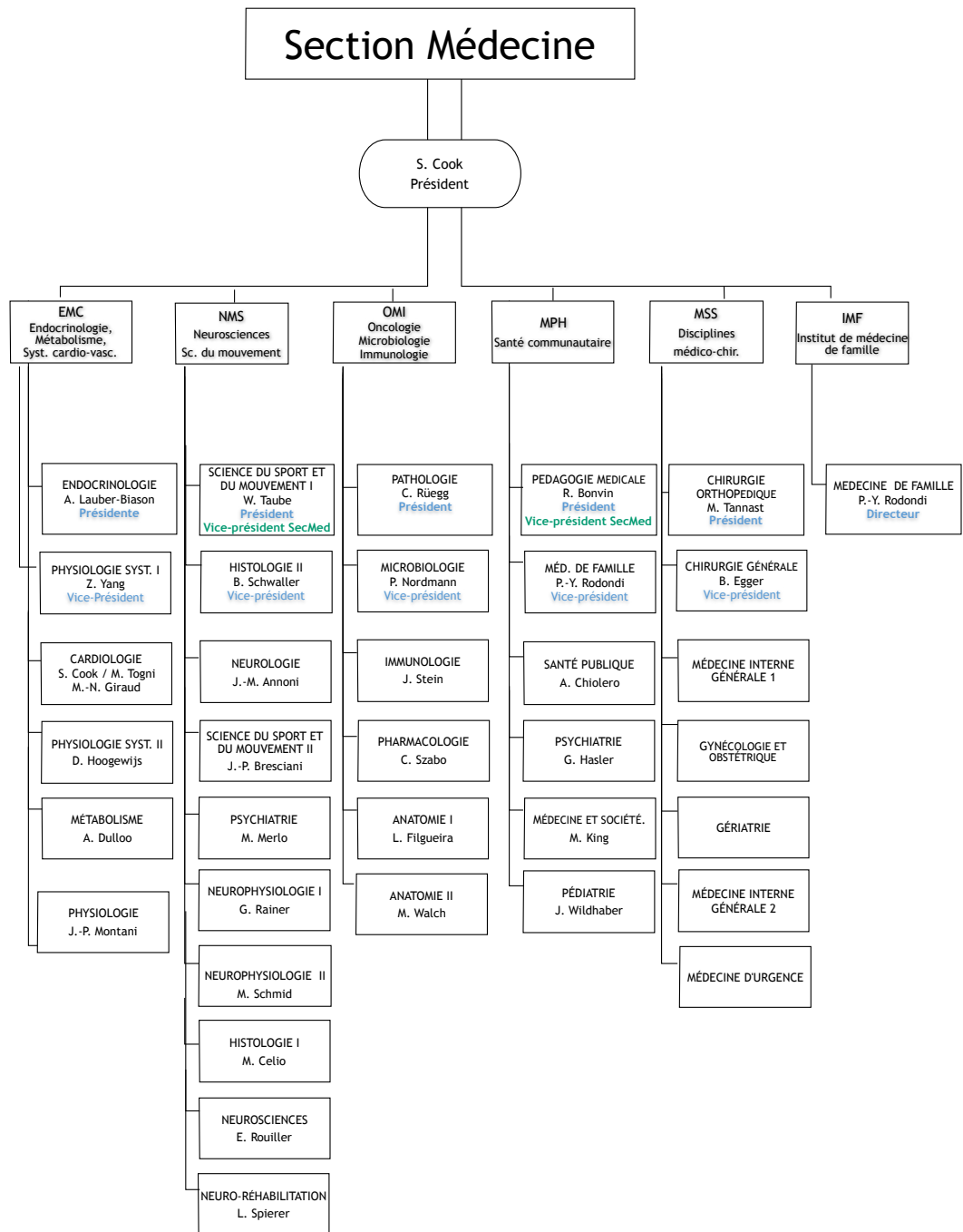


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CONTENTS

	6	Introduction	
Cardiovascular, Metabolism and Endocrinology	10	Anna Lauber-Biason	<i>Understanding human sex development: from bedside to animal models and back</i>
	13	Zhihong Yang	<i>Aging and age-associated diseases</i>
	16	Stéphane Cook	<i>Cardiology</i>
		Mario Togni	
		Marie-Noëlle Giraud	
	19	David Hoogewijs	<i>Integrative oxygen physiology</i>
	22	Abdul Dulloo	<i>Mechanisms driving fat storage during weight regain after caloric restriction</i>
	25	Jean-Pierre Montani	<i>Cardiovascular and metabolic responses to alcohol associated with sugar or festive meals</i>
Neurosciences and sciences of sport and movement	30	Beat Schwaller	<i>The role of specific calcium-binding proteins in neurodevelopmental and neuro-psychiatric disorders and cancer biology</i>
	33	Jean-Marie Annoni	<i>Interaction between Language and Frontal System</i>
	36	Jean-Pierre Bresciani	<i>Control and Perception of Movement</i>
	39	Marco C. G. Merlo	<i>Neurophysiological investigations of information processing and stress reactions in psychiatric disorders</i>
	42	Gregor Rainer	<i>Basal forebrain neuromodulatory circuits</i>
	44	Eric M. Rouiller	<i>Motor control in non-human primates</i>
	47	Lucas Spierer	<i>Metaplasticity of executive functions in the healthy and neurological brain</i>
Cancer, Microbiology and Immunology	52	Curzio Rüegg	<i>Tumor-host interactions in cancer progression and metastasis</i>
	55	Patrice Nordmann	<i>Emerging Antibiotic Resistance in Bacteria</i>
	58	Csaba Szabo	<i>Biological and pathophysiological roles of labile, diffusible small molecules</i>
	61	Michael Walch	<i>Host-pathogen interactions in the context of bacterial infections and malaria</i>
	63	Luis Filgueira	<i>Clinical Anatomy and Cell Biology</i>
Public Health	68	Martina King	<i>Medical Humanities</i>
	70	Gregor Hasler	<i>Discovering biomarkers and developing novel therapeutic options for severe psychiatric disorders (depression, psychosis)</i>
	74	Publications	
	86	Invited lectures and seminars given by department members	
	90	Third party funding to group leaders	
	92	Further achievements	
	94	Meetings organized by department members	
	95	Dissertations	
	97	Acknowledgments	
	98	Location	

Dear readers,
Dear colleagues,
Dear friends,

I take it as a great opportunity to write a short preface to this scientific report. This document is published every second year and aims to summarize the scientific activity of our Medicine Section.

What deserves mention?

A. New Organization and Governance of the Faculty.

In 2017, the Faculty of Sciences evolved into the Faculty of Sciences and Medicine. The two departments became sections, and the two sections have been organized into departments. In the medicine section, these departments are clustered depending on research synergies. There are 5 departments: Department of Endocrinology, Metabolism and Cardiovascular System (EMC, Chair: Prof. Anna Lauber-Biason), Department of Neurosciences and Movement Sciences (NMS, Chair: Prof. Wolfgang Taube), Department of Oncology, Microbiology and Immunology (IMO, Chair: Prof. Curzio Rüegg), Department of Community Health (MPH, Chair: Prof. Raphaël Bonvin), Department of Medico-Surgical Disciplines (MSS, Chair: Prof. Moritz Tannast). Adding two words and mixing up the departments may sound like details, but do not get mistaken: these are milestones in the recognition of the place the medicine took over time.

B. New Professors, New Chairs.

Since the last report, the section has welcomed new faculty members. In the so-called “Bachelor curriculum”: David Hoogewijs, Full Professor of Systemic Physiology; Martina King, Full Professor of Medical Humanities; Michael Schmid, Full Professor of Neurophysiology; Jens Volker Stein, Full Professor of Immunology; Csaba Szabo, Full Professor of Pharmacology; Michael Walch, Full Professor of Anatomy. Furthermore, more recently Mario Prsa arrived as Assistant Professor in the Laboratory of Cognitive Neuroscience. In addition, and with elaboration of the Master in human medicine, the section has been amplified with new professors and new chairs: Raphaël Bonvin, Professor of Medical Pedagogy; Arnaud Chiolero, Professor of Epidemiology and Public Health; Bernhard Egger, Professor of Surgery; Gregor Hasler, Professor of Psychiatry; Pierre-Yves Rodondi, Professor of Primary Care Medicine; Moritz Tannast, Professor of Orthopedic Surgery and Johannes Wildhaber, Professor of Pediatrics.

C. New Buildings, new Premises.

The “medicine pavilion” PER17 is the 4th building of our section on the plateau de Perolles. It mainly hosts the research groups of the IMO department: the groups led by Profs. Nordmann, Rüegg, and Szabo. The “master building” (MAS 16) is the second university “pouch” at the HFR-hôpital cantonal and welcomed the groups led by Prof. Egger and Tannast. Temporary locations at the Arsenaux (in the Swisscom building) host the groups of Prof. Bonvin, Chiolero, Rodondi, and Wildhaber.

D. New Programs.

In addition to existing programs, a unique venture has been set up to develop a comprehensive curriculum in human medicine.

The existing pregraduate programs are:

- A three-year Bachelor in Human Medicine,
- A three-year Bachelor in Biomedical Sciences,
- A three-year Bachelor in Sport Sciences and Motor Control.
- A 18-month Master in Sport Science and Motor Control,
- A 18-month Master in Experimental Biomedical Research.

The major novelty in education is the endorsement of a three-year Master in Human Medicine leading to the Federal Diploma of Medicine. The first cohort is limited to 40 selected students and started in September 2019. The master has been drafted to prepare the student to fulfill the needs of primary care medicine. By providing theoretical and practical knowledge based on a general medical curriculum, the students are however not limited to primary care medicine. We are even convinced that by providing a strong medical knowledge based on primary cares, our students will better perform in all medical specialties during the postgraduate training.

Since French and German are both official languages, UniFR emerges as the only bilingual university in Switzerland.

Furthermore, the section offers education at the postgraduate level with «Doctoral Schools» in human medicine, as well as neurosciences, in immunology and cancer with collaboration with all other Swiss universities.

Finally, our section of medicine has invested considerable efforts into promoting and fostering research, equal chance and succession at all levels.

What About Research?

In the introduction of the latest scientific report nicely written -and that I am currently reading to keep in the frame- Jean-Marie Annoni put forward the honourable rank (119th World, 64th European) of the UniFR in the 2015 Times Higher Education World University Rankings (1). We shortly learned that our funding was significantly lower than others competitors teaching medicine in Switzerland (from 2.3 to 4.5-time lower). The question you may ask is whether these means are sufficient to be competitive in the modern world where research is increasingly expensive. We can no longer afford cheap research. Regarding costs in research, I must confess that I remain a little jealous of the clinical research performed by my cousin James on his world tour 1772-1775: he simply allowed his sailors in a first boat to access fresh fruits and compared the risk of scurvy with other sailors accessing conventional (and unhealthy) diet in a second boat (2). The techniques evolved: genomics and proteomics are to the modern research what smartphones are to modern telephony. The budget followed accordingly. Of note, clinical research faces similar financial expansion due to new administrative quarrels and “help” of contract research organizations.

Yet, let's come back to the question about our ability to be competitive. As you will see in reading this scientific report, the answer to the question is yes (although an increase in university funding seems essential in the near future), we are competitive. Of course! Professors at the section of Medicine perform competitive research at molecular, cellular, preclinical and clinical levels, and in many topics, including neurosciences, cardiovascular medicine, metabolism, microbiology, immunology, cancer biology, psychiatry, medical humanities, surgery, orthopaedics and primary care medicine.

Although I neither have the pretension nor the knowledge to explain the secret of this success, the UniFR and all of us should be proud of our achievements. After saying it, let's try exploring some tracks:

Is it due to our campus ?

It might be one of the keys. The campus is well located with all modern facilities in a beautiful Swiss city with long academic and cultural traditions. Its central location makes it at close vicinity of all big Swiss universities and technological poles. As the Faculty of Medicine is embedded together with Sciences, we work, eat and live together with other scientists from Mathematics, Computer Science, Physics, Chemistry, Geosciences, Biology and the Adolf Merkle Institute for Soft Nano- and Material Science. This situation facilitates and impacts our networking. This situation is unique and opens interesting opportunities to collaborate, to define priorities and to raise common goals, such as the Life Sciences supported by the latest strategic plan of UniFR.

Yet, does its size matter? The architecture of the plateau de Perolles with these small pavilions are very close to the perfect size written in the "Tipping Point" by Malcom Gladwell and which describes the success of the company Gore (one of the world's most successful company, known in Switzerland for its textile division). A building with 150 employees represents the best architecture to allow people to interact and to maintain a social relationship (3). This "rule of 150" is true for Gore Associates and certainly holds true for us as well.

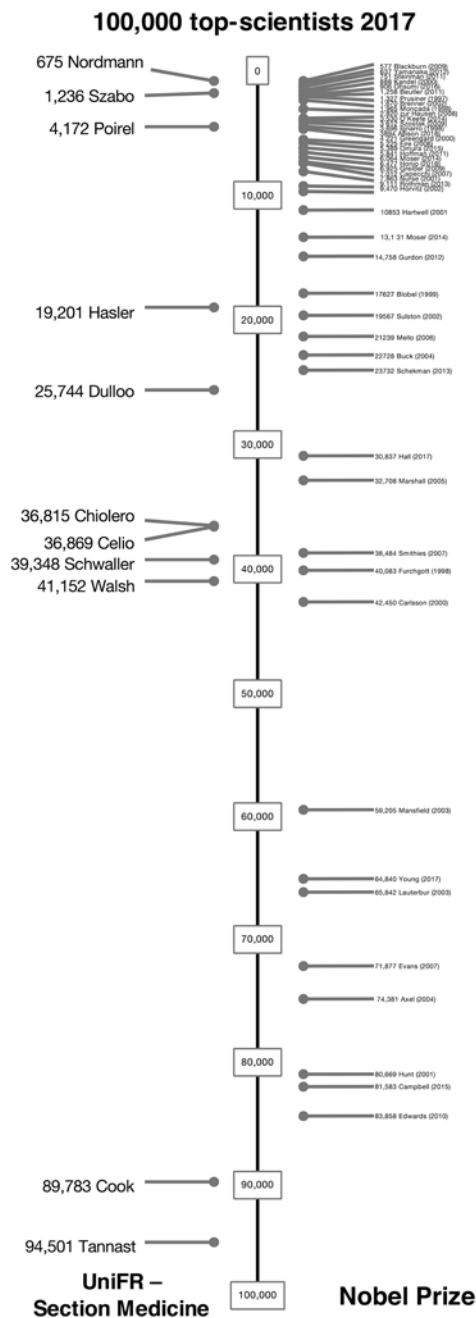
Is this due to our researchers?

To paraphrase Kaoru Ishikawa: the research quality of the section is closely linked to its researchers(4). A few days ago, I received an article from PLOS Biology 2019 (5). This article lists the best researchers in the any field of Science. The authors -John P. A. Ioannidis, Jeroen Baas, Richard Klavans and Kevin Boyack - report "a standardized quote metrics author database based on 22 scientific fields and 176 subfields". The study provides a ranking of the 100,000 most prolific scientists out of 6,880,389 (this makes 1.4% of scientists). With modern technology, we can easily consult the tables and sort for the representatives of our section. So did I ... with my costly and efficient smartphone. It's fun. Of course, one should not overinterpret this list and it is expected not to be listed (like 99% of the life sciences researchers and some nobel prize winners). To my surprise our small community was however well represented (Patrice Nordmann - Microbiology- n°675 and Csaba Szabo - Pharmacology-n°1236 at the top of rank) and at similar ranking than most Nobel Prize recipients (Figure)

In short and on behalf of all members and friends of the Section of Medicine, I wish you an interesting reading in the different fields of medical science and research.


Prof. Stéphane Cook

Président Section of Medicine



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2. **Stephen R. Bown**, *Scurvy: How a Surgeon, a Mariner, and a Gentleman Solved the Greatest Medical Mystery of the Age of Sail*, 2003, Thomas Dunne Books / St. Martin's Press. ISBN 0-312-31392-6
3. **Malcom Gladwell**, *Tipping Point*, 2000, Little, Brown and Company. ISBN: 9780316316965. A brilliant New Yorker journalist and essayist.
4. **Kaoru Ishikawa (1915-1989)** was an organizational theorist and developed the concept of quality circles in industrial processes. One of his quotes is « the quality of the compagny is closely linked to its employees». Another important quote is “.. the first concern of the company is the happiness of people who are connected with it. If the people do not feel happy and cannot be made happy, that company does not deserve to exist....”, as cited in: Howard S Gitlow, 2000, *Quality Management Systems: A Practical Guide*. ISBN 9781574442618
5. **Ioannidis JPA, Baas J, Klavans R, Boyack KW**. A standardized citation metrics author database annotated for scientific field. *PLoS Biol.* 2019;17(8):e3000384. Published 2019 Aug 12. doi:10.1371/journal.pbio.3000384

Cardiovascular, Metabolism and Endocrinology

Anna Lauber-Biason

Understanding human sex development: from
bedside to animal models and back

Zhihong Yang

Aging and age-associated diseases

Stéphane Cook

Mario Togni

Marie-Noëlle Giraud

Cardiology

David Hoogewijs

Integrative oxygen physiology

Abdul Dulloo

Mechanisms driving fat storage during weight
regain after caloric restriction

Anna Lauber-Biason

Understanding human sex development: from bedside to animal models and back

Introduction

Sex determination refers to the developmental processes by which the bipotential gonads develop as either testes or ovaries. Disorders of sexual development (DSD) are rare congenital conditions affecting more than 1 in 4500 newborns. Children with DSD face considerable challenges including surgical correction and gender assignment, as well as associated complications such as infertility and predisposition to gonadal tumors. Unfortunately, causative genetic mutations are found only in a minority of affected patients due to an incomplete understanding of the genetic programs and molecular pathways involved in sex determination and DSD.

We use state-of-the-art next generation sequencing and bioinformatics approaches to identify gene variants likely implicated in DSD patient phenotypes.

Our group described three new clinical entities leading to DSD in patients, the WNT4 deficiency (the *Biason-Lauber syndrome*), CBX2 defects and defects in the androgen *backdoor* pathway.



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Identification of new factor implicated in abnormal sex development in humans.

Currently, around 50% of patients presenting with disorders or differences of sexual development (DSD), do not have a diagnosis. Not only is this a hindrance in the management of the cases, but it is also stressful for the families and the patients concerned. In order to identify the genetic and molecular basis of disease, Whole Exome Sequencing (WES) has become one of the foremost methods of choice. In collaboration with national and international partners, we gathered samples of a large cohort of patients with unexplained DSD ($n > 150$) and used WES to identify genetic variants. We are currently analyzing the WES data obtained in order to make connections between the phenotype and the genotype of the undiagnosed DSD patients and to gain novel insights into the underlying process of human sex determination and differentiation.

Patrick Sproll

Of Man and Fly: *Drosophila melanogaster* as a model to study human disease.

Human genome wide next generation sequencing (NGS) assays, such as whole exome sequencing (WES) have successfully identified thousands of variants in human disease. These insights could lead the way to breakthrough treatments; however, several challenges hinder progress, making innovative approaches to accelerate the follow-up of results from WES an urgent priority.

Mouse models are often not entirely appropriate for investigating the functional consequences of the identified variant. Together with more traditional approaches, such as cell-based studies, we exploit the largely untapped and rather unconventional potential of the fruit fly, *Drosophila melanogaster*, for functional investigation of findings from human WES (4,5).

This newly acquired expertise will appeal to both human geneticists seeking innovative strategies for experimental validation of findings from WES, as well as the *Drosophila* research community, by whom ongoing investigations of the implicated genes will powerfully inform our understanding of human disease.

Ivan Domenech Mercadè

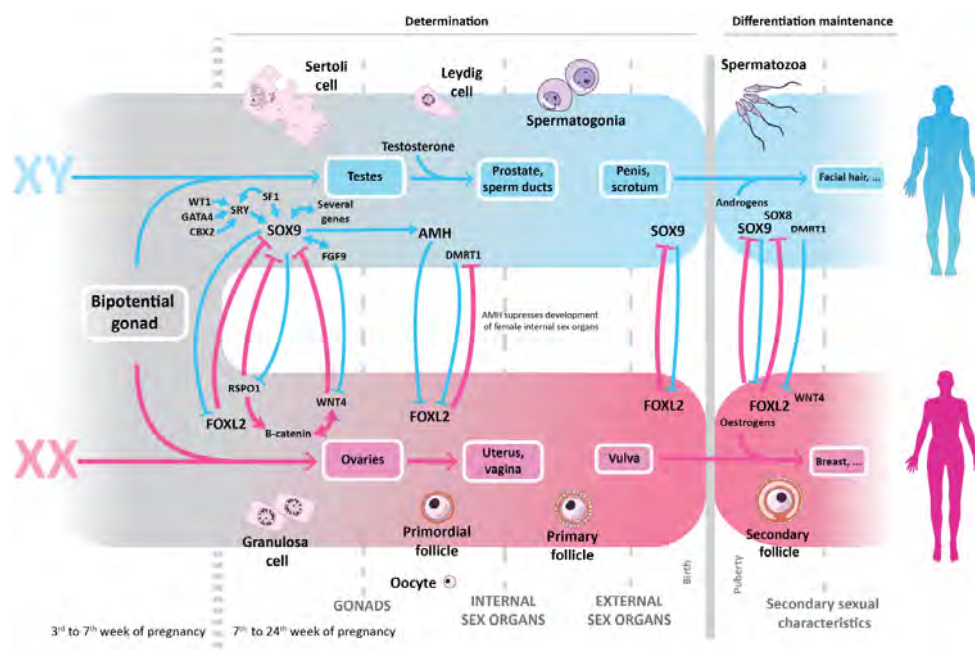


Figure 1: Human sex development. In blue the male pathway, in pink the female.
Abbreviations: AMH: Anti-Müllerian Hormone. CBX2: Chromobox2; FOXL2: ForkheadboxL2; RSP01: Root-plate specific Spondin1; SF1/NR5A1: Steroidogenic Factor 1; WT1: Wilms' Tumour suppressor 1; SOX9: SRY- box9; SRY: Sex determining Region Y; WNT4: Wingless Type MMTV integration site family, member 4; FGF9: Fibroblast Growth Factor 9; GATA4: GATA binding protein 4.

Generating human somatic gonadal cell models from induced pluripotent stem cells.

Human sex development relies on differentiation of the gonads, in which the Sertoli and granulosa cells play a key role respectively for men and women. Many differences of sex development (DSD) are due to alteration of these two cell types. The study of the mechanisms underlying these conditions is crucial for optimal clinical management of DSDs. The primary collection of these cells is painful for the patient and their culture extremely difficult due to their short lifespan and the loss of their unique characteristics when cultured in vitro. Additionally, the available cell models cannot reproduce the mechanism leading to disease in single DSD patients.

Human induced-pluripotent stem cells (iPSCs) are developing as exciting cell sources for applications in regenerative medicine and drug discovery, primarily based on their extensive similarities to their human embryonic stem cell counterparts and shared properties of self-renewal and multilineage differentiation capabilities. iPSCs can be derived from somatic cells like fibroblasts, peripheral blood mononuclear cells (PBMCs) or urinary progenitor cells (UPs) via ectopic expression of transcription factors SOX2, OCT4, KLF4, NANOG, C-MYC and LIN28. Further differentiation into male (Sertoli-like) and female (granulosa-like) cells is obtained by exposure of the patient-derived iPSCs to sex-specific factors, such as FGF9 or estradiol.

Daniel Rodriguez-Gutierrez & Dirk Hart

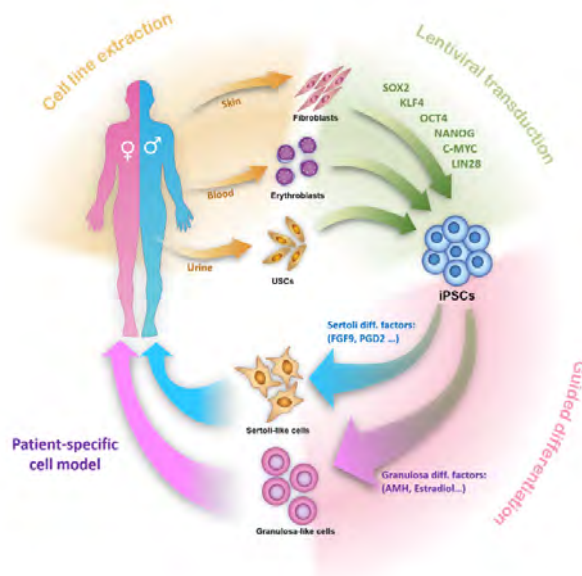


Figure 2: Conceptual scheme illustrating proposed research aiming to generate patient-specific cell models of Sertoli cells and granulosa cells by guided differentiation of iPSCs derived from patient cellular sources.

Selected Publications

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Assembling the jigsaw puzzle: CBX2 isoform 2 and its partners in Disorders/Differences of Sex Development. *Mol Gen Genom Medicine*. doi 10.1002/mgg3.445

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Estrogen Receptor beta is necessary for human ovarian development. *J Clin Endocrinol Metab*. doi 10.1210/je.2018-00769

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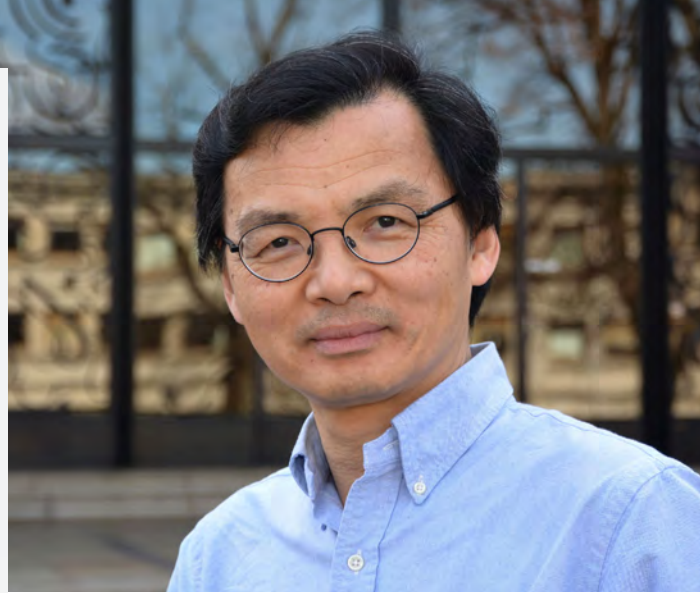
Generating a gonadal cell model from human induced pluripotent stem cells. *Front Genet* doi: 10.3389/fgene.2018.00498

Zhihong Yang

Aging and age-associated diseases

INTRODUCTION

Aging and age-associated diseases including cardiovascular disease, type-II diabetes, chronic kidney disease, etc, remain the great challenge for our society. The mechanisms of organismal aging and vulnerability of elderly individuals to chronic diseases remain largely unknown. Our research work in 2017 and 2018 have focused mainly on the roles of the enzyme arginase-II (Arg-II) which metabolizes L-arginine, in lifespan regulation, aging-associated pancreatic endocrine dysfunction, vascular aging and renal water handling.



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Molecular mechanisms of Arg-II induced mTORC1/S6K1 activation in vascular senescence and apoptosis:

As mentioned, Arg-II activates mTORC1/S6K1 pathway which contributes to cell senescence and apoptosis. In an attempt to elucidate the underlying mechanism and through a proteomic analytic approach using native and truncated Arg-II mutants, we identified myosin-1b (Myo1b) as a mediator. Our work shows that Arg-II is upregulated and promotes association of Myo1b with lysosomes in senescent vascular smooth muscle cells (SMC), which moves lysosomal positioning to cell periphery, resulting in spatial separation and dissociation of TSC from lysosome and in turn hyperactive mTORC1 signaling. This mechanism leads to vascular SMC apoptosis in vascular aging. The study discovers a novel mechanism, i.e., Arg-II/Myo1b/mTORC1 pathway, in vascular aging (Yu Y. et al., *Cell Death Dis.* 2018;9:313).

Role of Arg-II in age-associated pancreatic endocrine dysfunction:

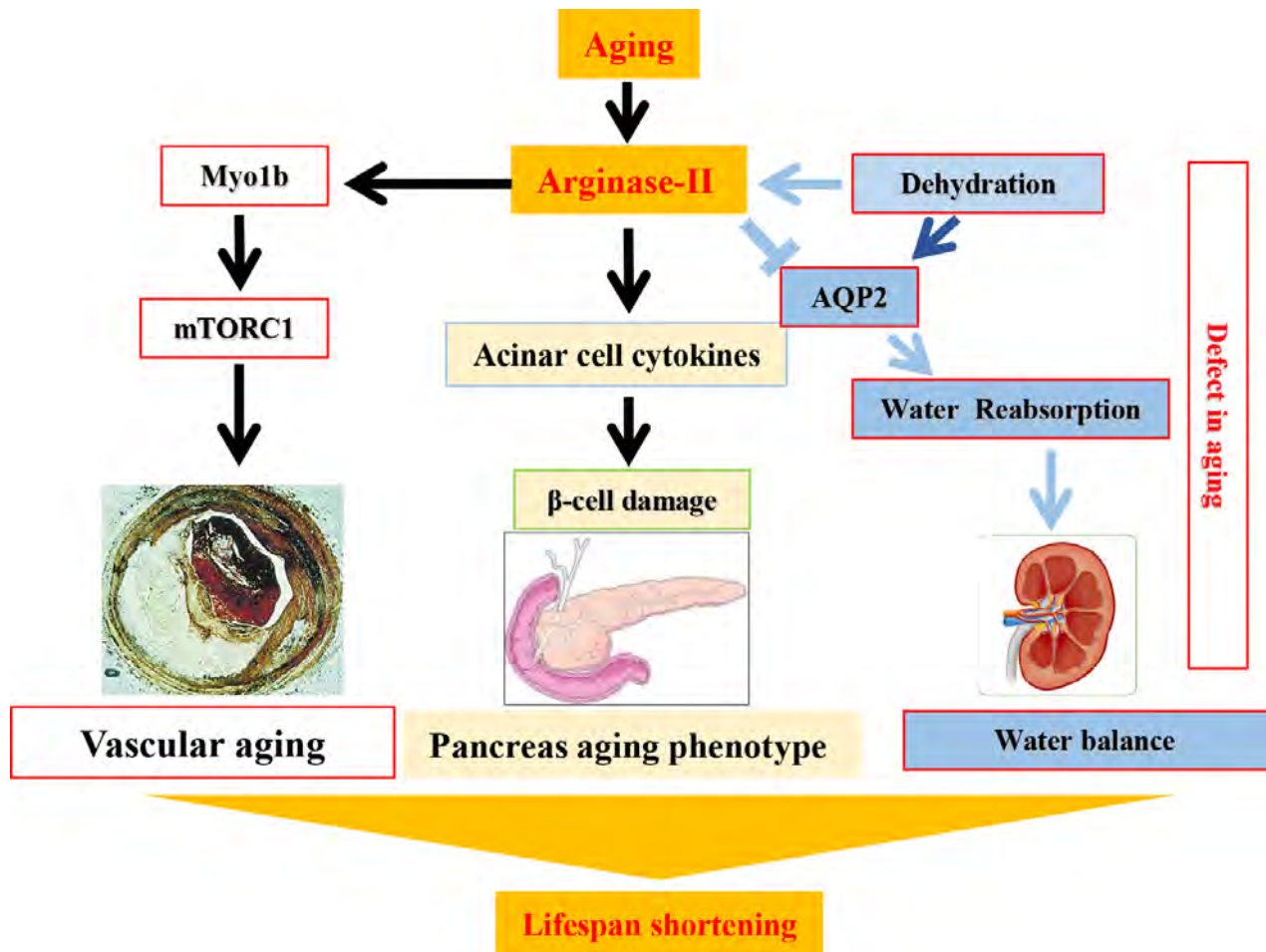
Aging is an important risk factor for pancreatic endocrine dysfunction. We further explored the role of Arg-II in this aspect in aging pancreas. We showed that Arg-II is mainly expressed in acinar cells of pancreas and upregulated in old mice, particularly in females. The age-associated augmentation of Arg-II in acinar cells enhances p38mapk activity, leading to increased TNF- α release which in turn causes β -cell apoptosis. Arg-II^{-/-} mice (particularly females) are protected from age-associated glucose intolerance and demonstrate greater glucose induced-insulin release, larger islet size and β -cell mass, more proliferative and less apoptotic β -cells as compared to the age-matched WT controls. Thus, this study demonstrates a role of Arg-II in crosstalk between acinar cells and β -cells, which plays a role in age-associated glucose intolerance (Xiong Y, et al., *Diabetes* 2017;66:1636-1649)

Role of Arg-II in renal water handling and function (Research work in frame of collaboration with NCCR-Kidney.CH):

We further explored the role of renal Arg-II in regulation of water balance, since Arg-II is highly expressed in the kidney. We show that Arg-II expression is enhanced in collecting ducts by water deprivation. The enhanced Arg-II levels in the collecting ducts under this condition negatively regulates the water channel AQP2 expression and function, leading to reduced urine concentrating capability in kidney, which is not through modulation of cAMP pathway and vasopressin release. This effect of Arg-II is lost in old mice (Huang J, et al., *FASEB J.* 2018;32:5520-5531). Furthermore, a collaboration with university of Zürich shows that mice with uninephrectomy (UNX) develop a small increase in blood pressure that is prevented by L-citrulline supplementation or arginase deficiency, two measures that appear to compensate for the impact of kidney mass reduction on L-arginine metabolism (Pillai SM et al., *J Am Heart Assoc.* 018;7:e008025). ▶

▶ Role of Arg-II in lifespan regulation:

Finally, we demonstrate a role of Arg-II in lifespan regulation in mouse model. We found an age-associated increase in Arg-II expression levels in different organs of WT mice accompanied with increase in p16INK4, S6K1 signaling, and p66Shc levels. These aging hallmarks are significantly attenuated in the Arg-II^{-/-} mice particularly in females. Accordingly, Arg-II^{-/-} mice have extended lifespan. The study suggests that targeting Arg-II in aging could prolong lifespan (Xiong Y, et al. *Front. Physiol.* 2017;8:682).



Summary of the major findings on the role of arginase-II (Arg-II) in aging and age-associated diseases.

Arg-II is upregulated in aging. In the vasculature, Arg-II activates mTORC1 signaling through Myosin 1b (Myo1b), leading to vascular cell senescence and apoptosis and vascular dysfunction; Enhanced Arg-II in pancreatic acinar cells in aging releases inflammatory cytokines which damage endocrine β -cells, leading to aging pancreatic aging phenotype; In the kidney, dehydration upregulates the water channel AQP2 in kidney collecting ducts and stimulates water reabsorption, but also upregulates Arg-II in the same cells. The upregulated Arg-II counter regulates renal water reabsorption and fine tunes the water balance. This interaction between Arg-II and AQP2 is not observed in the aging kidney, i.e., genetic disruption of Arg-II did not enhance water reabsorption in the aging kidney. Finally, our study demonstrates that Arg-II deficient mice reveal an extended lifespan as compared to the control wild type mice. Targeting Arg-II could be beneficial to slow down aging process and age-related chronic diseases.

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Arginase-II negatively regulates renal aquaporin-2 and water reabsorption. FASEB J. 32:5520-5531.

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.

In spite 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)

Throughout the years 2017 and 2018 the unit has conducted a 5-year angiographical and optical coherence tomography imaging follow-up in EVERBIO-II trial. Analysis and Interpretation of a sub-study that assessed vascular healing by optical coherence tomography in the studied devices is currently on-going.

The research group has the lead on several multicentre clinical registries and participate in various multicenter clinical trial in interventional cardiology.

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Ischemic injury damages myocardial tissue, resulting in an impairment of left or right ventricular function. Remodeling of infarcted myocardium leads 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 require new therapeutic approaches. The successes of HF treatment foresee the increased activity performance and quality of life of the patient, as well as delay or suppression of end-stage HF and cardiac remodeling, reduced rate of rehospitalization and mortality. To treat patients with chronic MI and reduced LVEF, several phases I/II clinical trials reported the safety and efficacy of an intramyocardial or epicardial application of selected BMDC. The general concept is that cells modify local inflammatory conditions, release factors involved in tissue repair, mitigate the progression of ventricular remodeling, and rescue the cardiac function. However, unsolved challenges have impaired the power of this treatment approach. The efficacy of the BMDC therapy remains dependent on an appropriate patient selection and the implementation of quality and functional tests of the cells.

The goals of the research group are 1) to develop an Advanced Therapy Medicinal Product (ATMP) consisting of a cellularized biomaterial composed of autologous BMDC and a matrix, 2) to develop a functional test for the cardiac regenerative capacity of the ATMP and 3) investigate the emerging regenerative function of the myocardium and the prevailing role of the immune system.

Optimization of the ATMP composition.

We have investigated various combinations of matrices and cells and developed a biological patch with the high potential for cardiac repair and consisting of a biologically active matrix and an unselected association of stromal and hematopoietic lineages cells, harvested from the bone marrow. The unique value of the ATMP is the activation of the cells with a matrix that potentiate their effect on the cardiac immune response and their associated repair capacity (**figure 1**).

Identify the immune response as a critical parameter is modulate for cardiac repair.

Cardiac remodeling post-MI is characterized by excessive deposition of extracellular matrix (fibrosis) and involve myofibroblasts and macrophages. We have quantified in vivo the anti- and pro-inflammatory phenotype switch in the infarct area induced by the BMDC/matrix treatment, resulting in functional improvement of treated heart.

Evaluation of the repair capacity of the ATMP.

We have established a functional test in vitro to test the regenerative capacity of the ATMP. Macrophages are cultured with conditioned medium from ATMP, and we evaluate their plasticity and phenotypes and the induction of the proliferation of cardiomyoblasts.

Recognize the existence of responders and non-responders in preclinical investigations.

We showed in animals, like patients, showed different outcomes to the ATMP treatment. The identification of this dichotomy (responders versus non-responders) is essential for the reproducibility of translational research. A degree of heterogeneity between phenotypical and genotypically similar animals may influence the response to the therapy. As we have demonstrated that the immune response is a significant player in cardiac repair induced by ATMP treatment, we now aim at evaluating individual specificity related to the immune system signature and the relationship with the response status of the animals treated with our biologic patch.

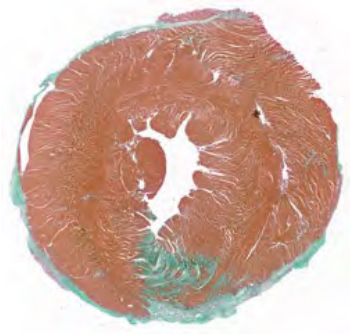


Figure 1: Goldner Staining of a cross section of an infarcted heart treated with cell/matrix and showing a reduced fibrotic scar.

Selected Publications

Arroyo DA, Schukraft S, Kallinikou Z, Stauffer JC, Baeriswyl G, Goy JJ, Togni M, Cook S, Puricel S. (2018).

Multianalysis with optical coherence tomography and vasomotion in everolimus-eluting stents and everolimus-eluting biovascular scaffolds: the MOVES trial. *Open Heart* doi:10.1136/openhrt-2017-000624.

Melly LF, Cerino G, Frobert A, Cook S, Giraud MN, Carrel TP, Tevæearai HT, Eckstein FS, Rondelet B, Marsano A, Banfi A. (2018)

Myocardial infarction stabilisation by cell-based expression of controlled VEGF levels. *J Cell Mol Med.* doi: 10.1111/jcmm.13511

Kröpf JM, Spengler CM, Frobert A, Ajalbert G, Manz M, Giraud MN. (2018)

Myocardial infarction does not affect circulating hematopoietic stem and progenitor cell proliferative capacity in a rat myocardial infarction model. *Exp Physiol.* 103:1-8

Varenne O, Cook S, Sideris G, Kedev S, Cuisset T, Carrié D, Hovasse T, Garot P, El Mahmoud R, Spaulding C, Helft G, Diaz Fernandez JF, Brugaletta S, Pinar-Bermudez E, Mauri Ferre J, Commeau P, Teiger E, Bogaerts K, Sabate M, Morice MC, Sinnaeve PR; SENIOR investigators. (2018).

Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet.* doi: 10.1016/S0140-6736.

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 alterations in the gene expression pattern, 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 DNA regions and oxygen-dependent erythropoietin gene expression.

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 O₂, CO and NO. Historically, the familiar vertebrate O₂-binding hemoglobin and myoglobin were among the first proteins whose sequences and structures were determined over 50 years ago. Most known globins fulfil respiratory functions. However, over the last two decades evidence has accrued indicating that globins exhibit additional, novel functions as enzymes, sensors and signaling molecules. 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 as fifth mammalian globin, with most abundant expression levels in testis. Remarkably, androglobin (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 (**Figure 1**). This newest member of the globin family is evolutionary ancient and extremely conserved, being present in mammals, more

basal animal clades and even unicellular organisms. Androglobin expression is associated with late stages of spermatogenesis. Male Adgb-deficient mice display a developmental defect during later stages of spermatogenesis. Furthermore, we could demonstrate auto-proteolytic activity of Adgb following recombinant expression in insect cells (Bracke et al. 2018). Ongoing research, funded by the German Research Foundation and the SNSF, aims at elucidating the physiological role, regulation and biomedical implications of this novel globin type.

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 (**Figure 2**).

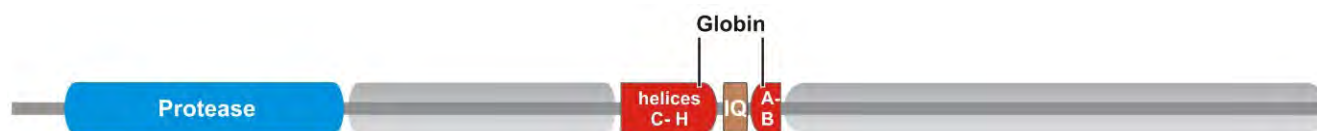


Figure 1. The chimeric domain structure of human androglobin.

The calpain-like protease domain, the rearranged globin domain and the calmodulin-binding IQ motif are indicated.

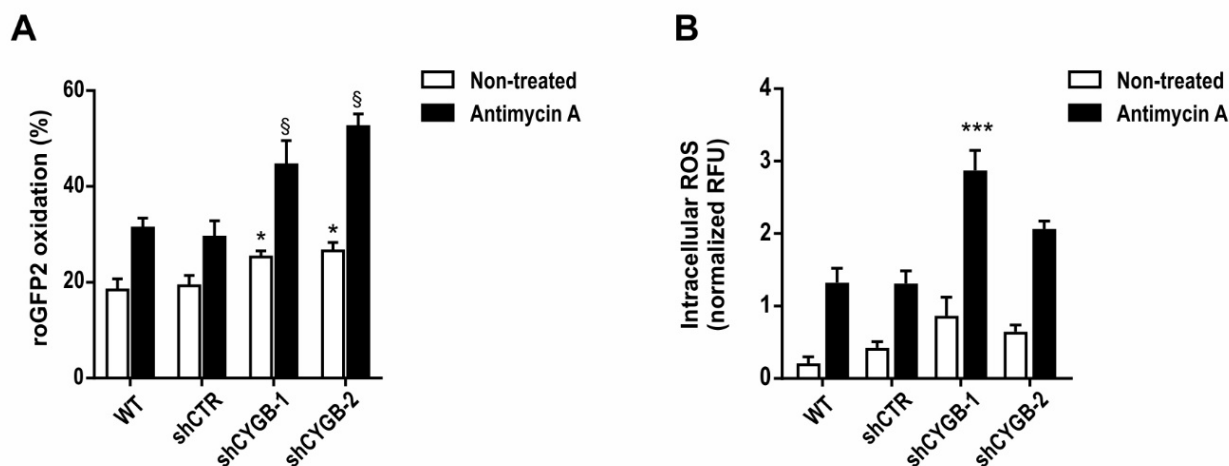


Figure 2: CYGB-deficiency increases oxidative stress

A) Podocyte cells were stably transfected with 2 independent short hairpin RNA (shRNA) sequences targeting human CYGB (shCYGB) and a control shRNA (shCTR). Quantification of the cytoplasmic redox-sensitive probe roGFP2-Orp1 oxidation in wild type (WT), shCTR and shCYGB cells under basal conditions (white bars) and upon treatment with Antimycin A, a mitochondrial complex III inhibitor (black bars). * $p < 0.05$ compared to non-treated WT. $§p < 0.05$ compared to Antimycin A treated WT.

B) Intracellular ROS production using a redox-sensitive DCF probe following Antimycin A treatment. *** $p < 0.001$

Hypoxia-dependent gene regulation

An additional research theme of our group represents the study of various aspects of the VHL/PHD/HIF oxygen sensing pathway. Hypoxia stabilizes hypoxia-inducible factor α subunits (HIF α) which together with the constitutive HIF β subunit form the active HIF-1 and HIF-2 transcription factors. HIFs induce several hundred genes following a drop in oxygen availability. While HIF-1 α is ubiquitously expressed and regulates a broad variety of target genes, HIF-2 α expression is more specific and its downstream functions are less established, but include erythropoietin (Epo) as target gene. Mutations in components of the oxygen sensing pathway have been described in patients suffering from increased red blood cell mass or erythrocytosis (**Figure 3**). We have functionally characterized several PHD2 mutations leading to abnormal HIF-2 α protein production, resulting in increased transcription and Epo production, which then drives the production of red blood cells. Recently we reported the discovery of mutations in a novel exon within the VHL gene leading to erythrocytosis (Lenglet et al. 2018), further substantiating that the underlying molecular cause of hereditary erythrocytosis is more complex than previously anticipated.

We studied several additional aspects of Epo gene regulation including the identification of a distant element regulating renal oxygen-dependent Epo transcription. Finally, using an Epo BAC transgenic mouse model we established renal cell lines capable of hypoxia regulated Epo production (Imeri et al. 2019). These cells represent an appropriate physiological model to investigate various candidate Epo regulating factors, studies currently funded by the NCCR Kidney.CH.

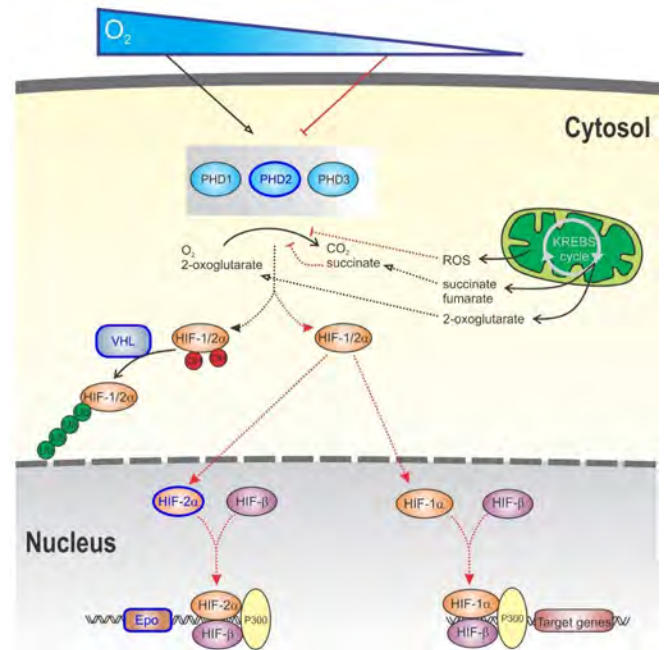


Figure 3: Schematic overview of the oxygen signalling cascade.

Under normoxic conditions, hydroxylation of HIF α subunits by oxygen sensing prolyl-4-hydroxylase domain (PHD) enzymes leads to the binding of the E3 ubiquitin ligase von Hippel–Lindau protein (VHL) followed by polyubiquitination and proteasomal destruction. Under hypoxic conditions, HIF α remains stable, heterodimerizes with HIF β and transcriptionally activates a large number of genes involved in the adaptation to decreased oxygen supply, including the gene encoding Epo. Hereditary erythrocytosis revealed PHD2, VHL and HIF-2 α (marked in blue) as key players in oxygen-regulated Epo gene expression.

Selected Publications

Bracke A, Hoogewijs D, Dewilde S. (2018).

Exploring three different expression systems for recombinant expression of globins: *Escherichia coli*, *Pichia pastoris* and *Spodoptera frugiperda*. *Anal Biochem.* 543: 62-70.

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A search for molecular mechanisms underlying male idiopathic infertility. *Reprod Biomed Online.* 36:327-339.

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Transcriptome-based network analysis reveals renal cell type-specific dysregulation of hypoxia-associated transcripts. *Sci Rep.* 7:8576.

Abdul Dulloo

Mechanisms driving fat storage during weight regain after caloric restriction

Introduction

There is strong epidemiological evidence of increased risks for obesity, type 2 diabetes and cardiovascular diseases in men and women who in young adulthood experienced weight fluctuations involving the recovery of body weight after weight loss - whether due to disease, famine, voluntary slimming by dieting or when weight fluctuations occurred much earlier in life and involved catch-up growth after earlier growth retardation. In addressing the pathways by which such weight fluctuations predispose to fatness and cardiometabolic diseases, our research focuses on the mechanisms that regulate body composition (fat mass and lean mass) during weight recovery, and how they confer increased susceptibility for development of insulin resistance. Over the period 2017-2018, our investigations were focused on two main topics: I.) the role of reduced skeletal muscle protein turnover and local thyroid hormone metabolism in the thrifty metabolism (i.e. suppressed thermogenesis) that facilitates body fat recovery during weight recovery, and II.) to integrate such thrifty metabolism driving preferential catch-up fat with the subsequent phenomenon of hyperphagia persisting after weight recovery and leading to body fat overshooting – a cardinal feature of a mechanistic explanation as to how dieting and weight cycling may predispose to increased fatness.



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I. Skeletal muscle hypothyroidism and diminished protein turnover in thrifty mechanisms driving body fat recovery

Using a rat model of semistarvation-refeeding in which catch-up fat is driven by suppressed thermogenesis, we measured in refed and control animals the following: (i) in-vivo rates of protein synthesis in hindlimb skeletal muscles using the flooding dose technique of ^{13}C -labeled valine incorporation in muscle protein, (ii) ex-vivo muscle assay of net formation of thyroid hormone triiodothyronine (T3) from precursor hormone thyroxine (T4), and (iii) protein expression of skeletal muscle deiodinases (type 1, 2 and 3). Our results indicate that after 1 week of calorie-controlled refeeding, the fractional protein synthesis rate was lower in skeletal muscles of refed animals than in controls (by 30-35%, $p < 0.01$) despite no between-group differences in the rate of skeletal muscle growth - thereby underscoring concomitant reductions in both protein synthesis and protein degradation rates in skeletal muscles of refed animals compared to controls. These differences in skeletal muscle protein turnover during catch-up fat were found to be independent of muscle fiber composition, and were associated with a slower net formation of muscle T3 from precursor hormone T4 (**Figure 1**), together with increases in muscle protein expression of deiodinases which convert T4 and T3 to inactive forms. Our results suggest that diminished skeletal muscle protein turnover, together with altered local muscle metabolism of thyroid hormones leading to diminished intracellular T3 availability are features of the thrifty metabolism that drives the rapid restoration of the fat reserves during weight regain after caloric restriction (1).

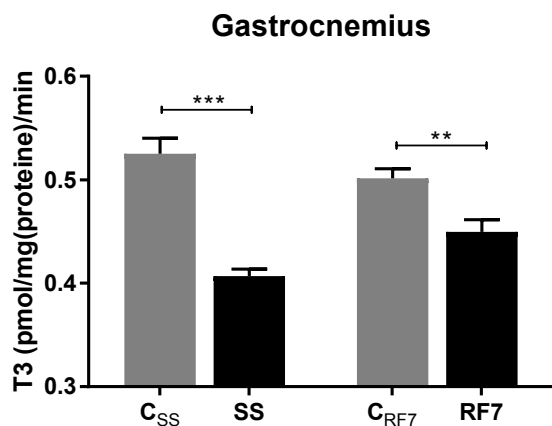


Figure 1 : Skeletal muscle hypothyroidism persists during refeeding.

Net T3 formation from its T4 precursor in skeletal muscle from (i) rats semistarved (SS) for 14 days and their controls (CSS), and (ii) rats refed for 7 days (RF7) and their controls (CRF7). The values are mean \pm SE ($n=6$). Statistical significance of differences are indicated as follows: ** $p < 0.01$; *** $p < 0.001$. Reproduced from Calonne et al. (1)

II. Collateral fattening: a novel concept in body composition autoregulation

In recent years, there has been a resurgence of interest into the role of body composition in the control of appetite/hunger, with particular focus on the role of lean mass or fat-free mass (FFM). In examining the role of FFM in the control of food intake, we have emphasized the 'V'- or 'U'-shaped relationship between appetite/hunger and FFM, and that a distinction should be made between a 'passive' vs. an 'active' role of FFM: the passive role being mediated by 'energy-sensing' mechanisms that translate FFM-induced energy requirements to energy intake, and the active role operating in the defense of FFM deficit by driving hyperphagia through putative 'proteinstat' signals (2). In particular, under conditions of a temporal desynchronization in the recovery of body composition, with complete recovery of fat mass preceding that of FFM, persistent hyperphagia driven by the need to complete the recovery of FFM will result in the excess fat deposition (hence collateral fattening) and fat overshooting (**Figure 2**) – a cardinal feature of human body composition autoregulation as to how dieting and weight cycling, as well as sedentariness, may predispose to increased fatness (3); **Figure 3**. This concept of collateral fattening emphasizes the importance of a healthy lifestyle centered on balanced diets and physical activity in the protection against lean mass deficits pertaining to both the prevention and treatment of obesity.

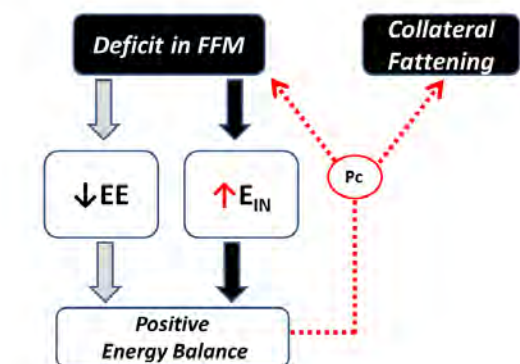


Figure 2 : Concept of 'Collateral Fattening'.

A deficit in FFM results not only in a lower energy expenditure (EE) and hence lower energy needs for weight maintenance, but also in the activation a feedback loop that drives energy intake (E_{IN}) in an attempt to restore FFM through the lean-to-fat partitioning characteristic (P_c) of the individual. Reproduced from Dulloo et al. (2)

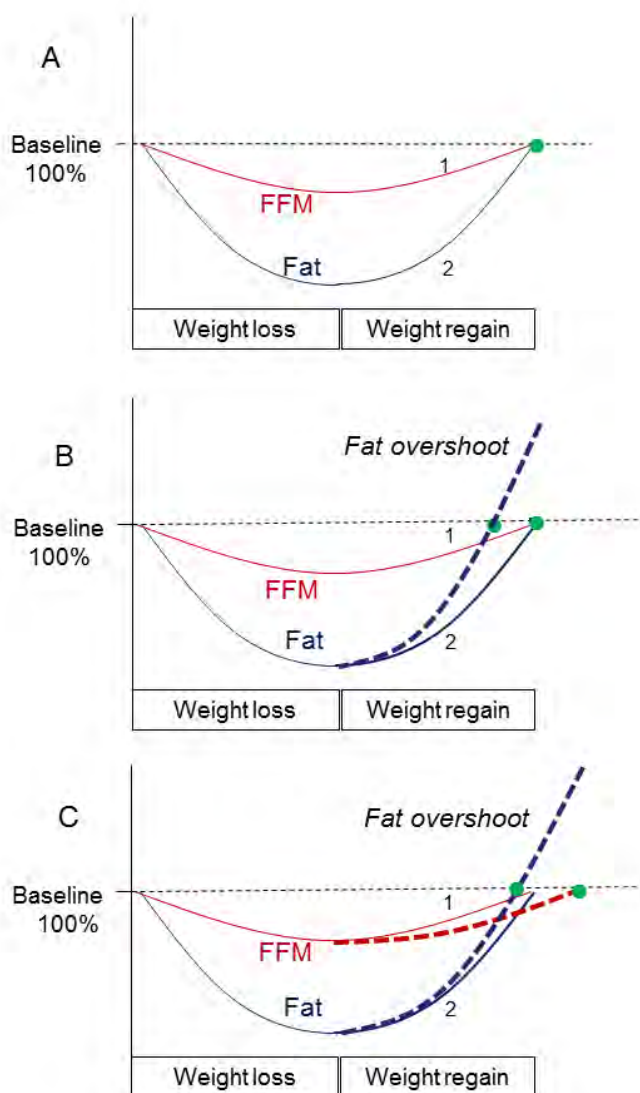


Figure 3: Models of collateral fattening and fat overshooting.

Dynamics of body composition recovery, with fat and FFM synchronization (panel A) or desynchronization (panel B and C) during weight recovery. The Y-axis represent changes in fat and FFM as a percentage of initial (baseline) values, and the number 1 and 2 represent synchronized fat and FFM recoveries, respectively, as determined by the intrinsic lean-fat partitioning characteristic of the individual.

Panel A): Fat and FFM reached complete (100%) recovery simultaneously; there is no fat overshoot.

Panel B): Fat recovery alone is accelerated (either by adaptive thermogenesis or by excessive hyperphagia or by both) such that this catch-up fat results in complete (100%) fat recovery before complete FFM recovery; this desynchronization (represented by the gap between the green filled circles) results in collateral fattening and fat overshoot.

Panel C): Altered intrinsic lean-fat partitioning at the expense of FFM (i.e. slower recovery of FFM- e.g. due to dietary protein or micronutrient deficiencies or lack of physical activity) and hence energy diverted to recovery of fat) also results in complete fat recovery being reached before complete FFM recovery; this desynchronization (represented by the gap between the green filled circles) results in collateral fattening and fat overshoot. Reproduced from Dulloo et al. (3)

Selected Publications

Dulloo AG, Jacquet J, Miles JL, Schutz Y. (2017)

Passive and active roles of fat-free mass in energy balance and body composition regulation. *Eur J Clin Nutr.* 71:353-357.

Dulloo AG, Miles-Chan JL, Schutz Y. (2017)

Collateral fattening in body composition autoregulation: its determinants and significance for obesity predisposition. *Eur J Clin Nutr.* 72:657-664.

Miles-Chan JL, Fares EJ, Berkachy R, Jacquet P, Isacco L, Schutz Y, Montani JP, Dulloo AG. (2017).

Standing economy: does the heterogeneity in the energy cost of posture maintenance reside in differential patterns of spontaneous weight-shifting? *Eur J Applied Physiol.* 117:795-807.

Jean-Pierre Montani

Cardiovascular and metabolic responses to alcohol associated with sugar or festive meals

Introduction

Our general research interests focus on the short-term impact of the ingestion of various meal types and drinks on cardiovascular and metabolic regulation. To that purpose, we study healthy young and older human subjects in randomized cross-over designs, with continuous non-invasive monitoring of cardiovascular variables (such as blood pressure, heart rate, cardiac output, skin blood flow) and of metabolic variables (such as energy expenditure, respiratory quotient and skin temperature). After a control baseline, subjects ingest a test meal or drink, and are monitored continuously for the following two or three hours. In the previous report, we presented our results of the ingestion of caffeinated energy drinks (Red Bull). In the current period, four specific questions were addressed in healthy human subjects, focusing on the response to alcohol associated with sugar (alcopop) or with festive meals as well as the impact of drink temperature on the ingestion of mixed wine and of herbal caffeinated tea.



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Does drinking alcohol with sugar (alcopop) impact the cardiovascular response more than drinking alcohol alone?

We compared the cardiovascular response in healthy young subjects sitting comfortably and during prolonged active standing with a 30-min baseline and following ingestion of 400 mL at 10°C of either: water, water + 48 g sugar (corresponding to a standard soft drink), water + vodka (1.28 mL/kg of body weight, providing 0.4 g alcohol/kg), water + sugar + vodka, according to a randomized cross-over design. Compared to alcohol alone and despite a lower breath alcohol concentration, ingestion of the combination of alcohol and sugar induced hypotension in sitting position related to acute vasodilation, an increase in cardiac load with greater tachycardia (**Figure 1**), and an impairment of the hemodynamic reserve during active standing compromising orthostatic tolerance. These results could be of clinical importance with higher doses of alcohol or if combined with other hypotensive challenges.

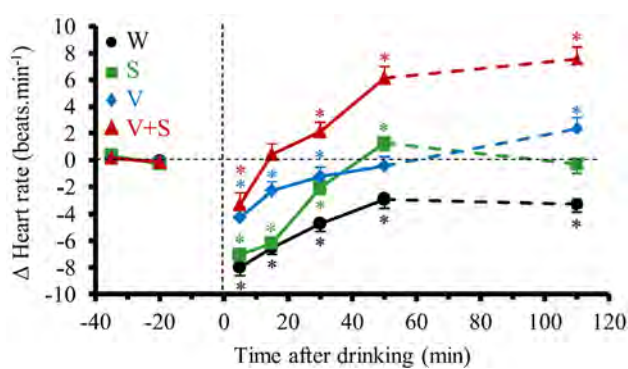


Fig 1 : Changes in heart rate after alcopop ingestion

Four drinks given on separate days were compared in the same individual. Water alone (W, black symbol) led to bradycardia whereas alcohol with sugar (V+S, red symbol) led to a much greater increase in heart rate than sugar (S, green symbol) or alcohol (V, blue symbol) alone.

Should we drink tea hot or cold?

We have previously shown that drinking cold water leads to cardiac unloading and bradycardia, not seen when water is drunk at body temperature. However, the importance of temperature of common drinks, such as tea or alcohol, has not been thoroughly investigated. We compared the cardiovascular and metabolic responses in healthy subjects during baseline and following 500 mL of unsweetened Yerba Mate tea ingested over 5 min either at cold (~3°C) or hot (~55°C) temperature. Compared to hot tea, cold tea induced a decrease in heart rate and an increase in baroreflex sensitivity, fat oxidation and energy expenditure (**Figure 2**). Ingestion of cold tea may be beneficial for weight control as it induced a greater stimulation of thermogenesis and fat oxidation than hot tea while decreasing cardiac load. >>

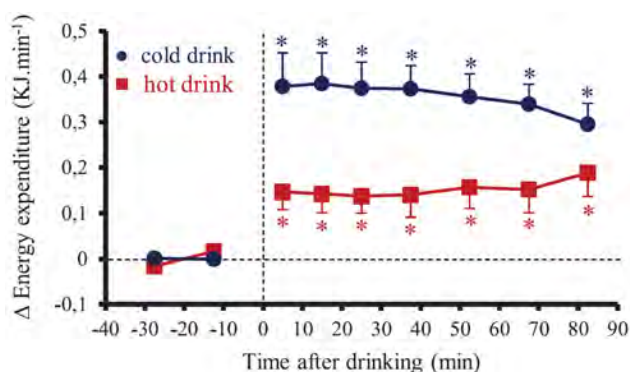


Fig 2 : Changes in energy expenditure after hot or cold tea ingestion

Ingestion of cold tea led to an 8.3% increase in energy expenditure (EE) over 90-min post ingestion whereas the increase was only 3.7% after hot tea. The increase in EE was much higher than what is required to warm up the cold drink to body temperature.

Is the response to a mixture of wine with sugar different when drunk hot rather than cold?

As a drink, red wine is sometimes consumed mixed with fruit juice or sugar and can then be drunk either cold (sangria) or hot (mulled wine). We compared the ingestion of mixed wine consumed at either cold (~3°C) or hot (~55°C) temperature. Alcholema was not altered by drink temperature. The magnitude and/or the directional change of most of study variables differed during the first 20 min following ingestion. By contrast, late changes were similar between cold and hot wine ingestion, underlying the typical effects of alcohol and sugar intake on the cardiovascular system.

Does a festive meal with alcohol load the heart and promote orthostatic hypotension?

We compared the postprandial hemodynamics responses after ingestion of a classical high-fat energy-dense meal versus a light ready-meal, both accompanied with wine. Consumption of the festive meal increased cardiac load as evidenced by higher increases in heart rate, cardiac output, double product and cardiac power output, and led to greater vasodilation and rises in skin blood flow and temperature. Greater increases in heart rate and double product were also observed during orthostatic challenges. The reduced hemodynamic reserve after a festive meal may impede the cardiovascular capacity in elderly subjects who are at greater risk for postprandial hypotension and cardiovascular diseases.

Selected Publications

Maufrais C, Charriere N, Montani JP (2017)

Cardiovascular and cutaneous responses to the combination of alcohol and soft drinks: the way to orthostatic intolerance? *Front Physiol.* 8:860

Maufrais C, Sarafian D, Dulloo A, Montani JP (2018).

Cardiovascular and metabolic responses to the ingestion of caffeinated herbal tea: drink it hot or cold? *Front Physiol.* 2018, 9:315

Sarafian D, Maufrais C, Montani JP (2018).

Early and late cardiovascular and metabolic responses to mixed wine: effect of drink temperature. *Front Physiol.* 9:1334

Neurosciences and sciences of sport and movement

Beat Schwaller

The role of specific calcium-binding proteins in
neurodevelopmental and neuro-psychiatric
disorders and cancer biology

Jean-Marie Annoni

Interaction between Language and
Frontal System

Jean-Pierre Bresciani

Control and Perception
of Movement

Marco C. G. Merlo

Neurophysiological investigations of
information processing and stress reactions
in psychiatric disorders

Gregor Rainer

Basal forebrain neuromodulatory circuits

Eric M. Rouiller

Motor control in non-human primates

Lucas Spierer

Metaplasticity of executive functions in
the healthy and neurological brain

Jean-Pierre Montani

Cardiovascular and metabolic responses to
alcohol associated with sugar or festive meals

Beat Schwaller

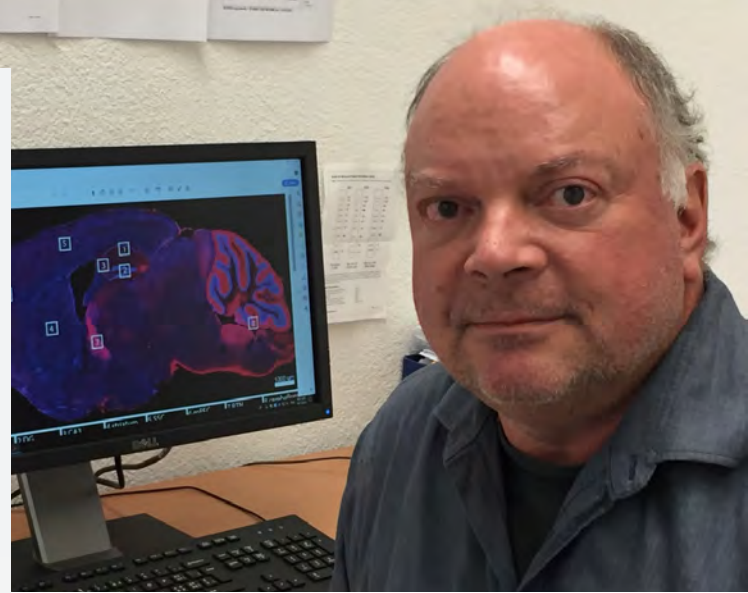
The role of specific calcium-binding proteins in neurodevelopmental and neuropsychiatric disorders and cancer biology

Introduction

Cytosolic Ca^{2+} -binding proteins act as modulators of intracellular Ca^{2+} signals and consequently are important for almost all aspects of biological processes. Together with the sophisticated machinery named the Ca^{2+} signaling toolkit that includes Ca^{2+} channels, pumps and organelles such as the (sarco)endoplasmic reticulum and mitochondria, Ca^{2+} -binding proteins (e.g. parvalbumin (PV) and calretinin (CR)) are implicated in shaping intracellular Ca^{2+} signals. In the currently main research **Topic 1**, we investigated the role of PV, a crucial modulator of Ca^{2+} signals, in a subpopulation of neurons, the so-called Pvalb neurons. A decrease of PV expression, mostly observed in *post mortem* brains of patients with autism disorder spectrum (ASD) and schizophrenia, as well as in mouse models of these neurodevelopmental disorders hints towards a causal role of PV in the etiology of these disorders.

In **Topic 2**, our focus is centered on the role of CR in malignant mesothelioma (MM), an asbestos exposure-associated aggressive and currently non-curable cancer type. At present CR immunohistochemistry is used for MM identification; our studies aim to elucidate the function and regulation of CR in MM cells with CR emerging as a potential therapeutic target.

Further analyses of Ca^{2+} signaling toolkit components are part of **Topic 3**.



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1. Decreased expression of PV, not loss of Pvalb neurons is the hallmark in certain ASD mouse models; PV re-expression rescues the ASD phenotype in mice

In the previous period (2015-16), we had reported that mice deficient for PV (PV^{-/-}) or with $\approx 50\%$ reduced PV expression levels (PV^{+/-}) display behavioral phenotypes with relevance to both ASD core symptoms, i.e. I) abnormal social interactions and deficiencies in communication, as well as II) repetitive and stereotyped patterns of behavior (Wöhr et al. 2015). They also show signs of ASD-associated comorbidities including reduced pain sensitivity and increased seizure susceptibility. Of utmost importance, staining of the Pvalb neurons with the second marker Vicia Villosa Agglutinin (VVA), a lectin recognizing the specific extracellular matrix enwrapping Pvalb neurons, revealed the Pvalb neuron population to be present in identical numbers (as in wildtype mice) in PV^{-/-} and PV^{+/-} brains, although the number of PV-immunoreactive (PV⁺) interneurons is either 0% and $\approx 65\%$ in these mice, respectively (Filice et al. 2016). This PV downregulation is not unique to PV^{+/-} mice, but also present in validated ASD mouse models including Shank1^{-/-}, Shank3B^{-/-} and Cntnap2^{-/-} mice (Lauber, Filice et al. 2018) representing genetic ASD models, as well as in utero valproic acid (VPA)-exposed mice, the latter representing a so-called environmental ASD model. The striatum was identified as a hotspot for PV downregulation in Shank3B^{-/-}, Cntnap2^{-/-} and VPA mice.

Knowing that the cortico-striato-thalamic circuitry is important for speech and language development, alterations in striatal PV expression and associated (homeostatic) adaptations are likely to play an important role in ASD etiology in mouse models (and possibly humans). In a “rescue strategy” approach, we first demonstrated that oral administration of 17- β estradiol (E2) from postnatal days 5-15, increased PV expression levels in treated male PV^{+/-} mice to values close to wildtype levels. This significantly attenuated sociability deficits selectively in PV^{+/-} mice in the direct reciprocal social interaction and the 3-chamber social approach assay, as well as decreased repetitive behaviors (Fig. 1) (Filice, Lauber et al. 2018). The absence of E2-linked amelioration of ASD-like behaviors in PV^{-/-} mice indicates that PV upregulation is required for the E2-mediated rescue of ASD-relevant behavioral impairments. Current experiments with a new transgenic mouse line aim to downregulate PV expression at specific time points of development and possibly detect the emergence of an ASD-like phenotype.

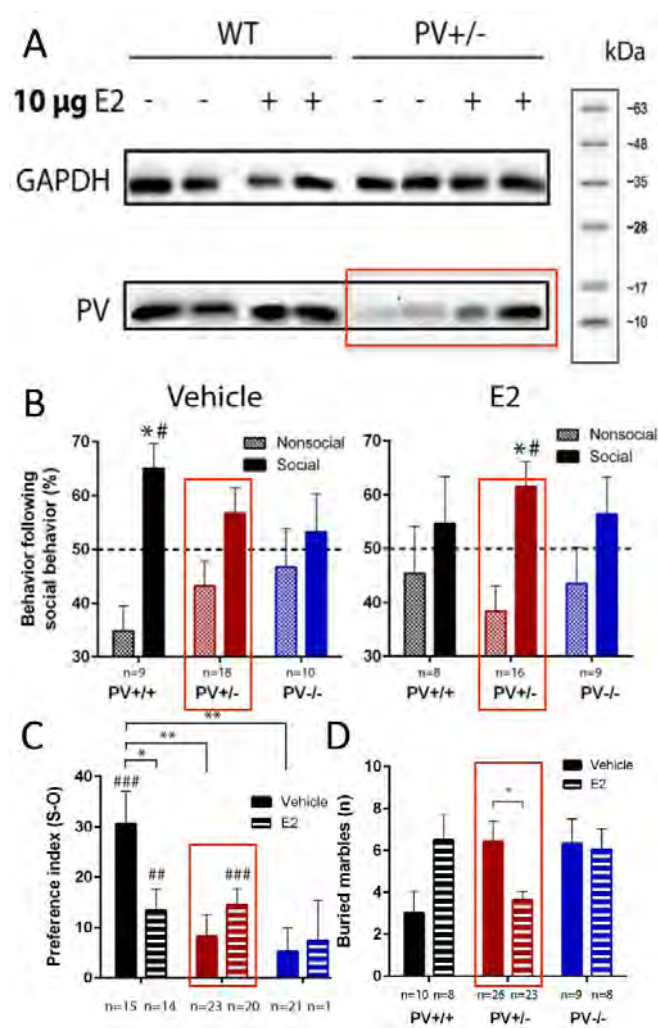


Fig. 1 **A**) 17- β Estradiol (E2) treatment from PND5 – 15 results in PV upregulation in male PV^{+/-} heterozygous mice (red boxed). **B**) Vehicle-treated PV^{+/-} mice show no preference for a social behavior following a social behavior in the reciprocal social interaction assay (left; red boxed). E2 treated PV^{+/-} mice show a clear preference for a social behavior following a social behavior (right; red boxed). **C**) The preference index (S-O) is increased in E2-treated PV^{+/-} mice in the 3-chamber assay (red boxed). **D**) Repetitive behavior tested in the marble-burying assay is decreased after E2 treatment of PV^{+/-} mice (red boxed). All results are indicative of an attenuation of ASD-like behaviors resulting from juvenile E2 treatment of PV^{+/-} mice. Figure modified from (Filice, Lauber et al. 2018).

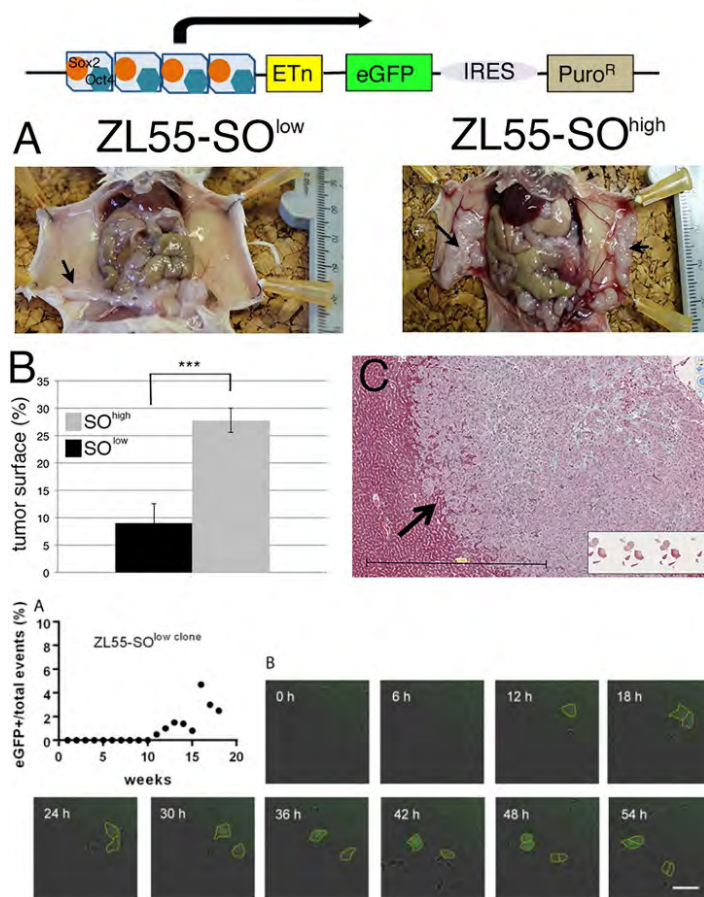


Fig. 2 Top Schematic representation of the lentiviral construct with OCT4 (blue) and SOX2 (orange) binding sites. OCT4/SOX2 binding initiates expression of eGFP and Puro^R. **Middle** Increased tumor growth of human ZL55-SO^{high} eGFP⁺ CSC cells in mice. **A)** Higher load of tumor nodules on the visceral pleura (arrows) in mice injected with eGFP⁺ CSC (right) compared to eGFP⁻ non-CSC (left). **B)** Quantification of images shown in A). **C)** Histological analyses of tumor nodules; a tumor nodule of CSC on the liver surface shows highly invasive edges (arrow). Images modified from (Blum, Pecze et al. 2017). **Bottom** **A)** Appearance of an eGFP⁺ CSC derived from a single eGFP⁻ non-CSC (ZL55-SO^{low}) clone; first evidence of CSC after 10 weeks in culture. **B)** Time-lapse series of a cultured eGFP⁻ non-CSC clone. At t=12 h, a single eGFP⁺ CSC cell (marked with a yellow line) appears that divides during the next 6 h. The two daughter cells divide once more (between 42 and 48 h), yielding four eGFP⁺ cells. Image modified from (Blum, Henzi et al. 2018)

Selected Publications

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Stem Cell Factor-Based Identification and Functional Properties of In Vitro-Selected Subpopulations of Malignant Mesothelioma Cells. *Stem Cell Reports*. 8: 1005-1017.

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Filice F, Lauber E, Vorckel KJ, Wöhr M, Schwaller B (2018)

17-beta estradiol increases parvalbumin levels in Pvalb heterozygous mice and attenuates behavioral phenotypes with relevance to autism core symptoms. *Mol Autism*. 9: 15.

Jean-Marie Annoni

Interaction between Language and Frontal System

Introduction

The 2017-2018 research was focused on executive functions and language, with a particular interest in mother and second language; the aim of the project was to demonstrate the impact of the modulation of prefrontal functions on language production in healthy controls and on language recovery in aphasic patients.

The main questions of this project were :

1. Does left frontal stimulation by transcranial Direct Current Stimulation (tDCS) improve language abilities in mother language (L1) and even more in the L2?
2. Does left frontal stimulation improve language abilities in aphasia recovery?
3. Is there a relationship between the recovery of executive functions and the recovery of different languages, particularly of the L2, in aphasic patients?



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1. Does left frontal stimulation by transcranial Direct Current Stimulation (tDCS) improve language abilities in mother language (L1) and even more in the L2?

In a first point we studied in a group of bilinguals he investigated how behavioral patterns and dynamics spatial-temporal brain differ in a translation compared to a control within-language word-generation task. This first work was important to tackle differences between intra-language and inter language lexical search. In our study, differences were characterized at the early lexical access by stronger early (< 200ms) attentional processes for between than within word generation and by distinct late (424-630ms) engagement of domain-general control networks, namely self-monitoring and lexical access interference. Then a series of three experiments studied specifically the level of effect of frontal modulation in language production. The first important result is that frontal neuromodulation does not seem to have an impact on behavioral output in high performing speakers such as university students. Secondly, we concluded that anodal-tDCS stimulation of the dorsolateral prefrontal cortex (DLPFC) had an effect at a neural level on phonological processes and specifically in L2.

In a second study applying inhibitory continuous theta burst stimulation (cTBS) over the left DLPFC on language production in healthy late bilingual subjects, we found no significant effects of cTBS on behavioral accuracy or response times in a Translation Task or in the non-verbal Flanker Task. For the Picture Naming Task, next to replicating previous studies showing faster responses for naming in L1 as compared to L2, the analysis also showed slower responses after cTBS as compared to Sham stimulation. This behavioral result was also reflected on the electrophysiological level: global field power (GFP) was higher after cTBS compared to Sham stimulation around 100 and 200ms post-stimulus. Source analyses showed that the left temporal regions including the superior temporal lobe, the posterior cingulate, the parahippocampal gyrus as well as the cuneus were more strongly activated after cTBS compared to Sham stimulation.

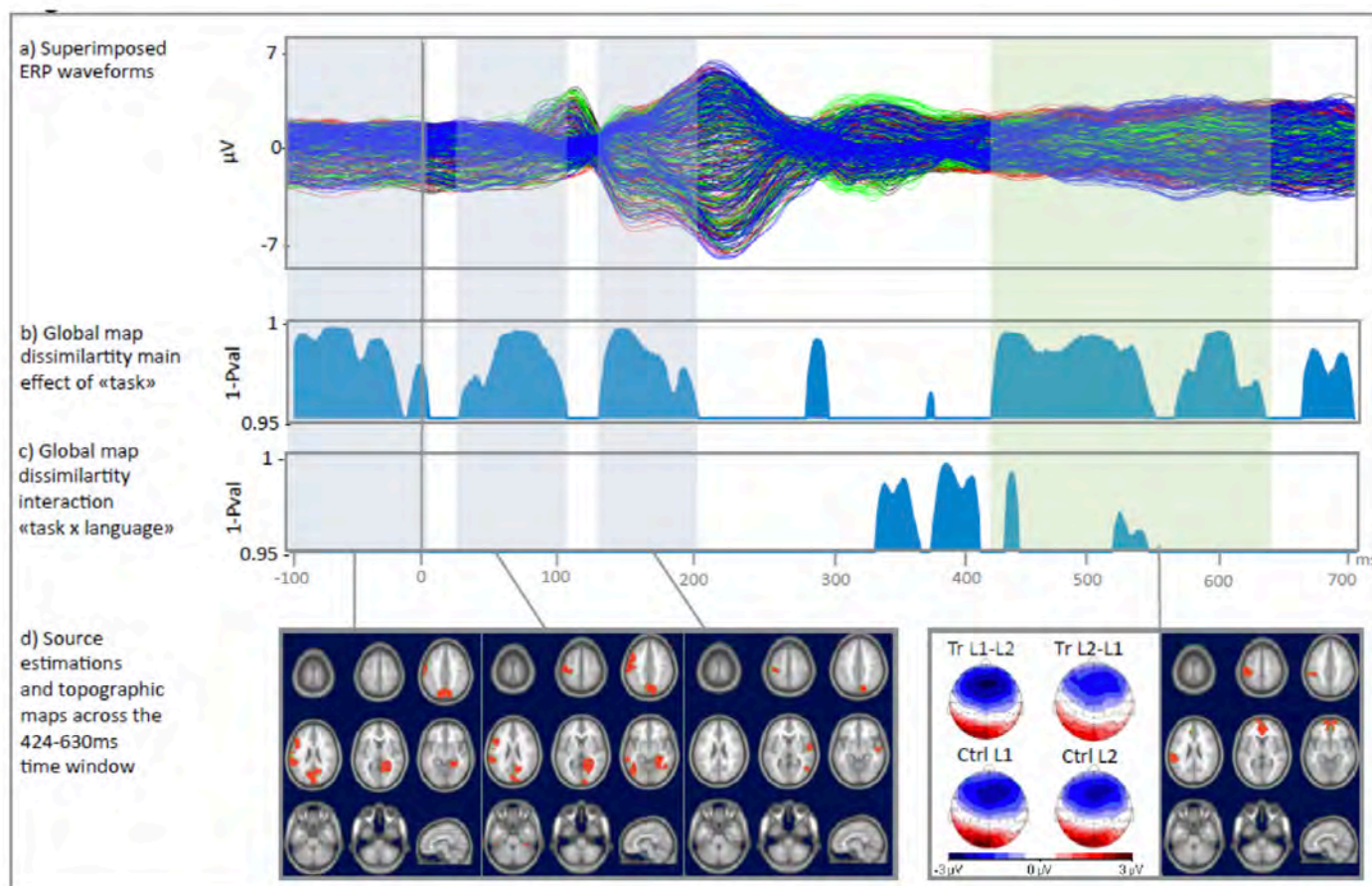
2. Does left frontal stimulation improve language abilities in aphasia recovery?

We investigated the effects of transcranial direct current stimulation (tDCS) of the pre-frontal cortex (PFC) on language production in chronic post-stroke aphasic patients. The results of this study suggest that the brain network dedicated to lexical retrieval processing can be facilitated by anodal tDCS over the left dorsolateral prefrontal cortex.

3. Is there a relationship between the recovery of executive functions and the recovery of different languages, particularly of the L2, in aphasic patients?

Applying dynamic causal modelling (DCM) analyses to the connections between language and control brain areas in a small group of late bilingual patients, we could demonstrate, consistent with the dynamic view of language recovery, a higher connectedness between language and control areas in the language with the better recovery. Our data suggest that engagement of the interconnected language-control network is crucial in the recovery of languages.

Fig. : neurophysiological signature of translation



a) Superimposed ERP waveforms for the four conditions of interest across all 128 electrodes.

b) Global map dissimilarity of the main effect of task ($p < 0.05$, > 52 TF) identifying topographic differences between the translation and the control task from -100 ms to 1ms, 24ms -104ms, 129ms-203ms and 424 – 630ms.

c) Global map dissimilarity of the interaction task x language, revealing significant topographic differences from 338-416ms ($p < .05$, > 52 TF). Of note, the time windows revealing a main effect of task and the time windows revealing a significant interaction task x language do not overlap.

d) Source estimations for the four significant time windows revealing a main effect of task as well as topographic maps for the four conditions (translation L1-L2, translation L2-L1, control task L1, control task L2) across the 424-630ms window.

Selected Publications

Diegues S, Kaeser M, Roux C, Cottet J, **Annoni JM**, Schmidlin E. (2017).

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Jost L, Radman N, Buetler K, **Annoni JM**. (2018)

Behavioral and electrophysiological signatures of word translation processes Neuropsychologia, 109:245-254.

Pestalozzi MI, Di Pietro M, Martins Gaytanidis C, Spierer L, Schnider A, Chouiter L, Colombo F, **Annoni JM**, Jost LB (2018).

Effects of prefrontal transcranial direct current stimulation on lexical access in chronic poststroke aphasia. Neurorehabil Neural Repair. 10:913-923.

Jean-Pierre Bresciani

Control and Perception of Movement

Introduction

Our sensory systems provide us with information about our body orientation and movements relative to the environment. These systems contribute to our perception of movement, notably allowing us to distinguish our own displacements in the world (self-motion perception) from movement of surrounding objects or individuals. These systems are also crucial to control our movements and adapt them to the physical constraints acting on the body, allowing us to generate stable and highly-adaptive Behavioral patterns in different contexts.

We combine motion capture, virtual reality technology and statistical methods to :

1. Investigate how sensory information is integrated to perceive movement and implement efficient motor strategies
2. Analyze human movement and develop applications to improve human performance and learning.



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Fall prevention

Because of population ageing, fall prevention represents a human, economic and social issue. Currently, fall risk is often evaluated by health professionals who assess balance abilities. Assessment protocols are often subjective and can greatly vary between examiners and clinical settings. In addition, clinical tests might be burdensome and are usually performed only when some risk has already been identified. More quantitative, accurate, and objective assessments of postural control would improve the appraisal of balance abilities.

We showed that fall risk can be quickly and reliably assessed by coupling a low cost ambient sensor with machine learning algorithms to monitor simple balance tasks such as standing with the eyes closed with a narrow stance or on a foam pad. The system that we propose is quick, easy to use, and it requires little space. Therefore, this system could be used with more flexibility and more routinely by a large number of health professionals, including family physicians, which would substantially improve fall prevention and facilitate a longer follow-up of patients.

We used the same system to monitor daily activities in a home-like environment in order to identify the behavioral parameters that best discriminate high fall risk from low fall risk individuals. This monitoring notably allowed us to show that behavioral parameters such as step length or the speed to stand up are very reliable indicators of fall risk.

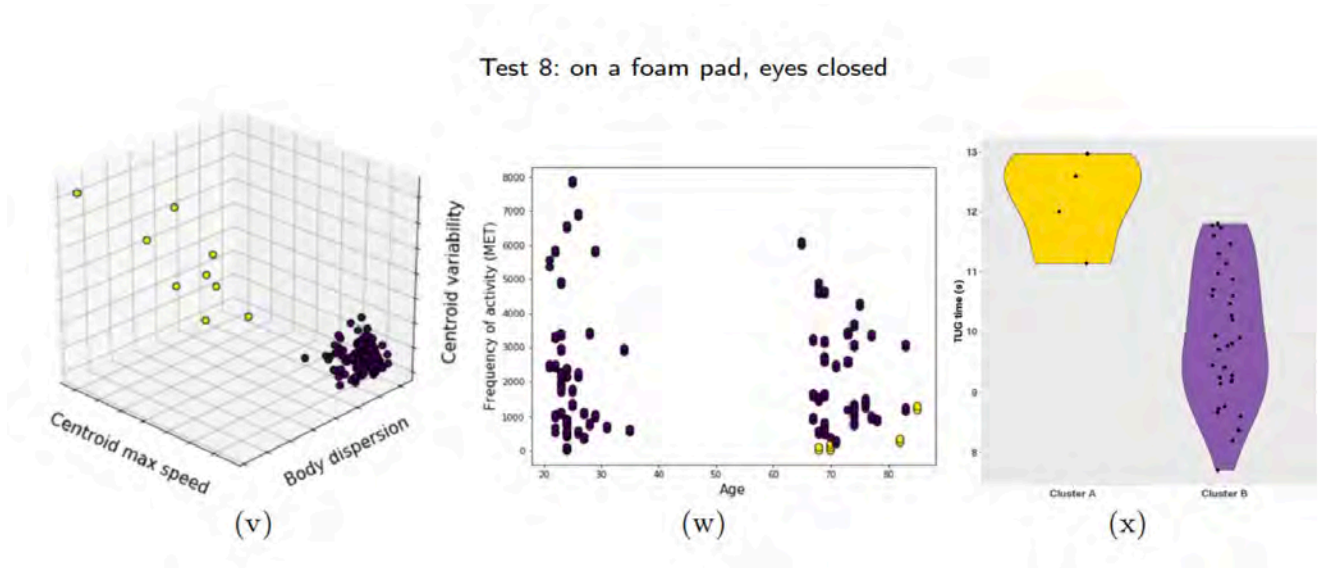


Figure 1. Example of balance task providing a good estimation of fall risk. (v) The K-means clustering method was used to cluster participants in two groups (cluster A for yellow dots and cluster B for purple dots) based on three standardized parameters of silhouette and dispersion (see the three axes). (w) The outcome of the K-means clustering methods based on the 'Maximum speed of the centroid' parameter is plotted as a function of the age and volume of physical activity of the participants. The dot color discriminates the two clusters A vs B (yellow vs purple). (x) Time required to perform the TUG test for the cluster A (yellow) and B (purple). Clusters A and B were formed using the 'Maximum speed of the centroid' parameter, and only elderly people are represented here.

Integration of visual and kinaesthetic/efferent information when running in virtual environments

Physical activity (PA) is fundamental for human health and well-being. It notably helps reducing the risk of many diseases and improving the quality of life. Treadmills constitute one of the most widely used pieces of equipment to train cardiovascular fitness indoors. However, treadmill locomotion is monotonous and can easily lead to boredom. Moreover, it fails to reproduce over-ground locomotion because it is characterized by a sensory discrepancy between kinaesthetic/motor and visual information. Coupling treadmills and virtual reality (VR) could contribute to improve the engagement and effort, and enhance physical experience.

However, in virtual and simulated environments, perception can differ from that experienced in the 'real' world. We investigated how visual and kinaesthetic/efferent information is integrated for speed perception when running in a treadmill-mediated virtual environment. At different running speeds, we measured the optical flow speed that is perceived as matching the actual running speed. For all tested speeds, visual speed was systematically underestimated relative to the actual running speed. The underestimation of visual speed was speed-dependent, the percentage of underestimation increasing when running speed increased.

Our results also showed that the underestimation of visual speed is larger for sedentary than for active participants. The volume of physical activity per week was found to be the best predictor of visual speed perception, whereas surprisingly, overall physical fitness turned out to be only a poor predictor of perceived visual speed. Taken together, these results suggest that when designing treadmill-mediated virtual environments, the type and level of PA of the user should be considered, and the environment should be tailored to the user's needs and preference in order to limit kinaesthetic-visual discrepancy.

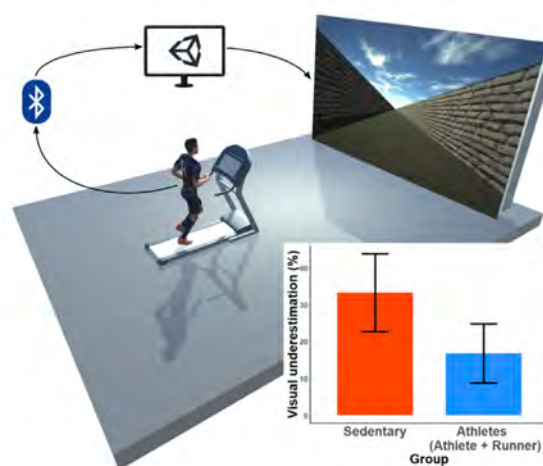


Figure 2. Participants ran at different speeds on a treadmill in front of a large screen displaying a moving virtual scene. They were asked to compare the speed of the moving visual scene to their running speed. The speed of the visual was systematically underestimated relative to running speed. The underestimation was larger for sedentary than for active participants.

Selected Publications

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Matching optical flow to motor speed in Virtual Reality while running on a treadmill. *PLoS One*, 2018, 13:e0195781

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Validation of an ambient system for the measurement of gait parameters. *Journal of Biomechanics*, 2018, 69:175-180

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Automating the timed up and go test using a depth camera. *Sensors*, 18, 14:s18010014

Marco C. G. Merlo

Neurophysiological investigations of information processing and stress reactions in psychiatric disorders

Introduction

Patients who develop major psychiatric disorders show early cognitive and emotional dysfunctions. These dysfunctions are often linked to difficulties in social cognition, which is strongly related to deficits in social functioning. Our research aims at investigating these dysfunctions with neurophysiological methods. Two main aspects of information processing engaged in brain processes during social interactions are: a) early information processing (sensorial, attentional and working memory) and b) decision-making functions. These two domains are compared between healthy subjects and psychotic patients. The results of three studies are presented in this report: a) the analysis of brain oscillations during a working memory task (n-back), and b) computation of event-related potential (ERP) data during a social decision making task (Ultimatum game). Data of a third domain, i.e. false memory, have been collected during this period and the results will soon be published.

Other research domains of our group involve neurophysiological evaluation of acute alcohol detoxification and of effects of mindfulness-based stress reduction program.



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A. The first study focused on investigating brain oscillation changes during the successful performance of an adapted n-back working memory (WM) task to address temporal connection activity as a dysfunctional mechanism underlying perceptual organization and working memory in patients with first episode psychosis (FEP).

Gamma band oscillations participate in the temporal binding needed to synchronize cortical networks, involved in early sensory and short-term memory processes. Although, alterations of these neurophysiological parameters were found in psychotic disorders, temporal dynamics and signal complexity of gamma band oscillations in FEP has not yet been explored. To address this issue, gamma band analysis was performed in 15 FEP and 18 healthy controls who performed an adapted 2-back working memory task. Multiple linear and logistic regression models were computed to explore the relationship between the cognitive status and gamma oscillation changes over time. Based on regression model results, phase diagrams were constructed and their complexity was estimated using fractal dimension, a mathematical tool that describes shapes as numeric values. When adjusted for gamma values at time lags -3 to -4 ms and -15 to -16 ms, FEP patients displayed significantly higher time-dependent changes than controls, independently of the nature of the task. **(fig.1)**

► The present results are consistent with a discoordination of the activity of cortical generators engaged by the stimulus apparition in FEP, leading to a global binding deficit, confirmed by the fractal analysis. Our results provide evidence for recruitment of supplementary cortical generators as compensating mechanisms and yield further understanding for the pathophysiology cognitive impairments in FEP.

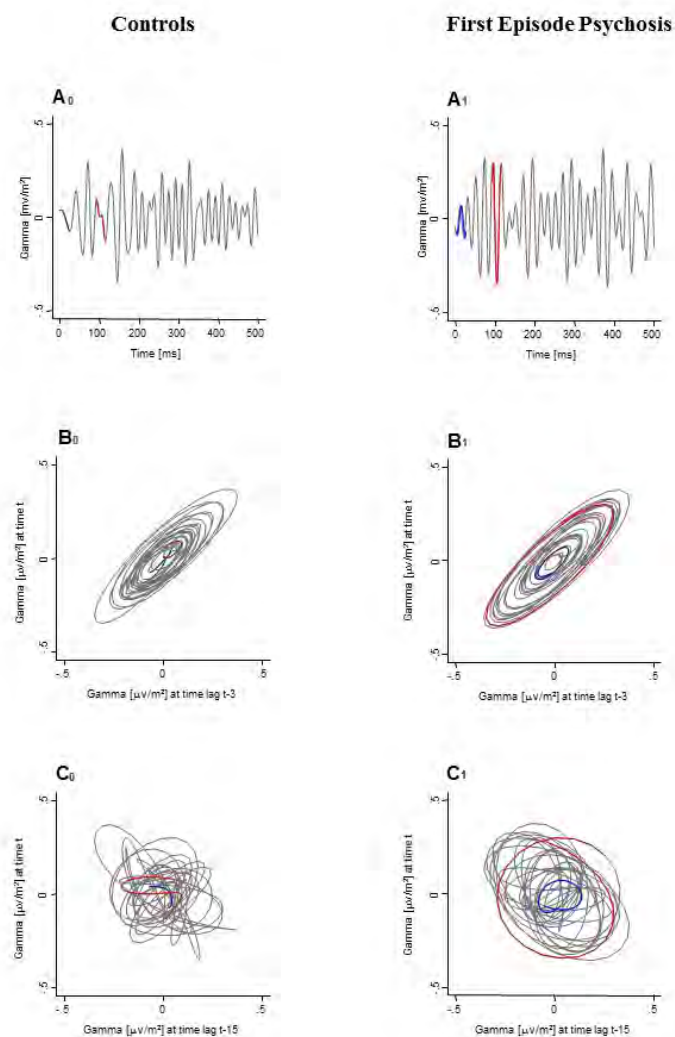


Figure 1. Phase diagram plots.

Average frontal gamma oscillation based on groups during the 2-back task as a function of time (A0/A1), and at time lags -3 (B0/B1) and -15 (C0/C1). Colored sections trace two exemplary time periods: blue for the period 0 ms\text25 ms, and red for the period 275 ms\text300 ms corresponding to different loops of the ellipse in controls (B0C0) and FEP (B1/C1).

B. The next two studies applied a socio-economic paradigm, i.e. the Ultimatum Game (UG) task, to measure neuropsychological parameters during social cognition.

The UG is a typical paradigm to investigate social decision-making. Although the behavior of humans in this task is already well established, the underlying brain processes remain poorly understood. Most importantly, the comparison of the ERP waveforms between the responder and proposer conditions has not been studied. Therefore, to investigate condition-related electrophysiological changes, we applied the UG paradigm and compared parameters of the P2, LPC and FRN components in twenty healthy participants. (**fig.2**)

Overall, our findings indicate that intensity and time-course of neuronal systems engaged in the decision-making processes diverge between both UG conditions, suggesting differential cognitive processes. ▶

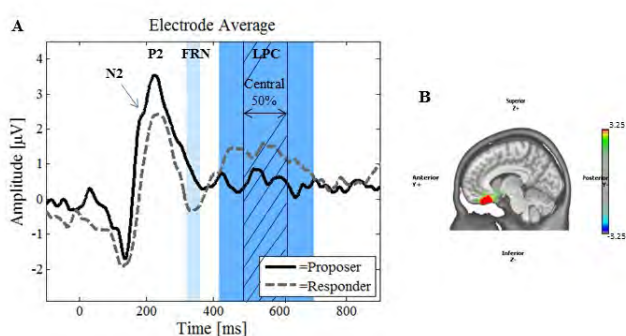


Figure 2.

(A) Grand average waveform of the proposer (solid black line) and responder (dashed gray line) conditions. The band around the LPC component represents the complete length of the component, whereas the shaded area stands for the middle 50%. In the responder condition, note the absence of a N2 component, the delayed latency and lowered amplitude for the P2, and the higher mean amplitude for the FRN and LPC.

(B) Source reconstruction of the N2. A significant higher activation around the anterior cingulate cortex was found for the proposer condition.

▶ Since deficits in decision-making and social interactions are predictive for functional outcome in psychotic disorders, understanding their brain correlates is of great importance to develop more specific therapeutic interventions. We then compared the neuronal bases of schizophrenic patients with healthy controls, while performing the UG. In the proposer condition, no differences were found in amplitude of the P2 and FRN components. In contrast, in the responder condition, significant differences were found for the amplitude of the FRN. (**fig.3**)

We suggest that the difference found in the FRN amplitude is associated with difficulties of patients in interpreting another's behavior. Although schizophrenic patients correctly activate neuronal bases in the proposer condition, they were not able to activate the same networks in the responder condition, thereby exposing their difficulties in social interaction.

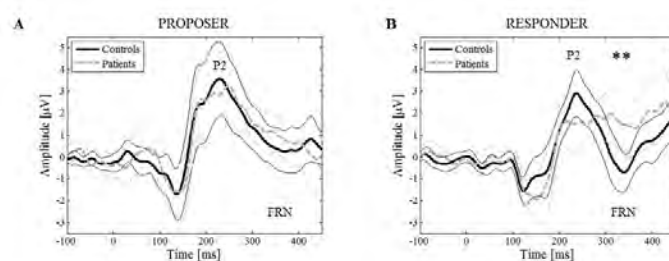


Figure 3.

Grand average waveform (FPz, AFz, Fz, FCz, Cz electrodes) for the electrode average for controls (solid black line) and patients (dashed grey line), including the 95% confidence interval (thinner lines) following proposer (A) and responder (B) decision-making. ** $p < 0.01$.

Selected Publications

Horat SK, Prévot A, Richiardi J, Herrmann FR, Favre G, Merlo MCG, Missonnier P (2017).

Differences in social decision-making between proposers and responders during the ultimatum game: An EEG Study. *Front Integr Neurosci.* 11: 11-13

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Gregor Rainer

Basal forebrain neuromodulatory circuits

Introduction

The basal forebrain contains is composed of a considerable number of nuclei, each of which can modulate activity in the brain areas that it innervates. Our laboratory focuses on understanding the specific impact of individual nuclei on sensory perception, attention, memory formation and brain state regulation. We use a combination of sophisticated behavioural analyses in freely moving animals, large scale recording of neural activity and optogenetic as well as electrical stimulation of brain circuits. At the center of our efforts at present are the basal forebrain modulatory influence sensory thalamic and visual and auditory cortical areas, as well as the role of the basal forebrain on promoting default mode brain state induction and maintenance.



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Research activity

Basal forebrain influence on auditory information processing and brain state

To understand the role of the basal forebrain in modulating sensory information encoding, we are focusing on the posterior section of the nucleus basalis of Meynert, which sends projections to auditory cortex as well as auditory thalamus. We study how information encoding in these target structures is affected by electrical or optogenetic activation of the basal forebrain, and how up or downregulation of basal forebrain activity impacts task participation and learning in an auditory discrimination task. These studies shed light on modulatory impact of the basal forebrain on processing of auditory information, and may provide a basis for promoting learning or brain plasticity.

Following our demonstration of pronounced gamma oscillations in the basal forebrain nucleus ventral pallidum, we are now proceeding to further characterize these prominent brain oscillations, for example by examining the involvement of different cell types in this phenomenon. These studies are complemented by behavioural work examining how optogenetic or electrical brain stimulation in this nucleus impacts learning performance and general behavioural state. Our findings further implicate the basal forebrain in promoting the default brain state, during which attention is directed internally away from the external environment and which is thought to reduce the detrimental impact of stress on brain function.

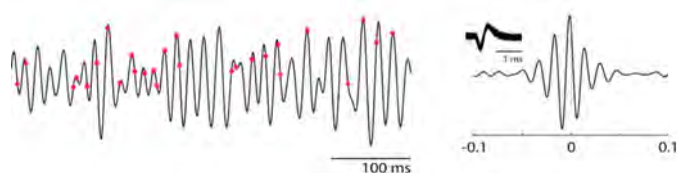


Fig.1 Gamma oscillations recorded in the ventral pallidum nucleus of the basal forebrain.

(left) raw traces showing local field potential fluctuations and action potentials (red dots) recorded on the same electrode. (right) Spike-triggered average of the local field potential and action potential waveform underline local generation of gamma oscillations in the basal forebrain.

Comparative neuroscience

A major challenge for translational neuroscience is using insights from animal experiments to develop applications that might be useful for humans. In this context, it is crucial that animal experiments are designed to elucidate general mechanisms of physiological regulation, rather than species-specific circuits. Comparative studies in different species are crucial to achieve this goal. Along these lines, we focus our experimental work on multiple mammalian species, allowing us to uncover and distinguish common mechanisms from specific adaptations. In particular, we are one of the few laboratories worldwide that study the behaviour and brain circuits of the tupaia, a small mammal native to southern Asia that is a close relative of primates. Tree shrews are highly intelligent and possess visual and auditory brain circuits that exhibit close homologies to those seen in primates.

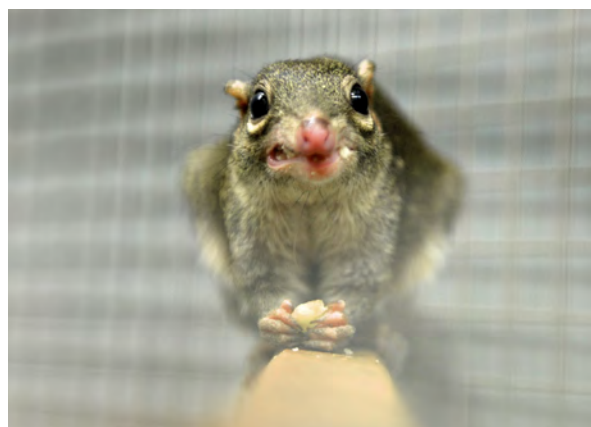


Fig.2 Image of a tree shrew (*tupaia belangeri*) eating a piece of fruit.

Selected Publications

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Eric M. Rouiller

Motor control in non-human primates

Introduction

The general theme of research in the laboratory is the plasticity of the central nervous system in relation to use (experience) or following injury/disease.

Based on non-human primate models (macaque monkeys), the benefit provided by autologous transplantation of adult neural progenitor cells (ANCE) was investigated in case of motor cortex lesion (confirming previous results from our laboratory) and also in case of Parkinson Disease (PD: MPTP monkeys). For both types of lesion (motor cortex lesion and PD), the ANCE cellular therapy provided a significant enhancement of functional recovery of manual dexterity: the treatment produced a rebound of recovered performance corresponding to a better ability to manipulate small objects with the hand affected by the lesion (motor cortex) or pathology (PD). Moreover, as a result of lesion and functional recovery, the connectivity in the motor system is rearranged, in particular the motor corticobulbar (corticoreticular) projection. In the context of therapy, previous work from our laboratory showed also a benefit for the functional recovery post-lesion of a treatment (anti-Nogo-A antibody) aimed at neutralizing the growth inhibiting effect of molecules such as Nogo-A (e.g. Freund et al., 2007; Wyss et al., 2013).



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In primates, the control of voluntary movements (e.g. manual dexterity) is ensured by the direct corticospinal projection (**green arrow in Fig. 1**). The CS projection includes an indirect connection to spinal motoneurons via spinal interneurons, as well as a direct projection to motoneurons, referred to as corticomotoneuronal (CM) projection system. The CM system is a specialty of primates, representing a crucial anatomical support for manual dexterity. However, other indirect descending projections also play a role (**red and orange arrows in Fig. 1**), in particular the “cortico-reticular (red arrow) + reticulo-spinal (orange arrow)” projection system.

We have studied the “cortico-reticular” projection (red arrow in Fig. 1) in adult macaque monkeys, comparing intact animals with animals subjected to 3 types of lesion or pathologies:

- Primary motor cortex (M1) lesion (focused on the hand area)
- Spinal cord injury (SCI=hemisection at cervical level)
- Parkinson disease (MPTP intoxication)

The corticoreticular projections were labelled with a neuroanatomical anterograde tracer, BDA (biotinylated dextran amine), injected in M1, or in the premotor cortex (PM) or in the supplementary motor area (SMA) in order to visualize their axonal terminals in the pontomedullary reticular formation (PMRF) in the brainstem. The BDA labelled axonal terminal boutons were plotted under the microscope in order to establish their spatial distribution and density.

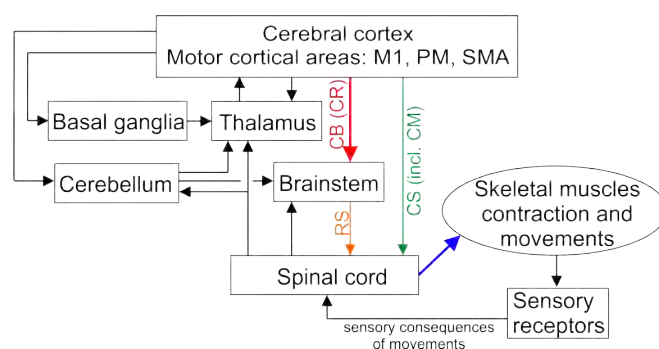


Figure 1: Schematic organization of the motor system in primates. Central motor control commands directed towards motoneurons in the spinal cord originate from the motor cortical areas (M1, PM, SMA) and/or from the brainstem, via descending pathways like the corticospinal projection (CS in green) and the corticobulbar (corticoreticular = CB (CR) in red) projections, respectively. From the brainstem, motor commands are transferred to the spinal cord via the reticulospinal projections (RS in orange, among others). The CS projection includes the indirect projection to motoneurons, via spinal interneurons, as well as the direct projection to motoneurons referred to as corticomotoneuronal (CM) projection. The data presented here are focused on the motor corticobulbar (corticoreticular) projections, either in intact monkeys or in monkeys subjected to a lesion (motor cortex, spinal cord injury) or pathology (PD). M1=primary motor cortex; PM=premotor cortex; SMA=supplementary motor cortex.

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In the intact macaques, the corticoreticular projection to PMRF was found to be significantly denser when originating from PM or SMA than that originating from M1 (Fregosi et al., 2017; **Fig. 2**). In addition, the corticoreticular projections from PM and SMA terminate predominantly on the ipsilateral PMRF, whereas that from M1 ends mostly on the contralateral PMRF (**Fig. 2**).

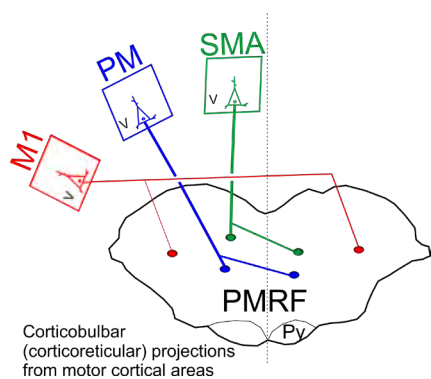


Figure 2: The corticobulbar (corticoreticular) projections to the ponto-medullary reticular formation (PMRF) from pre-motor (PM) and supplementary motor (SMA) cortical areas are denser than that originating from primary motor cortical area (M1). Corticobulbar axon terminals in PMRF coming from M1 are predominantly contralateral whereas PM and SMA project more densely ipsilaterally. When originating from PM and SMA, corticobulbar terminals are located more medially than when originating from M1.

In case of lesion (motor cortex or spinal cord), the CS projection is re-arranged (Freund et al., 2007; McNeal et al., 2010). Does the corticoreticular projection also reorganize after a lesion or pathology? The answer is yes. The corticoreticular projections from M1 and premotor cortex (PM) are significantly modified in the 3 pathologies (**Fig. 3**), possibly underlying in part the functional

recovery mechanisms (especially after treatment). In case of unilateral M1 lesion, the density of the corticoreticular projection from PM is significantly reduced, which is also the case for the projections from M1 and PM in PD monkeys (**Fig. 3**). In case of SCI, the density of corticoreticular projection from M1 is increased, when the anti-Nogo-A antibody treatment was applied. Reduction or enhancement of the corticoreticular projections leads to make the reticulospinal projection (orange arrow in **Fig. 1**) more independent, more dependent, respectively, from the cortical control, representing possible mechanisms of recovery (adaptation) post-lesion.

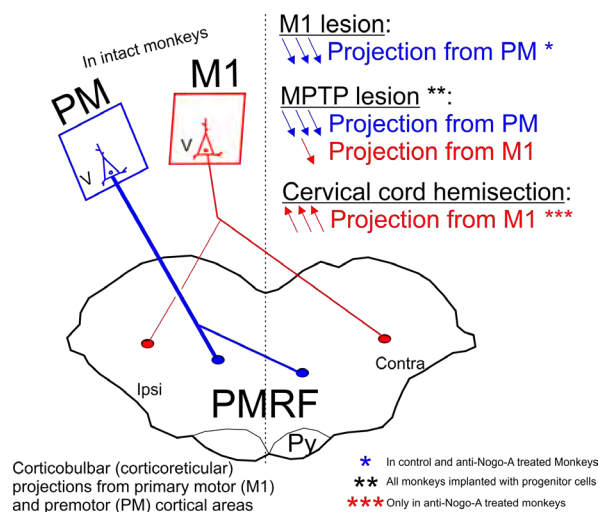


Figure 3: In intact adult macaques, the corticobulbar projections are denser when originating from PM than from M1. After unilateral lesion of M1, the projection from the ipsilesional PM was strongly reduced, both in presence or absence of anti-Nogo-A antibody treatment. After MPTP lesion (and following cell therapy), the projections from both PM and M1 also decreased. In contrast, after cervical cord hemi-section, the projection from M1 increased, but only in presence of anti-Nogo-A antibody treatment (Fregosi et al., 2018).

Selected Publications

Borgognon S, Cottet J, Moret V, Chatagny P, Ginovart N, Antonescu C, Bloch J, Brunet JF, Rouiller EM, Badoud S (2017).

Enhancement of striatal dopaminergic function following autologous neural cell ecosystems (ANCE) transplantation in a non-human primate model of Parkinson's Disease. *J. Alzheimers Dis Parkinsonism* doi: 10.4172/2161-0460.1000383

Fregosi M, Contestabile A, Badoud S, Borgognon S, Cottet J, Brunet JF, Bloch J, Schwab ME, Rouiller EM (2018).

Changes of motor corticobulbar projections following different lesion types affecting the central nervous system in adult macaque monkeys. *Eur. J Neurosci.* 48: 2050-2070

Fregosi M, Contestabile A, Badoud S, Borgognon S, Cottet J, Brunet JF, Bloch J, Schwab ME, Rouiller EM (2018).

Changes of motor corticobulbar projections following different lesion types affecting the central nervous system in adult macaque monkeys. *Eur. J Neurosci.* 48: 2050-2070

Lucas Spierer

Metaplasticity of executive functions in the healthy and neurological brain

Introduction

Dr Spierer's Laboratory for Neurorehabilitation Science aims at establishing fundamental neurocognitive models of training-induced plasticity in the healthy and neurological brain, and on this basis to develop and validate neurophysiologically-informed training programs for the rehabilitation of clinical populations. We further investigate how our interventions may help modifying health-related behaviors ranging from eating habits to addictions by influencing implicit neurocognitive processes.



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Our capacity to inhibit unwanted thoughts, emotions or actions is typically referred to as «Inhibitory control». This core component of executive functions allows flexible adaptation to ever-changing goals and environmental contingencies. While the fronto-striatal brain network supporting inhibitory control is relatively well described, how this capacity can be influenced with training and the supporting neurophysiological mechanisms remain largely unresolved. We focus on the neural correlates of inhibitory control plasticity and on how plasticity can be controlled to help patients recovering when inhibitory control is impaired after brain lesions.

We more specifically investigate :

- The anatomo-functional brain correlates of neuroplasticity in inhibitory control, and how the reward system, brain lesions and neurodegeneration interact with these neuroplastic changes.
- The neuropsychopharmacological factors modulating the capacity of executive functions (mainly motor inhibitory control) to express experience-dependent functional and structural neuroplasticity (i.e. the metaplasticity of executive functions), and notably the effect of aging, GABAergic transmission and post-lesion delays on the expression of brain plasticity.

Our objectives further include assessing whether the efficacy of neurocognitive interventions and training-induced plasticity could be potentiated by i) deep-brain stimulation and pharmacological interventions; and ii) the dynamic updating of training tasks or neurostimulation parameters based on participants' neurocognitive state (closed-loop technologies).

In parallel, and based on the neurocognitive models of training-induced plasticity in executive functions we have established over the last 10 years, we develop standalone rehabilitation software and validate them with series of randomized controlled trials in healthy and neurologic populations. With videogame professionals, we have notably developed serious games involving closed-loop technologies designed to enhance or help the recovery of executive functions.

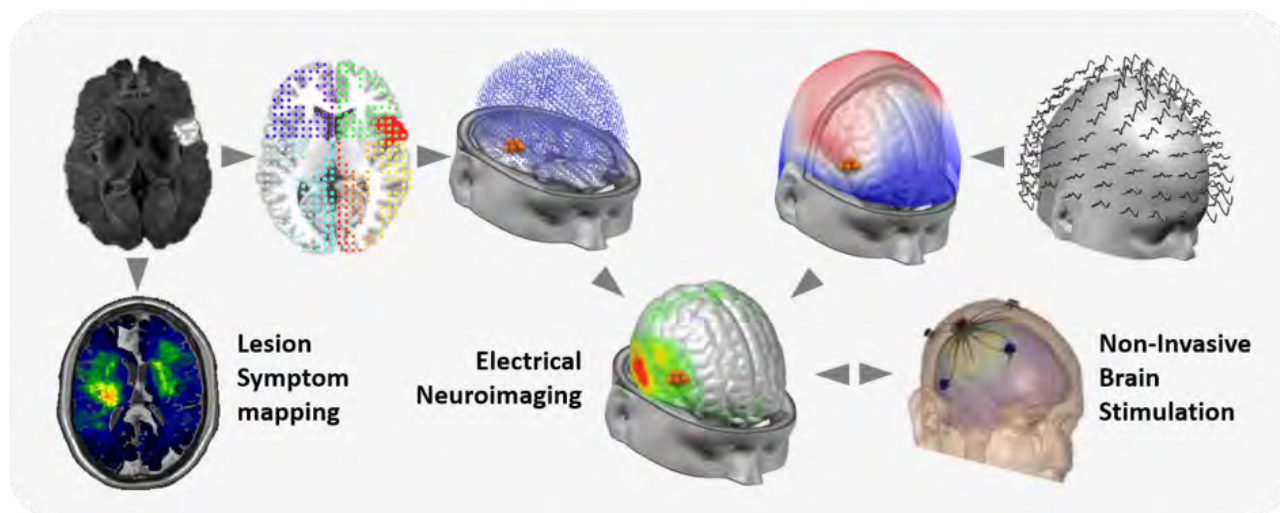


Figure 1. We combine brain lesion analyses, electrical neuroimaging and brain stimulations methods to measure training-induced plasticity in healthy and neurologic populations. These methods are available to other groups via the platform for Brain Imaging and Stimulation we run at the Faculty level in addition to our laboratory.

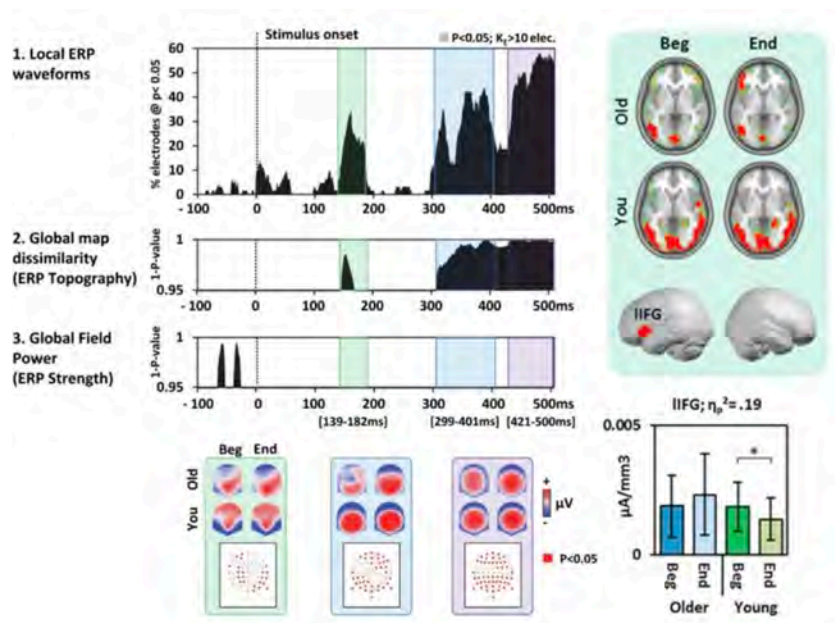


Figure 2. Example of event-related potential and parametric mapping analyses of distributed electrical sources estimations comparing the effect of executive control training in young vs older population, and showing that training intervention interaction with aging.

Together with our other publications, these findings indicate that cognitive interventions to prevent age-related cognitive declines should not focus on normalizing older adults functional brain organization but rather on reinforcing the neurocognitive strategies developed spontaneously by the individuals to compensate for age-related structural deteriorations.

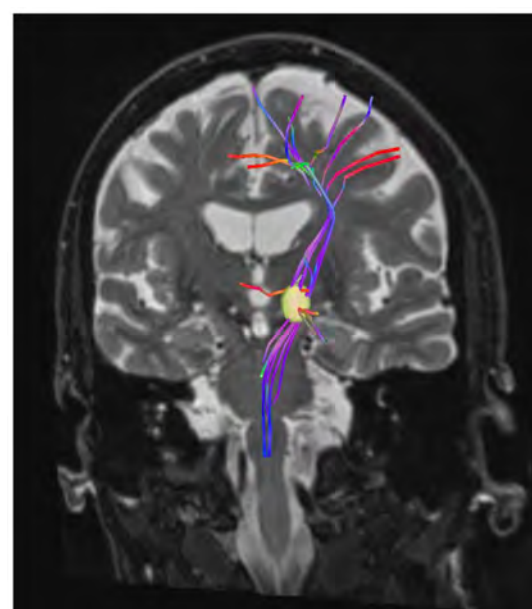


Figure 3. Estimation of volume of tissue activated by subthalamic nucleus deep-brain stimulation (DBS) in a Parkinson patient, and a reconstruction of the stimulated fibers bundles.

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.

Selected Publications

De Pretto M, Rochat L, Spierer L (2017).

Spatiotemporal brain dynamics supporting the immediate automatization of inhibitory control by implementation intentions.
Sci Rep doi: 10.1038/s41598-017-10832-x

Chavan C, Mouthon M, Simonet M, Hoogewoud HM, Draganski B, Van Der Zwaag W, Spierer L (2017).

Sustained enhancements in inhibitory control depend primarily on the reinforcement of fronto-basal anatomical connectivity.
Brain Structure Funct 222, 635-643.

Cancer, Microbiology and Immunology

Curzio Rüegg

Tumor-host interactions in cancer progression
and metastasis

Patrice Nordmann

Emerging Antibiotic Resistance in Bacteria

Csaba Szabo

Biological and pathophysiological roles
of labile, diffusible small molecules

Michael Walch

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

Luis Filgueira

Clinical Anatomy and Cell Biology

Curzio Rüegg

Tumor-host interactions in cancer progression and metastasis

INTRODUCTION

Tumorigenesis requires the accumulation of genetic and epigenetic modifications of the DNA, leading to uncontrolled cell proliferation, survival, loss of differentiation capabilities, modified metabolism and increased motility. The latter represents a first step toward local invasion, dissemination and metastasis formation. However, to form a clinically relevant tumor, cancer cells need a supportive microenvironment consisting of modified extracellular matrix and distinct cell types, including blood and lymphatic endothelial cells, carcinoma-associated fibroblasts, inflammatory, myeloid and lymphoid cells. Angiogenic vessels promote local tumor growth and tumor cells escape, while inflammatory cells, in particular monocytic and granulocytic myeloid cells provide many tumor promoting factors and facilitates metastasis formation. Metastasis formation involves a series of steps in which cancer cells leave the primary tumor through blood or lymphatic vessels, circulate in the blood and seed at distant sites. Distant organ colonization and outgrowth require matching signals from the tumor cells and the new microenvironment supporting cancer cells survival and growth. Vascular and inflammatory cells at distant sites provide essential cues to the formation for macroscopic metastases. Metastatic disease is for most cancers the eventual cause of death, and as of today there are essentially no curative therapies for metastatic cancer. The main research interest of our laboratory focuses on tumor-host interaction and the unravelling mechanisms of metastasis in breast cancer.



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Understanding mechanism of breast cancer metastasis

Breast cancer is the main cause of cancer-related mortality for women. The development of therapy-resistant metastases in vital organs, leading to organ disruption and failure, is the ultimate cause of death in relapsing patients. Early detection by mammography, surgery and adjuvant treatments, in particular anti-oestrogen (eg. tamoxifen) and anti-HER2 (e.g. Herceptin) based-treatments for ER⁺ and HER2⁺ cancers, respectively, have improved survival by about 30% of the past three decades. For TNBC there are still no specific therapies due to lack of defined targets, and radio- and chemotherapies are commonly used instead. Further significant improvement in the survival of relapsing breast cancer patients can only be achieved by improving early detection developing treatment controlling recurrent and metastatic disease. In our laboratory we are addressing several questions related to breast cancer metastasis:

- How do cells of the microenvironment, promote tumor growth and metastasis? How do therapeutic interventions modify the tumor microenvironment and how do these modifications impact tumor behavior?

- How does tumor angiogenesis modulate tumor dormancy, tumor growth and metastasis? How can we therapeutically exploit this tumor cell - endothelial cell interaction?

- How do tumor cells adapt and evade anticancer therapies? How do tumors and the microenvironment react to anticancer therapies?

Selected projects

1. Mechanisms of metastasis. We established the first model of spontaneous breast cancer metastasis to the brain based on the 4T1 cells and extensively validated with other murine and human cell lines and patient's data. We show that the colonization step of the brain is rate limiting and we identified a novel mechanism of brain metastasis including two candidate target molecules that may be used for treating patients with brain metastasis. All together we consider this an important study in the field of brain metastasis (G. Lorusso et al, in revision). We investigated the role of CYR61 in breast cancer metastasis. We could show that ▶

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▶ CYR61 promotes survival in a β 1 integrin- and AMPK α -dependent manner and favors cancer cell extravasation from the blood into the distant tissue (Fig. 1) (Huang *et al*, 2017, Oncotarget). We demonstrated that anti-VEGF therapy prevents breast cancer lung metastasis by enhancing the anti-tumor immune response. Anti-VEGF therapy induces Arg-1 in CD11b⁺ cells and its suppression improved tumor control (Secondini *et al.*, 2017, Oncoimmunology).

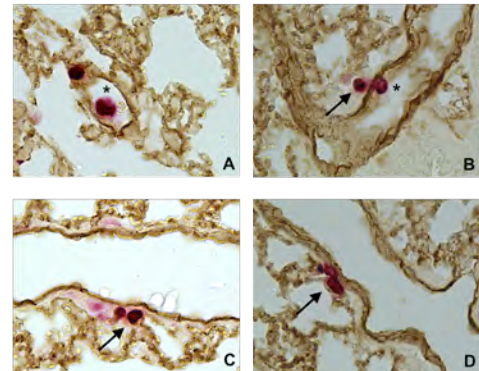
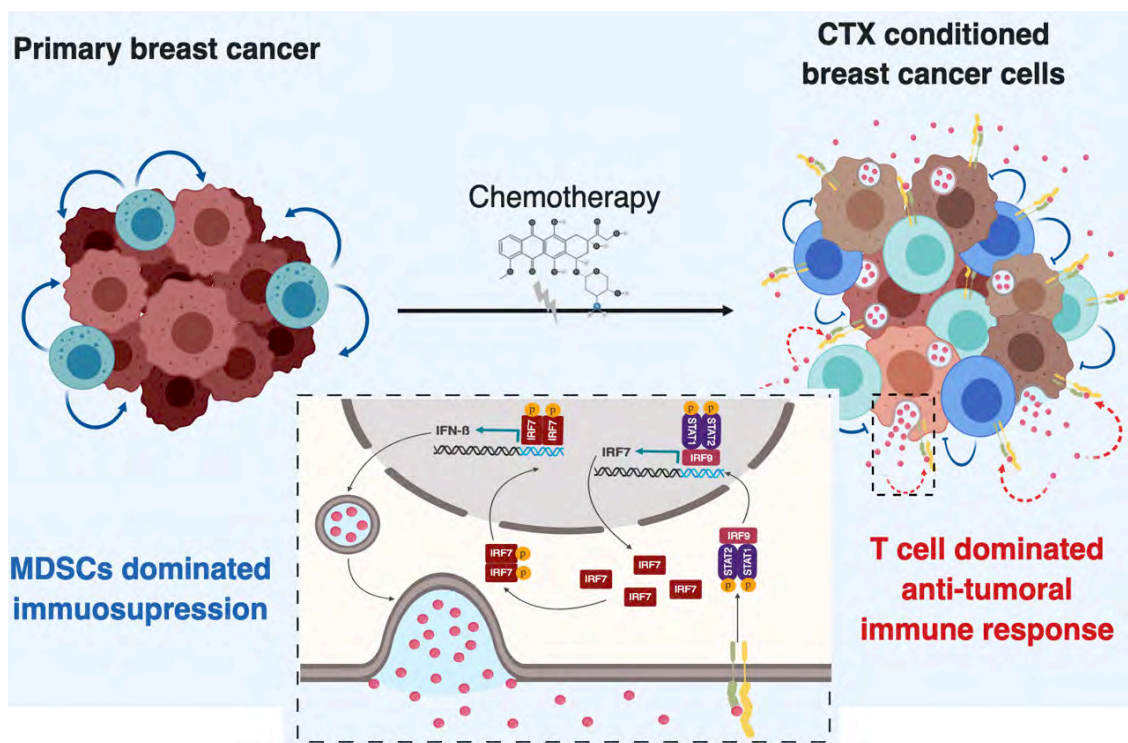


Figure 1. Silencing CYR61 reduces cancer cell extravasation to the lung. (A-B) Breast cancer cells with silenced CYR61 remained inside lung vessels 25 hours after iv injections (asterisks), while non silenced cancer cells (C-D) were mostly located outside of vessels (black arrows).

2. Effect of obesity on breast cancer metastasis. Using a mouse model of postmenopausal obesity, we demonstrated that obesity promotes breast cancer metastasis by inducing EMT and expansion of claudin low-TNBC-like metastasis-initiating cells. These data demonstrate that a pro-metastatic effect of obesity occurs in the primary tumor independently of the microenvironment of the secondary site (M. Bousquenaud, et al, Breast Cancer Res 2018).

3. Mechanisms of breast cancer dormancy. We have generated a new model of chemotherapy-induced breast cancer dormancy. The hallmark of this dormant phenotype is the sustained activation of the IRF7/IFN- β /IFNAR pathway in tumor cells that survived chemotherapy. IFN- β twists the MDSC dominated tumor-promoting immune response to into a CD4⁺/CD8⁺ T cell dominated anti-tumor response. Human data corroborated experimental data. This study may open new opportunities to improve activity of chemotherapy in combination with IFN type I (Lan *et al*, Oncogene, 2018).

Model of chemotherapy-induced immunological dormancy. Chemotherapy induces a type I IFN response in treated tumor cells, resulting in an autocrine and self-sustained increase of IRF7 expression and activation, which in turn induces expression and secretion of IFN- β . IFNARs signaling in tumor cells activates STAT1/STAT2/IRF9 complex which further induces the expression of IFN- β responsive genes. Paracrine activation of IFNARs on immune cells stimulates the expansion of tumor suppressive lymphocytes (e.g. CD4⁺ and CD8⁺ T cells) and prevents the mobilization of MDSCs, resulting in the switch from a immunosuppressive to a anti-tumoral immune response.



Model of chemotherapy-induced immunological dormancy.

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Selected Publications

Breasson L, Becattini B, Molinaro A, Zani F, Marone R, Botindari F, Bousquenaud M, **Ruegg C**, Wymann MP, Solinas G (2018).

PI3K Activity within Leukocytes Promotes Adipose Tissue Inflammation and Early-Onset Insulin Resistance During Obesity. *Science Signal.* doi: 10.1126/scisignal.aaf2969.

Bousquenaud M, Fico F, Solinas G, **Ruegg* C**, Santamaria-Martinez A* (2018).

Obesity promotes the expansion of metastasis-initiating cells. *Breast Cancer Res*, 2018,. doi: 10.1186/s13058-018-1029-4.

Lan Q, Peyvandi S, Huang YT, Duffey N, Barras D, Held W, Richard F, Delorenzi M, Sotiriou C, Desmedt C, Lorusso G, **Ruegg C** (2018).

Type I interferon response to chemotherapy elicits immunological dormancy in breast cancer. *Oncogene.* doi: 10.1038/s41388-018-0624-2.

Patrice Nordmann

Emerging Antibiotic Resistance in Bacteria

Introduction

The rise of antibiotic resistance in human and veterinary medicine is becoming one of the main health issue worldwide. It can predominately be explained by the spread of antibiotic resistance genes in clinically-significant organisms and spread of multidrug resistant clones. Those resistance genes may be transferred vertically or horizontally. Therefore, an early detection of their acquisition by clinically relevant micro-organismly identification of antibiotic resistance genes is becoming mandatory. This includes search for resistance genes resistance among human pathogens and bacterial species acting as the reservoirs of natural resistance genes as well as their identification in the environment, including in the food chain and in animals. Multidrug resistance (MDR) in Gram-negative bacteria is currently dominated by the emergence of extended-spectrum β -lactamase (ESBL) and carbapenemase producers, pan aminoglycoside resistance genes, and more recently, to the last resort antibiotics, polymyxins (colistin). The MDR gram-negatives that are clinically important for human medicine are Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* for which our research focuses. 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 preven its spread (iii) decrease antibiotic consumption, and (iv) development of novel antibiotic molecules.



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Research activity

The overall aim of our unit is to early identify emerging antibiotic resistance traits and their natural reservoir among the most clinically-relevant antibiotic-resistant pathogens that are now Gram-negative bacteria (Enterobacterales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*). Combined molecular biology, biochemistry and microbiology approaches altogether contribute to those identifications. We have focused on resistance to expanded-spectrum cephalosporins, to carbapenems, and to polymyxins. We have associated this fundamental approach to the development of tests for rapid identification of those resistance traits.

Extended-spectrum β -lactamases and carbapenemases; biochemical and genetic analyses, mobility and spread.

We have contributed to unravel several genetic mechanisms as the source of spread of emerging resistance carbapenemase genes in Gram-negatives and to identify and characterize novel carbapenemase genes of potential clinical impact. The mobility of the extended- spectrum β -lactamase (β L) genes *bla*_{BEL-1} and ▶

▶ *bla*_{PER-1} has also been studied. The mobility of the *bel-1* gene cassette located in a class 1 integron was detected in *E. coli* upon overproduction of the class 1 integrase gene (**Fig.1**).

The *bla*_{PER-1} gene is located in composite transposon Tn1213 in *Pseudomonas aeruginosa* made by two distinct insertion sequences, namely ISPa12 and ISPa13. In-vitro mobilization assays performed in *E. coli* showed that Tn1213 is functional and can mobilize the *bla*_{PER-1} gene. The efficient mobilization process we identified explains the spread of this resistance gene in hospital-acquired *P. aeruginosa*. Additionally, β L evolution and resistance to β L/ β L inhibitor combinations has been studied. We have demonstrated that β L GES-1 may evolve through few amino acid substitutions that can significantly modify its spectrum of activity. A significant increased hydrolytic activity against broad-spectrum cephalosporins, monobactams, and carbapenems may be observed, as well as resistance to β -lactamase inhibitors. Several ESBLs of the GES, PER- and BEL-types and conferring resistance to ceftolozane/tazobactam and to ceftazidime/avibactam (PER) in *E. coli* and *P. aeruginosa* have also been identified. Those findings are important since they indicated that specific ESBLs that are already widespread maybe the source of resistance to totally novel antibiotics. We have contributed to identify carbapenemase that are spreading in several countries such as in Angola and Sao Tome in Africa.

Resistance to polymyxins

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. In *K. pneumoniae*, point mutation changes in the chromosome-encoded *ccrB*, *pmrB* and *mrgB*, *phoB*, *phoPQ* genes involved in the LPS biosynthesis are important as a source of polymyxin resistance. Following the identification of a plasmid-mediated polymyxin resistance determinant (corresponding to the production of the phosphoethanolamine transferase MCR-1 in Asia, we have demonstrated that the *mcr-1* gene is part of a cassette promoting its own expression and was able to be mobilizable by an ISAp1-related transposition process. The reservoirs of many MCR-like determinants was identified as being *Moraxella* species indicating its animal reservoir. We have identified also novel MCR-like proteins, including MCR-3.1 for which we demonstrated its functionality.

Rapid Diagnostic tests

We have developed rapid techniques for identification of emerging antibiotic resistance based on biochemical and rapid culture techniques. We have also developed tests for rapid detection of polymyxin resistance in Enterobacterales, *P. aeruginosa*, and *A. baumannii* (Fig. 2) and for detection of pandrug resistance to aminoglycosides. Those tests are based on rapid cultures containing specific culture media and a defined concentration of the antibiotic to be tested..

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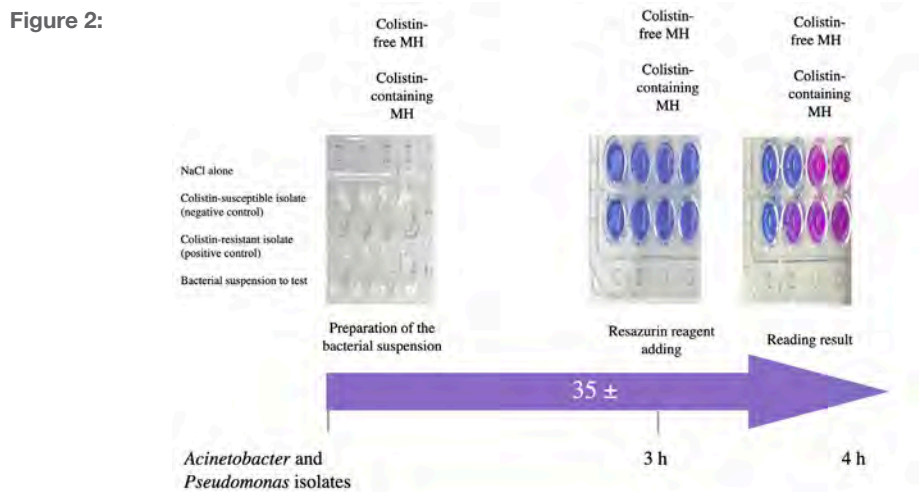
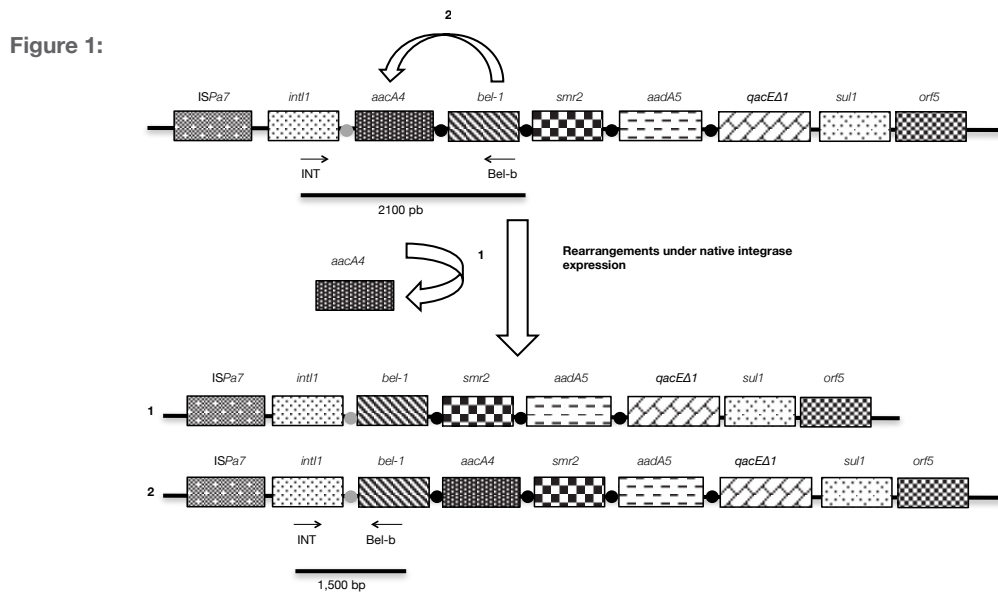
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They have excellent sensibility and specificity (92-100 %) that meet the criteria of clinical usage. We have also developed home-made molecular tests for diagnostic of plasmid-mediated polymyxin resistance determinants.



Selected Publications

Lescat M., Poirel L., Tinguely C., Nordmann P. (2018).

A resazurin reduction-based assay for rapid detection of polymyxin resistance in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *J Clin Microbiol.* doi: 10.1128/JCM.01563-18.

Mancini S., Poirel L., Kieffer N., Nordmann P. (2018).

Transposition of Tn1213 encoding the PER-1 extended-spectrum β -lactamase. *Antimicrob. Agents Chemother.* pii: e02453-17

Poirel L., Aires-de-Sousa M., Kudyba P., Nordmann P. (2018).

Screening and characterization of multidrug Gram negative bacteria from a remote African Area, Sao Tome and Principe. *Antimicrob Agents Chemother.* doi: 10.1128/AAC.01021-18.

Csaba Szabo

Biological and pathophysiological roles of labile, diffusible small molecules

INTRODUCTION

Csaba Szabo has joined the University of Fribourg in 2018. 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 (H₂S) 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 H₂S biology, where he studies the pathophysiology, pharmacology and experimental therapy of various diseases (vascular, metabolic, cancer) in the context of alterations in H₂S homeostasis.

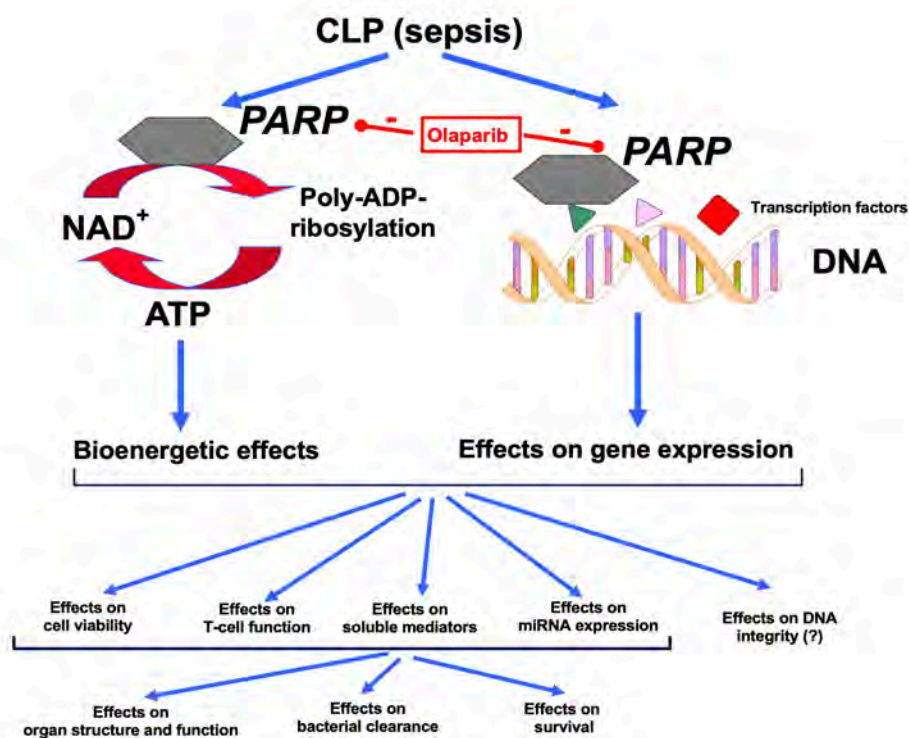


Fig. 1. Pathophysiological roles of the PARP pathway and opportunities for therapeutic repurposing. In various disease conditions (inflammation, reperfusion injury, sepsis, ARDS), the constitutive enzyme poly (ADP-ribose) polymerase (PARP) becomes pathologically overactivated. This triggers cellular 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.

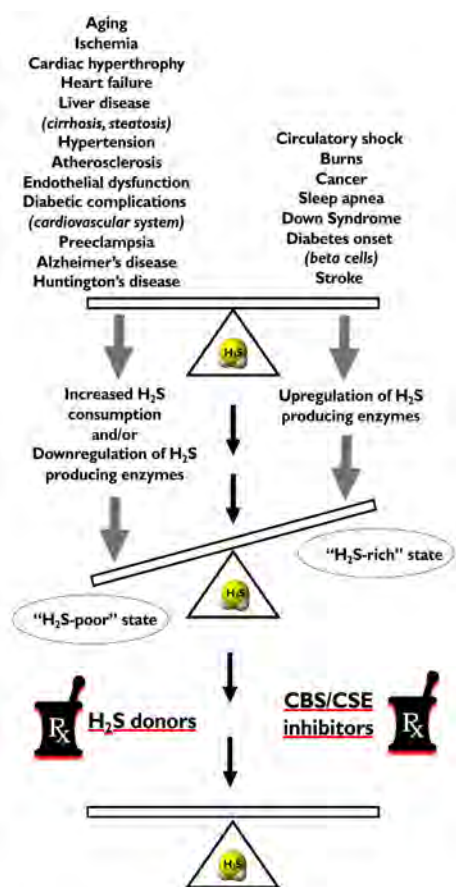


Fig. 3. H₂S-rich and H₂S-poor pathophysiological states.

In several diseases, hydrogen sulfide (H₂S) consumption is accelerated or its production is diminished. In such conditions, pharmacological increase in H₂S levels (with H₂S donor molecules) can exert beneficial effects. In other conditions, H₂S levels are increased to levels that exert adverse effects. In these conditions, pharmacological inhibitors of the three H₂S-producing enzymes CBS, CSE and 3-MPST can exert beneficial effects in preclinical models. Understanding the changes in H₂S homeostasis in various pathophysiological conditions is necessary; translation of these findings to experimental therapeutic agents is important.

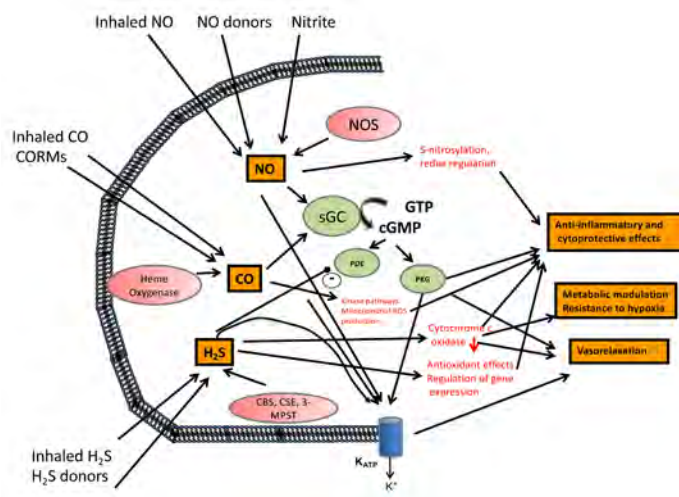


Fig. 2. Interactions of the three gasotransmitters NO, CO and H₂S. The three gasotransmitters nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H₂S) share many properties in terms of chemical and biological character, cell signaling pathways and biological roles. In some cases, there are additive or synergistic cooperative mechanisms at play. Defining these mechanisms unveils fundamental roles in biology, and malfunction of these processes can underlie many disease states in cardiovascular biology, immunology and oncology.

Selected Publications

Toliver-Kinsky T, Cui W, Törö G, Lee SJ, Shatalin K, Nudler E, Szabo C. (2018)

H₂S, a bacterial defense mechanism against the host immune response. Infect Immun 87. pii: e00272-18.

Szczesny B, Marcatti M, Ahmad A, Montalbano M, Brunyánszki A, Bibli SI, Papapetropoulos A, Szabo C. (2018).

Mitochondrial DNA damage and subsequent activation of Z-DNA binding protein 1 links oxidative stress to inflammation in epithelial cells. Sci Rep. 8:914.

Augsburger F, Szabo C. (2018).

Potential role of the 3-mercaptopyruvate sulfurtransferase (3-MST)-hydrogen sulfide (H₂S) pathway in cancer cells. Pharmacol Res. pii: S1043-6618(18)31594-9.

Michael Walch

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 (Walch et al. Cell, 2014; Dotiwala et al. Nature Medicine, 2016).

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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(left the institute at the end of 2017)

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(Doc mobility at Harvard University, 2018-2020)

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Matteo Zoia (2018-2019)

BMS BACHELOR STUDENTS

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Katharina Happ (until 2017)

Filippo Cattalani (until 2017)

TECHNICIANS

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Marianne Blanchard

Patricia Matthey, 50%

Brigitte Solari, 50%

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, 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 Safaa Bouheraoua, 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. In somewhat related work, we additionally found that nano-silver enabled human osteoclasts to kill intracellular, multi-drug resistant *Staphylococcus aureus*, potentially by attenuating the virulence of these problematic pathogens.

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

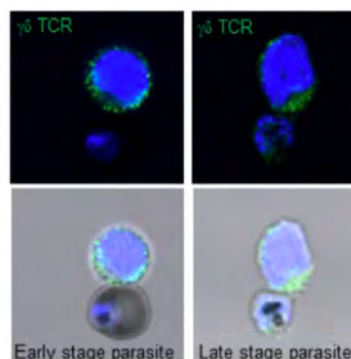
Plasmodium spp., the cause of malaria, have a complex life cycle. However, the exponential growth of the parasites in the blood is responsible for almost all the clinical symptoms of malaria and the associated morbidity and mortality. Therefore, to prevent malaria pathogenesis and progression toward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



γδ T cells form immune conjugates with early and late stage parasitized red blood cells to kill intracellular *Plasmodium falciparum*

Selected Publications

Aurore, V, Caldana, F, Blanchard, M, Kharoubi Hess, S, Lannes, N, Mantel, PY, Filgueira L?, Walch, M (2018).

Silver-nanoparticles increase bactericidal activity and radical oxygen responses against bacterial pathogens in human osteoclasts. *Nanomedicine*. 14:601-607.

Babatunde, K. A, Mbagwu, S, Hernández-Castañeda, MA, Adapa, SR, Walch, M, Filgueira, L, Falquet, L, Jiang, RHY, Ghiran I, Mantel PY (2018).

Malaria infected red blood cells release small regulatory RNAs through extracellular vesicles. *Sci Rep*, 8:884.

Lopez Leon, D, Fellay, I, Mantel PY, Walch M (2017).

Killing Bacteria with Cytotoxic Effector Proteins of Human Killer Immune Cells: Granzymes, Granulysin, and Perforin *Methods Mol Biol*. 1535:275-284.

Luis Filgueira

Clinical Anatomy and Cell Biology

Introduction

The areas of research interest of Luis Filgueira has been clinical anatomy, cell biology, immunology and educational research, addressing various topics. The following report shall focus on three 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 Dr K Grob (St Gallen and University of Western Australia). 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 N Lannes, in collaboration with Prof A Summerfield, University of Bern).

The third topic covers educational research, done in collaboration with members of the University of Western Australia, Dr E. Eppler (University of Zurich and University of Basel) and Dr K Link focussing on medical and biomedical curricula and especially on anatomy teaching.



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POST-DOCS

Alexey Larionov (50%)

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Smart Ikechukwu Mbagwu (ongoing)
Babatunde Adebayo Kehinde (ongoing)

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Christiane Marti

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ANATOMY LAB MANAGER

Franz Jungo

ANATOMY LAB TECHNICIAN

Marco Gagliano

VISITING PROFESSOR

Prof Aysun Uz, *Anatomy, Medical School, University of Ankara, Turkey (September – December 2018)*

Topic 1: New discoveries in gross anatomy

New approaches in medical imaging and surgical treatment of the skeletal system require verification and discovery of new concepts in clinical anatomy. Here, we report on the outcome of just two of several successful projects that has investigated the anatomy of the shoulder girdle from a clinical perspective, and which have been completed and published. (**Fig. 1**; A Larionov et al., SM Journal of Clinical Anatomy, 2018:2(3):1015; K Grob et al., Journal of shoulder and elbow surgery, 2018:27(4),635-640)

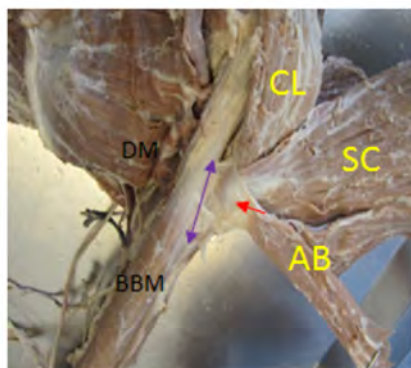


Figure 1: Exposure by dissection of the tendon of the pectoralis major muscle with its various layers (Larionov et al. 2018)

Topic 2: Infectious Immunology

For this report, we focus on Japanese encephalitis virus (JEV) (**Figure 2**). In that respect, it is important to realise that JEV is transmitted by mosquitos and infects and reproduces in monocytes, dendritic cells, microvascular endothelial cells, microglia, astrocytes and most importantly neurons. The focus of this project has been to further investigate the inflammatory response of JEV-infected microglia (N Lannes et al., Virol J 2017; N Lannes et al., J Neuroinfl 2017). Thereby, a new mechanism of cell-to-cell transmission of infectious viral genomic RNA has been discovered, which will be further clarified (N Lannes et al., Sci Rep. 2019)

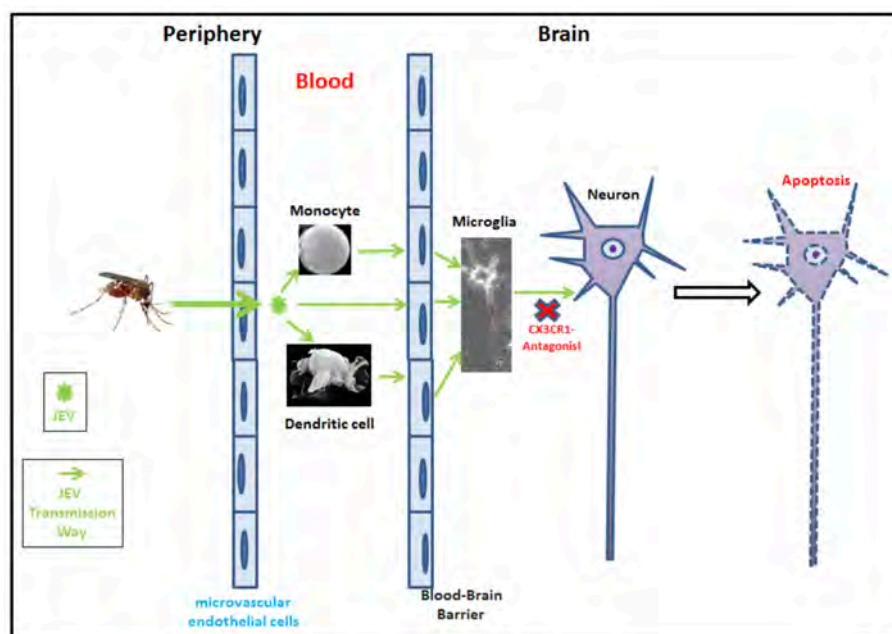


Figure 2: Proposed entry of Japanese encephalitis virus from the transmission by the mosquito to the blood circulation, through the blood-brain barrier into the. Of note is the fact that JEV infects blood monocytes, dendritic cells, as well as endothelial cells of the microcirculation, a prerequisite for transmission through the blood-brain barrier.

Topic 3: Educational research in medical and biomedical teaching

We have explored and evaluated new teaching approaches in tertiary anatomy and biomedical teaching, in collaboration with academic members of the University of Western Australia and the University of Basel (Dr E. Eppler). There have been various educational projects that have explored new teaching and learning methods and have been completed and submitted for publication (E Eppler et al., *Ant Sci Edu* 2018; E Eppler et al., *Res Sci Edu* 2018), including a project where feasibility, student satisfaction and enhanced anatomy learning through body painting, ultrasound and clinical investigation have been investigated.

Selected Publications

Eppler E, Serowy S, Link K, Filgueira L. (2018).

Experience from an optional dissection course in a clinically-orientated concept to complement system-based anatomy in a reformed curriculum. *Anat Sci Educ* 11:32-43. doi: 10.1002/ase.1707

Babatunde KA, Mbagwu S, Hernández-Castañeda MA, Adapa SR, Walch M, Filgueira L, Falquet L, Jiang RHY, Ghiran I, Mantel PY. (2018).

Malaria infected red blood cells release small regulatory RNAs through extracellular vesicles. *Sci Reports* doi: 10.1038/s41598-018-19149-9

Lannes N, Neuhaus V, Scolari B, Kharoubi-Hess S, Walch M, Summerfield A, Filgueira L. (2017).

Interactions of human microglia cells with Japanese encephalitis virus. *Virology J* doi: 10.1186/s12985-016-0675-3.

Public Health

Martina King

Medical Humanities

Gregor Hasler

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

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, conceived as a social and scientific system. It mainly includes philosophy, literary and cultural studies, history of medicine, medical sociology and medical anthropology, which altogether offer a complementary perspective on medicine. They look from the outside on clinical communication and interaction, on scientific expert roles and patient-doctor-relations; hence, these disciplines promote critical 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, to train 'better' doctors. So the whole endeavour has to be regarded primarily as a reform movement within academic teaching – and this implies strong normative claims. The idea of improving future doctors' capacities of self-reflection and ethical consciousness by implementing philosophical and literary courses in their curriculum has swept from USA to Europe and has left its traces in many curricula. Now if Medical Humanities are basically a teaching programme, how about research? This remains a difficult question which is much less clear than the pedagogic aim.

It is our conviction at the Chair of Medical Humanities in Fribourg that a strict distinction should be made between teaching and research – in order to avoid the contamination of one's research topics with normative claims and practical, operational purposes and to keep research as detached, objective, analytical and historical as good research practice within the humanities requires. Therefore, as scholars, we stick to our individual disciplines – which include literary studies, history of medicine and history of science – and to the theories, methodologies, sources and approaches that each of these disciplines offer. Using one's specific disciplinary skills and tools, we develop medicine-directed research questions that explore various aspects, both historical and systematic; from medical case reporting in late enlightenment to the history of physiology in the 19th century and conceptions of the sick child in mass media, from scientific travel writing to written clinical communication in our present. The central focus of all these research questions is how medical knowledge and medical practice are intimately linked to their textual and media representations. Being fundamentally hermeneutic, our research projects contribute to a richer, broader, more-encompassing picture of medicine as a clinical practice and scientific discipline; to a better understanding of its historical evolution, differentiation, communicative codes, actors and epistemological principles.



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Dr. Thomas Augais

Dr. Martina Diaz

DOCTORAL ASSISTANT

Bénédicte Prot

IT

Adriano Perlini

Topic 1: Doctors stories: on the history, structure and epistemology of medical narratives (Martina King).

The recent emphasis on patients' narratives and embodied experience within the so called 'Narrative Medicine' – a certainly justified and welcomed movement – has overshadowed the other side of clinical communication: doctors' narratives. Almost all clinical communication between medical experts implies some kind of storytelling, taken as a very basic, cognitive form of representation of particular events in time. The practice of describing and explaining courses of illness in written narrative form can be traced back to antiquity, and it gradually takes modern shape during the 18th and 19th centuries. Against this background, our research focusses firstly on the development of the case report since 1800 and secondly on some other expert genres that have obviously evolved from the case report such as surgical report and discharge letter. Using narrative theory, we try to understand how clinical experts tell, classify and explain individual courses of illness in these genres.

Topic 2: 'Raising a well-grown child' – on the media history of childhood health and childhood illness in the 19th century (Felix Rietmann)

During the 19th century, children moved into the focus of a blossoming material and media culture. A growing market of parent advice literature offered information on topics ranging from nutrition to moral education. An increasingly broad range of toys and educational devices, such as baby walkers and writing helps, sought to assist and discipline the child during learning. The nascent specialty of pediatrics was deeply embedded and participated in this culture. Medical practitioners wrote advice, developed medical tinctures, and patented devices for healthy growth and upbringing. The project investigates how these new material, media, and medical cultures of childhood produced ideas and discourses about health and illness, and normal and pathological development. It explores how childhood was discovered as a subject for health care in the public sphere and inquires into the cultural and medical meanings that have thus become attached to it.



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**'DOCTORS STORIES' REVISITED:
ON THE HISTORY, STRUCTURE
AND EPISTEMOLOGY OF
MEDICAL NARRATIVES**
Interdisciplinary Workshop

6.5 – 7.5.2019

Organisation:
Martina King, Lea Bühlmann
Location:
Pavillon Vert, Botanical Garden,
Chemin du Musée 10, CH-1700 Freiburg

FACULTY OF SCIENCE AND MEDICINE
DEPARTMENT OF MEDICAL HUMANITIES
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Topic 3: Internalised environments, externalised organisms: the concept of 'self-regulation' in medicine and life sciences in the 19th century (Lea Bühlmann)

This project explores the interwoven history of physiology, clinical medicine and life sciences in the 19th century by focusing on a central idea which links these disciplines: it is the relationship between living organisms and their environment. This idea can be pursued throughout various disciplinary attempts in the 19th century to conceive the nature of life: natural philosophers in medicine and biology around 1800 – such as Andreas Röschlaub and Jean-Baptiste Lamarck – deduce the relationship between organism and external factors, whereas the experimentalist Claude Bernard puts it on 'experimental feet': internalizing the environment as "milieu intérieure", as extracellular fluid space, Bernard lays the foundations of modern physiology. At the end of the century, exponents of neo-holism such as the environmental biologist Jakob von Üxküll reformulate the concept in the sense of self-regulation.

Selected Publications

King M. (2018)

Bild oder Erzählung? Explorative und dynamische Dimensionen von bakteriologischen Metaphern um 1900, in: Gunhild Berg, Martina King, Reto Rössler (Eds.): Special issue 'Metaphorologien der Exploration und Dynamik 1800/1900. Archiv für Begriffsgeschichte 59 : 157-181.

King M. (2017)

«Ich habe im Sommer des Jahres 1838 eine Reihe von Beobachtungen angestellt»: Naturwissenschaftliches Erzählen im frühen 19. Jahrhundert, in: DIEGESIS 6/1 (June 2017), p. 20-44. <https://www.diegesis.uni-wuppertal.de/index.php/diegesis/article/view/261>

Knebusch J, Wenger A, Augais T, Diaz M(Eds.):

La figure du poète-médecin, XXe-XXIe siècles, Chêne-Bourg, Georg éditeur 2018

Gregor Hasler

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

Introduction

Depression is a major health concern with increasing personal and societal relevance. Up to 20% of the general population have experienced a major depressive episode at least once in their lifetime. Currently available antidepressants have a very similar neurobiological effect, i.e., increasing monoamines in the synaptic cleft. Using these drugs, only 40-60% of patients with depression a symptom-free state (remission). As a result, novel therapeutic options with new therapeutic mechanisms are highly needed. The major research focus of the group is application and development such therapeutic strategies, including the use of ketamine, botulinum toxin A, repeated trans-magnetic current stimulation (rTMS), eHealth technology and specific combinations of pharmacotherapy and psychotherapy.

In order to develop personalized treatments in psychiatry that target specific disease processes, discovery of biomarkers (including digital biomarkers) is crucially important. The group is examining biomarkers for major psychiatric disorders, contributing to the fundament of personalized psychiatry, using molecular imaging (magnetic resonance spectroscopy, positron emission tomography), structural and functional MR imaging and momentary ecological assessments (EMA).



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PD Dr. Valerie Treyer, PET Center, University of Zurich (PET)

Prof. Dr. Simon Ametamey, ETH Zurich (PET tracer)

COLLABORATORS WHO LEFT THE TAB

Isabelle, Fischer

Dr. Stefanie Müller

The groups most visible and influential findings in the last five years relate to the central glutamate system, the target of ketamine, which has rapid and robust antidepressant effects even in patients not responding to classical antidepressant. In collaboration with the ETH Zurich the group determined binding to the metabotropic glutamate receptor 5 (mGluR5) in various psychiatric conditions including depression and schizophrenia. Preclinical research shows that this receptor is involved in reward processing, anxiety and addiction.

In particular, the group showed that mGluR5 binding is reduced in depression. This finding encouraged research in Switzerland and the United States to examine mGluR5 in terms of antidepressant treatments, including sleep deprivation and ketamine infusions. In obsessive-compulsive disorder, the group found increased mGluR5 binding related to anxiety traits.

This finding encouraged Novartis to design and conduct the clinical trial NCT01813019 «Study to Evaluate the Effect of AFQ056 in Obsessive Compulsive Disorder (OCD) Patients Resistant to Selective Serotonin Reuptake Inhibitor (SSRI) Therapy».

The most consistent finding on mGluR5 the group recently published relates to addiction. They demonstrated global marked reductions of mGluR5 in smoking. Even in individuals with schizophrenia, they found that smoking is the most important factor to understand reduced mGluR5 binding. This is an important insight because it strongly suggests to take smoking into account when investigating the glutamate system and psychiatric research and when conducting treatment trials using compounds that target the glutamatergic system. The group followed-up on these findings by demonstrating that nicotine consumption leads to reductions in mGluR5 binding in rats.

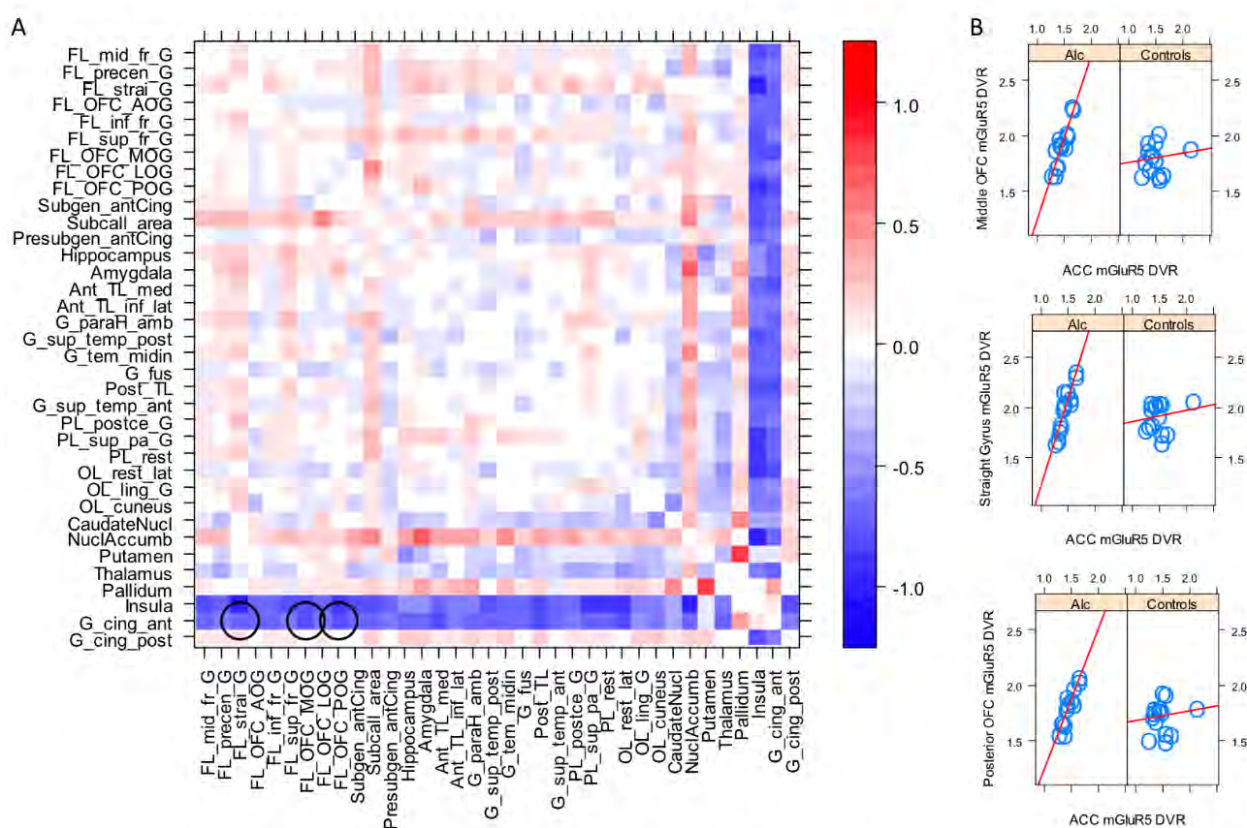


Fig. 2 Inter-regional mGluR5 DVR correlations across various brain structures differ between healthy controls and patients with alcohol use disorder. **a** For each inter-regional correlation the numeric difference between healthy controls and patients is shown, calculated as $r_{controls} - r_{patients}$. Color heat represents the direction and magnitude of this difference, as indicated in the color bar. Thus, red squares indicate higher correlation in controls than in patients, whereas blue indicates higher correlation in patients than in controls. Black circles highlight the most pronounced differences in ACC–OFC and ACC–straight gyrus mGluR5 DVR correlations between patients and controls ($p < 0.001$, one-tailed, uncorrected for multiple comparisons). **b** Shown are the highlighted correlations in each group separately. The red line represents a linear regression estimate

Regarding predictive biomarkers for currently available antidepressants, the group demonstrated that catecholamine depletion and serotonin depletion induce different types of depressive symptoms in individuals at high risk for depression and eating disorders. In addition, they showed that different brain circuits underlie depressive and bulimic symptoms related to catecholamine and serotonin deficiencies. These findings encourage studies on stratified treatments in depression, using currently available antidepressants.

Currently, the group is focusing on the development and testing of novel antidepressant treatments

- Study on the psychological and antidepressant effects of botulinum toxin A (“botox”) injections in the glabella, using psychological experiments in combination with EEG and momentary ecological assessments
- Discovering and testing of specific ways to combine ketamine’s antidepressant effect with psychological interventions
- Cohort study to evaluate GABA, glutamate and glutamine, as assessed using magnetic resonance spectroscopy (MRS), to predict the onset and course of mood and anxiety disorders
- Combined MRS / Positron Emission Tomography (mGluR5) study to assess glutamate pathologies in the early course of psychosis and bipolar disorder.
- Development of an unobtrusive ecological momentary assessment using smartphone sensor data to predict relapse in patients with severe psychiatric disorders

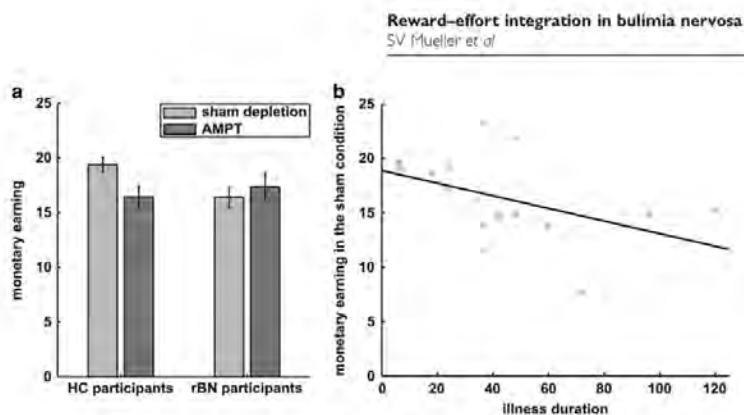


Figure 2 Monetary earning. (a) Mean (bars) and standard error (error bars) of the monetary earning in both participant groups (rBN and HC participants) and drug conditions (catecholamine and sham depletion). Catecholamine depletion was induced by the administration of AMPT. (b) Scatter plot of the amount of money earned in the sham condition and illness duration in rBN participants (Spearman’s rho rank correlation: $\rho = -0.51$, $p = 0.039$).

Selected Publications

Akkus F, Mihov Y, Treyer V, Ametamey S.M., Johayem A., Senn S., Rosner S., Buck A., Hasler G. (2018).

Metabotropic glutamate receptor 5 binding in male patients with alcohol use disorder. *Transl Psychiatry*. 8:17-26.

Mueller S.V., Morishima Y., Schwab S., Wiest R., Federspiel A., Hasler G. (2018).

Neural Correlates of Impaired Reward-Effort Integration in Remitted Bulimia Nervosa. *Neuropsychopharmacol.* 43:868-876.

Mueller S.V, Mihov Y, Federspiel A, Wiest R., Hasler G.. (2017)?

Neural response to catecholamine depletion in remitted bulimia nervosa: Relation to depression and relapse. *Eur Neuropsychopharmacol.* 27:633-646.

PUBLICATIONS

Group Jean-Marie Annoni

Neuhaus M., Bagutti S., Yaldizli Ö., Zwahlen D., Schaub S., Frey B., Fischer-Barnicol B., Burgunder J.M., Martory M.D., Pöttgen J., **Annoni J.M.**, Penner I.K. (2018).

Characterization of social cognition impairment in multiple sclerosis. (* cor auth.) Eur J Neurol. 25:90-96.

Jost L.B., Radman N., Buetler K.A., **Annoni J.M.** (2018).

Behavioral and electrophysiological signatures of word translation processes. Neuropsychologia 109:245-254.

Ruffieux J., Mouthon A., Keller M., Mouthon M., **Annoni J.M.**, Taube W. (2018).

Balance training reduces brain activity during motor simulation of a challenging balance task in older adults: an fMRI Study. Front Behav Neurosci. 12:10.

Neuhaus M., Calabrese P., **Annoni J.M.** (2018).

Decision-making in multiple sclerosis patients: a systematic review. Multiple Sclerosis Internat <https://doi.org/10.1155/2018/7835952>

Mouthon A., Ruffieux J., Mouthon M., Hoogewoud H.M., **Annoni J.M.**, Taube W. (2018).

Age-related differences in cortical and subcortical activities during observation and motor imagery of dynamic postural tasks: an fMRI Study. Neural Plast. doi: 10.1155/2018/1598178.

Preisig B.C., Eggenberger N., Cazzoli D., Nyfeler T., Gutbrod K., **Annoni J.M.**, Meichtry J.R., Nef T., Müri R.M. (2018).

Multimodal communication in Aphasia: perception and production of co-speech gestures during face-to-face conversation. Front Hum Neurosci. 12:200.

Radman N., Britz J., Buetler K., Weekes B.S., Spierer L., **Annoni J.M.** (2018)

Dorsolateral prefrontal transcranial direct current stimulation modulates language processing but does Not facilitate overt second language word production. Front. Neurosci. doi: 10.3389/fnins.2018.00490

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Group Lucas Spierer

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Group Csaba Szabo

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- Group Michael Walch**
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- Group Zhihong Yang**
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INVITED LECTURES AND SEMINARS GIVEN BY DEPARTMENT MEMBERS

Group Abdul Dulloo

29ème Journée de Nutrition Genevoise de Nutrition Clinique et Diétothérapie. Le jeûne et l'après jeûne: biochimie et physiologie. Genève, March 2017.

Is dieting contributing to the obesity epidemic? Euroscicon Life Science Events On-line The obesity epidemic: Discussing the global health crisis.
www.lifescienceevents.com/obesity-health
April 2017.

Symposium: Functional Body Composition, Obesity & Cardiometabolic Health: Beyond the Adipocentric View Collateral fattening: when a deficit in lean body mass drives overeating.
24th European Congress on Obesity (ECO), Porto (Portugal) May 2017.

Conference of the Autonomous University of Baja California (UABC). Does dieting and weight cycling make people fatter? And The search for thermogenic compounds for obesity management: from pharmaceuticals to nutraceuticals.
Tijuana (Mexico), 6-8 September 2017.

9th Fribourg Obesity Research Conference. Issues in targeting thermogenesis for weight maintenance and healthy catch-up growth
Fribourg, October 19, 2017.

4th Recent Advances & Controversies in Measurement of Energy Metabolism. Novel approaches in phenotyping human variability in thermogenesis.
Fribourg, October 21, 2017.

4th Recent Advances & Controversies in Measurement of Energy Metabolism, Satellite Symposium. The companionship of lean mass and fat mass revisited: towards novel concepts in body composition and cardiometabolic diseases.
Fribourg October 21, 2017.

Annual conference of l'association suisse des diététiciens-nes, Tissu adipeux: physiologie, qualité et actualités.
Neuchâtel, HE Arc, 6-7 March 2018.

11th International Symposium on In-Vivo Body Composition Studies, Role of body composition in the control of energy intake.
Columbia University, New York (USA), June 25-27, 2018.

Translational research. International Mini-symposium, The search of thrifty (energy conservation) phenotypes.
Fribourg, September 25, 2018.

International Symposium on Understanding the Double Burden of Malnutrition for Effective Interventions. Organized by the International Atomic Energy Agency (IAEA) in cooperation with the World Health Organization (WHO) and United Nations Children's Fund (UNICEF)? The companionship of lean

mass and fat mass revisited: towards novel concepts in human body composition autoregulation.
Vienna (Austria), December 10-13, 2018.

Group Marie-Noëlle Giraud

Federation of European Physiological Societies annual meeting (FEPS) Cardiac Bone Marrow derived cell-based therapy associated with scaffold for heart repair.
Vienna (Austria), Sept 13-15, 2017.

CABMM Spring seminar Biotissue based approaches for cardiac repair.
Zürich, May 31, 2018.

Group Gregor Hasler

World Federation of Societies of Biological Psychiatry (WFSBP). Catecholamines, anhedonia and depression.
June 11, 2017.

Remission in depression: what roles are played by positive emotions? World Psychiatry Association (WPA).
Berlin (Germany), October 10, 2017.

World Psychiatry Association (WPA), Hypomethylation of cg03636183 and cg05575921 in Smokers: an Imaging-Epigenetics Study. S. Müller.
Berlin (Germany), October 10, 2017.

Discovering biomarkers for bipolar disorders. Annual meeting of the International Society for Bipolar Disorders.
Washington DC (USA), May 5, 2017.

Annual meeting of the Swiss Society of Psychiatry and Psychotherapy. S. Suker. Safety of off-label use of ketamine in depression.
Bern, September 2017.

S. Müller. GABAGEN study: epigenetics of smoking. Winter Seminars on Biological Psychiatry.
Oberlech (Austria), March 21, 2017.

Neurotalk-2018, key note lecture and lecture on glutamate in affective disorders.
Bangkok (Thailand), May 16, 2018.

eFORUM. Opportunities and risks of digitalized social relationships.
Bern, March 27, 2018

Neuroeconomics and psychiatry.
Columbia University, New York, NY (USA), September 8, 2018.

World Federation of Societies of Biological Psychiatry (WFSBP). Metabotropic glutamate receptor 5 imaging in schizophrenia and depression.
June 6, 2018.

Meeting of the German-American Institute. On the stress epidemic.
Heidelberg (Germany), March 24, 2018.

Winter Seminars on Biological Psychiatry. Glutamine in the pathogenesis of depression.
Oberlech (Austria), March 19, 2018.

Masterclass Psychopharmacology. Ketamine as a novel treatment option in depression.
Roma (Italy), November 22, 2018.

Group David Hoogewijs

XXth International Conference on Oxygen Binding and Sensing Proteins. Genetic ablation of androglobin reveals multiple phenotypes.
Barcelona (Spain), September 2018.

BEAT-PCD COST Action BM1407 meeting. Genetic ablation of androglobin, the 5th mammalian globin, leads to multiple phenotypes.
Lisbon (Portugal), February 2018.

45th annual meeting of the International Society on Oxygen Transport to Tissue (ISOTT) Analysis of candidate transcription factors contributing to erythropoietin gene expression.
Halle (Germany), August 2017.

Departmental Seminar on Drug Sciences, Faculty of Pharmacy. The cellular oxygen sensing pathway: updates and its potential for targeting.
Basel, May 2017.

Medizinischen Klinik mit Schwerpunkt Nephrologie Seminar, Charité Universitätsmedizin, Distal hypoxia response elements mediate HIF regulated gene expression.
Berlin (Germany), January 2017.

Swiss society of Pharmacology and Toxicology. (A. Keppner). Androglobin: a newly identified globin required for male fertility in mice.
Bern, April 2017

NCCR Kidney.CH retreat (A. Keppner). Concerted action of the serine protease CAP2 and the glucocorticoid receptor on renal adaptation to potassium depletion.
Murten (Switzerland), January 2018.

8th meeting of the French-Swiss Renal Physiology (A. Keppner). Concerted action of the serine protease CAP2 and the glucocorticoid receptor on renal adaptation to potassium depletion.
Lausanne, March 2018.

Swiss PCD meeting (A. Keppner). Genetic ablation of androglobin reveals multiple phenotypes.
Bern, October 2018.

Group Martina King

International Conference „Aussteigen und Aussteiger – eine Vision der Jahrhundertwende“, Luftbad, Zelleninzenst und Absinthin: Esoterische Medizinkonzepte und ihre Bedeutung für die ästhetische Moderne.
Ascona (Switzerland) Augst 15-18, 2018.

International Conference «Textumgebungen. Kontextologie der Gegenwartsliteratur» Historische Narratologie: ein Weg zur Kontextualisierung von Textstrukturen.
Innsbruck (Austria) December 6-7, 2018.

Conférences de l'Institut des Humanités en

Médecine, Doctors' stories': how can narrative theory provide a better understanding of clinical communication?
Lausanne, December 17, 2018.

Interdisciplinary workshop »Tracking Contemporary Metabolisms – Historicizing Ecological Epistemologies Lea Bühlmann: Historicizing Homeostasis with Georges Canguilhem.
Erfurt (Germany), December 11-12, 2018.

Journée d'études La lettre et la machine: Soigner à distance, se soigner à domicile,: Robots, avatars et scanners relationnels: auto-soins dans la pédopsychiatrie du XXIe siècle? Felix Rietmann Faculté des Lettres.
Le Mans (France), September 4, 2018.

Conférences de l'Institut des Humanités en Médecine. From Bits, Pixels, and Meshes: Glimpses of a Digital Infant Psychiatry Felix Rietmann.
Lausanne, April 19, 2018.

History of Science Society Annual Meeting. Tape, Mother, Child: Video and the Rise of Infant Mental Health, Felix Rietmann.
Toronto (Canada), November 11, 2017.

Julien Knebusch: Poétique(s) de la chirurgie , avec Thomas Augais, Journée d'étude Le geste chirurgical : poétique, philosophie et cinéma, Fonds national suisse de la recherche scientifique (FNS), Académie de médecine (Paris), January 11, 2018.

Séminaire annuel de la Société suisse d'éthique biomédicale, Focus « Humanités médicales ». Julien Knebusch. Le style chirurgical entre éthique et esthétique.
Bigoirio, November 23-25, 2017.

Congrès international de la Société d'Étude de la Littérature et de Langue françaises du 20e et 21e siècles Emmanuel Venet, médecin et écrivain, Extension du domaine des lettres. Julien Knebusch.
Aix-en-Provence/Marseille (France), September 14-16, 2017.

Colloque international, Water History Conference .A notorious swimmer. Body, health and openness to the world in the works of Paul Morand. Julien Knebusch.
University of Michigan (USA), June 15, 2017.

Journée d'études "Formes d'écritures et savoirs". Connaissance scientifique et écriture littéraire dans le dialogue chirurgical entre Henri Mondor (1885-1962) et René Leriche (1879-1955). Julien Knebusch.
Paris, May 12, 2017.

Henri Cazalis /Jean Lahor : la construction d'une figure du poète-médecin, Colloque international La figure du poète-médecin. Julien Knebusch. Fribourg/FNS.
March 30-April 1, 2017.

Group Anna Lauber

Clinic, genetic and structural basis of CAH, « Endo-Ern: Rare Endocrine Diseases. Padova (Italy), September 22-23, 2018.

3rd DSDnet training School, Organogenesis of the gonads.
Budapest (Hungary) September 28 -30, 2018.

XIV ICPLM Meeting, Defects of Steroidogenesis.
Durban (South Africa), October 20- 22, 2018.

iDSD/DSDnet, Ja-PED Meeting.
Freiburg i.B. (Germany), November 17-19 , 2018.

Group Jean-Marie Montani

Symposium on Gravitational Physiology, Aging and Medicine, International Union of Physiological Sciences. Post-prandial orthostatic hypotension in the elderly: precipitating factors and countermeasures.
Rio de Janeiro (Brazil), August 5, 2017.

RACMEM 2017. The contribution of Swiss scientists to the assessment of energy metabolism.
Fribourg, October 20, 2017.

Group Patrice Nordmann

Patrice Nordmann

Congrès annuel de la Société Française de Réanimation de Langue française. Résistances : Quelles tendances épidémiologiques en 2017?
Paris , January 11-13, 2017.

Formation continue et post-graduée en médecine moderne, Médecin et Biologistes du canton de Neuchâtel. Résistance aux antibiotiques: état des lieux.
Hôpital de Pourtales, Neuchâtel, March 14, 2017.

Journée médicale d'infectiologie. Médecin de famille. Résistances aux antibiotiques en 2017: mythes ou réalité.
Carouge (Switzerland), March 30, 2017.

Coopération Asie-Pacifique bioMerieux, Indonesia & Singapore. Emerging Antibiotic Resistance, focus now on carbapenem and colistin resistance.
Singapore, April 3-7, 2017,

Festveranstaltung symposium workshop.Is the antibacterial drug pipeline really empty?
Frankfurt (Germany), April 10-11, 2017.

27th, European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Emerging Resistance in Gram negatives.
Vienna (Austria), April 22-25, 2017.

Turning the tide of antimicrobial resistance. Resistance to polymyxins: the fall of the last soldier and Rapid diagnostic of emerging antibiotic resistance.
Oslo (Norway), April, 27-28, 2017.

Formation médicale continue des médecins et personnel médical du canton de Fribourg, « Résistance émergentes aux antibiotiques », Fribourg, May 4, 2017.

Antibiotikaresistenz meeting. Résistance aux

antibiotiques dans le monde et en Suisse.
Soleure (Switzerland), May 2017.

Pfizer Shape Zavicefta Symposium. Global threat of Gram-negative antimicrobial resistance
Berlin (Germany), June 16, 2017.

Journées Nationales d'Infectiologie, Tour du monde des résistances.
Saint-Malo (France), June 21, 2017.

11th International symposium on the biology of Acinetobacter. Multidrug resistance in Acinetobacter baumannii.
Seville (Spain), September 20-22, 2017.

Drug resistance in Infectious Diseases Updates. Spread and evolution of broad spectrum β -lactamases.
Hambourg (Germany), September 28-30, 2017.

Colloque experts praticiens infectiologie. Les β -lactamases et les inhibiteurs.
Paris (France), November 9-10, 2017.

60ème Journée de l'hôpital Claude Bernard, Paris (France), November 16, 2017, « EPC: optimisme ou réalisme? ».
Paris (France), November 16, 2017.

Antibiotic stewardship and Antimicrobial Resistance, 11th International Congress of clinical microbiology. New diagnostic methods in Microbiology.
Shiraz (Iran), November 21-23, 2017.

Les avancées en pneumologie 2017 AztraZeneca. Antibiorésistance: la peste du XXIème siècle?
Paris (France), December 1-2, 2017.

37ème Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse: RICAI, Résistances aux antibiotiques : émergences et impact clinique, Bactéries à Gram négatif.
Paris, December 18-19, 2017.

ESCMID Post-Graduate Education Course .Carbapenemases in the world, Rapid diagnostics.
Fribourg, Sept 14-15, 2017.

Département des Laboratoires_ Formation continue/ Résistance émergente aux antibiotiques, peste du XXI siècle?
Lausanne, January 23, 2018.

DZIF-/GRID-Seminar Series. Emerging antibiotic Resistance in 2018.
Universität Giessen (Germany), January 25, 2018.

NRP Antimicrobial Resistance. Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram-negative bacteria.
Nottwil (Switzerland), April 18- 19, 2018.

28th European Congress of Clinical Microbiology and Infectious Diseases. Stability of cefiderocol against clinically-significant broad-spectrum oxacillinases.
Madrid (Spain), April 20-21, 2018.

Ateliers pluridisciplinaires de MSD en Infectiologie. Migration des bactéries : Quels enjeux dans nos institutions de soins ? Lyon (France), May 15, 2018.

19ème journées Nationales d'infectiologie. Gestion de l'antibiorésistance: bilan de la résistance à la colistine en France. Nantes (France), June 13-15, 2018.

17th ESCMID Summer School. Rapid diagnostic tests as useful tools for combating superbugs - recent developments. Paris, July 1-7, 2018.

Annual Congress 2018 of the Swiss Society for Microbiology (SSM), Multidrug resistance and carbapenemase producers in Gram negatives bacteria. Lausanne, August 28-30, 2018.

7ème journée de formation en microbiologie diagnostique. Résistance aux aminoglycosides, à la colistine, épidémiologie et mécanismes de résistance et détection. Lausanne, October 2, 2018.

Antibiotic Resistance Symposium. Emerging Antibiotic Resistance and their diagnostic. Karolina University, Stockholm (Sweden), September 17-18, 2018.

Antimicrobial Therapy in Immunocompromised and Critically Ill Patients: Management and Perspectives. New therapies against Gram bacteria. Lugano (Switzerland), October 4-5, 2018.

Genome Maintenance and Turning the Tide of Antimicrobial resistance (GMM5/TTA3), Emerging Resistances to Antibiotics in 2018. Oslo (Norway), October 9-12, 2018.

Symposium Antibiotic Resistance. Résistances émergentes aux antibiotiques en 2018: focus sur les Bêta-lactamases, leurs inhibiteurs et les alternatives aux carbapénèmes. Groupement Hospitalier du Territoire (GHT) Léman - Mont-Blanc, Contamine Sur Arve (France), October 16, 2018.

The 7th Congress of the European Academy of Paediatric Societies. Carbapenemase-producing enterobacteriaceae : Resistance mechanisms. Paris , October 30-November 3, 2018.

Symposium BAG sur la résistance aux antibiotiques 2018, La résistance aux antibiotiques, un défi mondial: faits et chiffres. Bern, November 16, 2018.

Formation pour médecins et personnel médical. Résistances émergentes aux antibiotiques. Villars-Sur-Glâne (Switzerland), November 27, 2018.
Journée du personnel de la direction générale de la santé (DGS). Epidémiologie et situation actuelle de la Résistance dans le monde. Genève (Switzerland), December 4, 2018.

38ème Réunion interdisciplinaire de chimiothérapie anti-infectieuse (RICAI).. Erreur dia-

gnostique en microbiologie, Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse. What else ? nouveaux aminosides et nouvelles tetracyclines, Résistance aux carbapénèmes. Paris (France), December 17-18, 2018

Laurent Poirel

8th International Congress of the Asia Pacific Society of Infection Control. The threatening problem of multidrug-resistant Gram negatives in healthcare settings ; new problems, new strategies. Bangkok (Thailand) Feb 2017.

Seminars in Microbiology, Medical Faculty. Genetics of acquisition of carbapenemases. University of Geneva, Geneva, Feb 2017.

7th Symposium on Antimicrobial Resistance in Animals and the Environment. Plasmid-mediated resistance to polymyxins; animals as reservoirs for humans ? Braunschweig, (Germany,) June 2017.

ASM Microbe meeting. Plasmid-mediated colistin resistance; the ultimate menace. New Orleans (USA); June 1-5, 2017.

16th European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Summer School/ Resistance to polymyxins: mechanisms, detection, recent emerging issues. Borstel (Germany); July 1-8, 2017.

ESCMID Post-Graduate Education Course, Acquired resistance to colistin in Gram negatives; an emerging issue and Carbapenemase-producing bacteria: genetic transmission. Fribourg, Sept 14-15, 2017.

Cluster Food & Nutrition. Conférence sur l'antibiorésistance en agroalimentaire. Combattre l'Antibiorésistance en rapprochant Médecine Humaine et Médecine Vétérinaire; le concept de la « One-Health Approach ». Zollikofen, Switzerland, June 2017.

Singapore International Infectious Disease Conference (SIIDC). Role of rapid diagnostics in prevention and control of multidrug-resistant bacteria; the tools are here. Singapore, August 2017.

2nd International Conference "Oxtenidine; prevention and control". The threatening problem of multidrug-resistant Gram negatives in healthcare settings: new problems, new solutions. Lisbon, (Portugal) Sept 30, 2017.

29th Congress of Brazilian Microbiology. Opportunities for joined research projects and Characterization of new beta-lactamases; step by step. Foz Do Iguaçu (Brazil) October 2017.

17th European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Summer School. How to publish in a good journal. Paris, France, July 1-7, 2018.

BEFRI Genomics Day..Prospective screening of acquired resistance to polymyxin antibiotics in Escherichia coli in the human popula-

tion; identification of resistance mechanisms by use of next-generation sequencing. Fribourg, June 22, 2018.

Group Eric Rouiller

Training Module in Animal Experimentation LTK20E. "Non-human primates as laboratory animals in biomedical research". Fribourg, February 21,, 2018.

Group Csaba Szabo

PARP2017 Meeting Opportunities for the therapeutic repurposing of clinically approved PARP inhibitors for non-oncological indications. Budapest (Hungary), May 19, 2017.

University of Exeter. H2S and mitochondrial function. Exeter (England), May 5, 2017.

Shock Society Annual Meeting. H2S and critical illness. Ft. Lauderdale (USA), May 6, 2017.

University of Kansas Medical Center. H2S and mitochondrial function. Kansas City (USA), June 23, 2017.

New York University Medical College. H2S and mitochondrial function. New York (USA), June 27, 2017.

World Mitochondria Society Annual Meeting. H2S and mitochondrial function. Berlin, (Germany), October 20, 2017..

Science Day. Paracrine signaling in epithelial cells: mitochondrial DNA release acts as a link between chronic low-level oxidative stress and local inflammation. University of Fribourg, March 21, 2018.

Goethe University. H2S in cancer: regulation of cell metabolism, cell proliferation and tumor angiogenesis», Frankfurt (Germany), June 13, 2018.

University of Bern. The vascular roles of H2S in health and disease. Bern, May 16, 2018.

15th Sepsis Forum. Gaseous transmitters: what are they? Sao Paulo (Brazil), May 31, 2018.

15th Sepsis Forum. Repurposing PARP inhibitors for treatment of critical illness. Sao Paulo, (Brazil), May 31, 2018.

15th Sepsis Forum. Can we protect the mitochondria in critical illness? Sao Paulo (Brazil) June 1, 2018.

5th World Congress on Hydrogen Sulfide in Biology & Medicine. H2S in cancer: what we know and what we don't know. Toronto (Canada), June 2, 2018.

Group Eric Rüegg

7th Conference on tumor host interaction.

Chemotherapy induced immunological dormancy. Monte Verita, Ascona, June 2017.

Biointerfaces International Conference BIC Translating research discoveries into products. Zürich, August 2018.

20th International Vascular Biology Meeting (IVBM2018). Helsinki (Finland), June 2018.

Group Michaël Walch

Michaël Walch

Private University of the Principality of Liechtenstein. Contribution to the lecture series Health and Life Science. October 2018.

Pierre-Yves Mantel

American Society of Tropical Medicine and Hygiene Annual meeting. Regulation of pathogen-host interactions by extracellular vesicles during malaria. New Orleans (USA), October 2018.

Karolinska Institute. Mechanisms of cellular communication during malaria. Stockholm (Sweden) December 2017.

Symposium in Neglected Tropical Diseases. Extracellular vesicles in the regulation of host-pathogen interactions during malaria. Swiss TPH, Basel 2017.

Group Zhihong Yang

Spring Meeting of the Swiss Society of Pharmacology and Toxicology Animal Models of Aging. Inselspital Bern, Bern, April 20, 2017.

THIRD PARTY FUNDING TO GROUP LEADERS

Group Jean-Marie Annoni

ZHAW institute Bilateral research collaboration with South Asia and Iran 2017 – 2020. versus close language-pair bilingualism: does language distance affect the effective connectivity between language and control systems?" 12 months. CHF 16.800.

SNF 25130_182594 Motor-language interaction in the first and late second language: experimental data and clinical implications. 2018- 2021. CHF 525'000.

Lithuanian-Swiss cooperation program to reduce economic and social disparities within the enlarged European Union under project agreement. 2016-2017. CHF 230'000.

Group Jean-Pierre Bresciani

J. Hasler Foundation. Ad Vitam: Adaptive Driver-Vehicle InTerAction to Make future driving safer. Co-investigator. 2018-2020. CHF 525'000.

Group Abdul Dulloo

SNF. Phenotyping for thrifty metabolic traits in young adults born small: a risk factor for obesity and cardiometabolic diseases. 2018-2020. CHF 457'495.

Group Marie-Noëlle Giraud

CTI grant. 3D-printed bioresorbable polymeric coronary scaffold (PriPoS). 2016-2019. CHF 426'750.

Co-host group SystemsX.ch - Transition Post-doc Fellowship Modelling Mechano-biology of the artery to drive the design of novel bioresorbable stents. 2015-2017. CHF 223'884.

Group Gregor Hasler

OPO Foundation. mGluR5 imaging in schizophrenia. 2017-2020. CHF 80'000.

Group David Hoogewijs

SNF. Functional analysis of androglobin, a novel oxygen-binding protein associated with male infertility. 2017-2021.

Human clinical cooperative project (HCP). National Centre of Competence in Research (NCCR) Kidney.CH. Novel Epo regulating factors. 2017-2019.

German Research Foundation (DFG). Functional analysis of androglobin, a novel oxygen-binding protein associated with male infertility. 2017-2020.

Group Martina King

DFG grant. Epistemologische Moderne. Zur Empirisierung von Natur und Kultur um 1830 (DFG/DACH 2019-2021). 2018-2021, 220.000 euros.

Group Anna Lauber

Research Pool University of Fribourg Generating human Sertoli cells from induced pluripotent stem cells as "Principal investigator" 2016-2017- CHF 20'000.

Group Jean-Pierre Montani

Swiss Heart Foundation. Acute cardiovascular and energy expenditure response to the ingestion of tea (Yerba Mate): comparing hot versus cold tea. 2017-2018. CHF 50'000.

Swiss Foundation for Alcohol Research .Cardiovascular interaction of acute alcohol consumption with soft drinks (alcopops). 2017-2018. CHF 66'870.

SNF. Cardiovascular effects of acute alcohol consumption: interaction with festive meals. 2015-2017. CHF 157'105.

SNF/NCCR-Kidney.CH, phase II. Kidney control of homeostasis. P.I. François Verrey, UniZH. JP Montani, project leader on: Dietary impact of amino acids. 2014-2018. CHF 600'000.

Group Patrice Nordmann

Ministry of Health, Bern (co-PI, P. Nordmann). Molecular biology and epidemiology of polymyxin resistance. 2018. CHF 150'0000.

ANAES (France) Rapid diagnostic immunology-based test for detection of polymyxin resistance. 2018-2020. 65,000 E

Ministry of Health; Bern National Reference Center for Emerging Antibiotic Resistance (NARA). 2017-2019. CHF 1'050 000.

South America -Swiss cooperation program. Antibiotic resistance in Colombia. CHF 25 000. 2017.

National Research Program (PNR72)/FNS). Swiss National Science Foundation (SNSF). Rapid diagnostic tests for detection of antibiotic resistance in clinically-significant Gram negative bacteria. 2018-2021. CHF 298,000.

Institut National de la Santé et de la Recherche Médicale (INSERM). Laboratoire Etranger associé. 2017-2020. 30 000 euros.

National Research Program (PNR72) (Principle investigator L. Poirel). Swiss National Science Foundation (SNSF) and JPI-AMR. Escherichia coli ST131 a model for high-risk transmission dynamics of antimicrobial resistance. 2017-2020. CHF 216,000.

National Research Program (PNR72) (Principle investigator L. Poirel). Swiss National Science Foundation (SNSF) and JPI-AMR. Dynamics of transmission of polymyxin resistance genes. 2018-2021. CHF 313,000.

Group Gregor Rainer

SNF-MOST bilateral initiative. Translational neuropeptidomics of major depressive disorder. 2015-2020. CHF 192'000.

Group Beat Schwaller

Novartis Foundation for medical-biological research. Parvalbumin deficiency – a common endpoint mouse model for Autism Spectrum Disorders. 2017-2018. CHF 59'500.

Group Lucas Spierer

SNF. State-dependency of Inhibitory control plasticity. 2018-2022. CHF 600'000.

Velux Stiftung. Online executive function training in elderly. 2017-2019. CHF 120'000.

Swiss Foundation for Alcohol research. Alcohol-induced disruption of task automatization: towards a new account for the emergence of impulse control failures during intoxication? 2018-2019. CHF 50'000.

Parkinson Suisse (Co-Applicant). Selecting the right target for deep brain stimulation in parkinson's disease. 2018-2019. CHF 50'000.

Group Csaba Szabo

SNF. Cardiovascular and metabolic roles of the 3-mercaptopyruvate sulfurtransferase/H2S pathway. 2018 – 2022. CHF 800'000.

Novartis Stiftung für Medizinisch-Biologische Forschung targeting the 3- mercaptopyruvate sulfurtransferase /hydrogen sulfide pathway in cancer cells. 2018 –2019. CHF 60'000.

Group Michaël Walch

SNF, PI M. Walch, Characterization of cytotoxic lymphocyte responses against blood-stage malaria. 2017-2020.

Olga Mayenfisch. Walch, PI, Immune proteases substrates as targets for antibacterial therapy. 2018-2019.

Gottfried und Julia Bangerter-Rhyner-Stiftung, P.-Y. Mantel, PI, Cellular communication on neutrophil function during malaria. 2017-2019.

Clas Groschinsky foundation, P.-Y. Mantel, PI, Exploring the potential of extracellular RNAs in the identification of malaria patients. 2017-2019.

Group Curzio Rüegg

SNF, Unravelling mechanisms of metastatic dormancy and colonization in breast cancer. 2018-2022. CHF 800'000.

Swiss Cancer League, Mechanisms and therapeutic targets of breast cancer metastatic colonization. 2018-2021. CHF 357'800.

NCCR – Bioinspired mat. Phase II, Trapping cancer cells with self-assembling biomolecules, 2018-2022. CHF 450'000.

Swiss Heart Foundation. C. Rüegg (Co- Applicant). Unraveling the role of MAGI1 in cardiovascular diseases.

2018-2020. CHF 90'000.

Group Zhihong Yang

Swiss Heart Foundation, PI Xiu-Fen Ming,
2018 –2019. CHF 67'000.

Marie-Curie IKPP2. Fellowship Zhilong Ren.
2017 –2018. CHF 83'230.

FURTHER ACHIEVEMENTS

Group Jean-Marie Annoni

Public outreach activities

23 July 2017: Interview of professor Annoni in the newspaper *Le Matin*, «Le bilinguisme augmente les réserves cognitives».

11 April 2017: Interview of professor Annoni in the newspaper *La Liberté*, «Une mémoire de moins en moins vive».

Group Abdul Dulloo

Public outreach activities

Le Matin: Gras « Plus qu'un stock d'énergie, le tissu adipeux est un organe » <https://www.lematin.ch/sante-environnement/sante/qu-stock-denergie-tissu-adipeux-organe/story/30816166>

Radio TV Suisse (RTS) <https://www.rts.ch/info/sciences-tech/10201553-la-graisse-brune-offre-un-nouvel-espoir-pour-la-perde-de-poids.html>

Group Marie-Noëlle Giraud

Member of the Center for Applied Biotechnology and Molecular Medicine (CABMM) Zurich
Member of the steering committee of the Swiss Translational And Clinical BioManufacturing (TCBM) Platform

Group Gregor Hasler

Member of the scientific advisory panel of the European College of Neuropharmacology and member of the Targeting Cognition Task Force of the International Society for Bipolar Disorders (ISBD)

President of the Swiss Society of Bipolar Disorders, president of the Swiss Society of Pharmacovigilance in Psychiatry, and Secretary of the Section on Pharmacopsychiatry of the World Psychiatric Association (WPA)

Public outreach activities

G. Hasler presented the group's work on Swiss TV, Swiss Radio, in several Swiss and German newspapers.

In 2018, there was a full page portrait on G. Hasler and his scientific work in *Tagesanzeiger*.

Group David Hoogewijs

External expert in Scientific Commission of United States-Israel Binational Science Foundation, January 2018.

Group Anna Lauber

Network 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>) and Study Sessions (e.g. IFCAH). Several collaborations with colleagues inland and abroad

Significant contribution in communicating ad-

vances in DSD research and understanding to the community

Most recent Horizons https://issuu.com/snsf/docs/hoizons_107-en-is-sue?e=1883535/31585077;

Tages Anzeiger 02.03.2016, page 58, <https://www.tagesanzeiger.ch/Anna-Lauber-Biason/story/31876338>.

Henning Andersen Prize (2018), European Society for Pediatric Endocrinology (with D. Rodriguez and W.Eid), 3000 Euro.

SGED/SSED Prize for best Poster (2018) to D. Rodriguez CHF 1'500.

Group Jean-Pierre Montani

Member of the Scientific Committee of the Marcel Benoist Swiss Science Prize, also known as the 'Swiss Nobel Prize' <https://marcel-benoist.ch/en/> (renewal by the Federal Council until end of 2020)

Ombudsman of the Faculty of Biology and Medicine, University of Lausanne, 2016-2018

Public outreach activities

Press Reports for the Yerba Mate Tea publication and Interview on the Swiss Radio (Emission CQFD, 2018-07-05, Le thé froid est bon pour le cœur... quand il n'est pas sucré.) <http://pages.rts.ch/la-1ere/programmes/cqfd/05-07-2018>

Group Patrice Nordmann

Creation of novel structures

2017: Laboratoire Etranger Associé (LEA), INSERM at the University of Fribourg. "Résistances Emergentes aux antibiotiques". National Institute for Health and Medical Research (Paris, France). This is the only INSERM research Unit (regardless the research field) that is located in Switzerland. It contributes to strengthen the research relationships between the Switzerland and France in the field of Medical Sciences.

2017: National Reference Centre for Emerging Antibiotic Resistance (NARA), Bundesamt für Gesundheit (BAG), Switzerland. This novel structure for Switzerland is aimed to analyze the emerging antibiotic resistance mechanisms that are occurring in Switzerland, and to contribute to the prevention of outbreaks caused by multidrug-resistant bacteria. Molecular and biochemical analyses of bacterial strains received from any medical labs from Switzerland are performed on a daily basis.

Awards

2017. Thomson Reuters ISI Awards 2017 to 1% most cited scientific papers worldwide (all scientific fields: 3,200 nominees worldwide, 72 for Switzerland, 98 for France). Ranking of P. Nordmann and L. Poirel in Pharmacology and P. Nordmann in addition in Microbiology/Immunology. Ranked both in Switzerland and in France.

2018. Clarivate (previously Thomson Reuters) ISI Awards 2018 to 1% most cited scientific papers worldwide (all scientific fields:

4,100 nominees worldwide, 111 for Switzerland; 137 for France). Ranking of P. Nordmann and L. Poirel in Pharmacology and P. Nordmann in addition in Microbiology/Immunology. Ranked both in Switzerland and in France.

Patents and Industrial development

- Dimercaptosuccinic acid as β -lactamase inhibitor. 2018. University of Fribourg. EP14306230.5. (Nordmann P, Poirel L, Girlich D).
- Methods, method and kits for detecting and kit, for detecting multiple aminoglycoside resistance including 16S rRNA methylase mediated resistance in Gram negative bacteria. 2017 University of Fribourg. PCT/EP2017/076277 (Nordmann P, Poirel L).
- Kit and Methods for the Rapid Detection of the Absence or Presence of a β -Lactamase in Samples of Body Fluids. 2017. University of Fribourg PCT/EP2016/074001 (Nordmann P, Poirel L, Kieffer K).
- Rapid detection of colistin resistance in enterobacteriales. patented on behalf of the University of Fribourg. (Nordmann P, Poirel L, Jayol A) European market by Feb 1, 2017 (ELITech Microbiology Ltd.).
- Selective culture medium for polymyxin-resistant Gram-negative bacteria, «SuperPolymyxin» patented on behalf of the University of Fribourg. (Nordmann P, Poirel L, Jayol A) European market by Feb 1, 2017 (ELITech Microbiology Ltd.).

Public outreach activities

18.02.2017: *La liberté*, presse écrite. Fribourg étudie l'antibiorésistance.

17.02.2017: *Radio Fribourg*, Résistances émergentes aux antibiotiques

20.02.2017: *RTS*, résistances émergentes aux antibiotiques

01.03.2017: *20 min*, presse écrite. Superbactéries: Comment lutter contre la résistance aux antibiotiques?

01.03.2017: *Dental Tribune*, Neueröffnung in Freiburg: Zentrum für Antibiotikaresistenzen

07.03.2017: *La Gruyère*, centre national sur sol Fribourgeois

09.03.2017: *Université de Fribourg* : Résistances aux antibiotiques: Mythes et réalité

22.03.2017: Alma & Georges, Les brevets, toute une culture

14.03.2017: *La Liberté* : «Résistance aux antibiotiques: état des lieux»

02.04.2017: *Lab Times* : Publication analysis 2007-2013, Microbiologie

09.2017: *LaborJournal* : Mikrobiologie Publikation Analyse 2011-2015. Pp 33-35

2017: *Ecoscope* : Prof. Patrice Nordmann: Les résistances aux antibiotiques gagnent du

terrain en Suisse et dans le monde entier

01.11.2017: *La news du mois* : Faut-il revoir la durée des traitements antibiotiques ?

30.10.2017: *Table ronde* : Antibiotique: Appel de la science et de l'industrie pour une meilleure utilisation de la capacité d'innovation de la Suisse dans la lutte contre l'antibiorésistance et dans le développement de nouveaux antibiotiques

11.11.2017: *La Liberté*, il faut prévenir les résistances

13.11.2017: Université de Fribourg, Prof. Patrice Nordmann: présentation «Résistantes émergentes aux antibiotiques, situations nationales et internationales»

14.11.2017: Ecoplan AG, Berne Star-M: NARA

2017: Clarivate Analytics 2017 Highly Cited Researchers : UNIFR doubles its number of highly cited researcher

04.06.2018: Rapport annuel 2017 de l'Université de Fribourg. Résistances émergentes aux antibiotiques

05.06.2018: Mme Bauer, *Swiss TV*, Interview Multidrug Resistance et NDM-1

04.07.2018: Mme Guardiola, *Valeurs Mutualistes*, revue de la Mgen, l'antibiorésistance : est-on en train d'inverser la tendance ?

September 2018: *Valeurs mutualistes no 313* : La lutte contre la résistance aux antibiotiques se poursuit

December 2018: *Essentiel Santé magazine*, Vrai/Faux : Antibiotiques

Winter 2018 : le *magazine de la Fondation pour la Recherche Médicale R&S N° 157*, Antibiorésistance : la lutte continue ou les antibiotiques : une ressource à protéger.

Group Gregor Rainer

President of the Swiss Society for Neuroscience, and board member of several Swiss societies that promote transparency and open communication in biomedical research.

Group Eric Rouiller

Creation of the Platform of Translational Neurosciences (2017-2020), common initiative of University of Fribourg (CH), EPFL and Wyss Center (Ge) to conduct research on non-human primates at the site of University of Fribourg, Section of Medicine, Dept. of Neurosciences (Director: Prof. Eric M. Rouiller).

Honorary Member of Swiss Neuroscience Society (SSN)

Pfizer Prize evaluation committee for Best publication (domain Neurosciences)

Public outreach activities

TV: *Le 19h30*, RTS (télévision Suisse romande TSR 1) 24.09.2018: *Grand format*, expérimentation animale, interview de Prof. E.M. Rouiller
Press: «Si je pouvais mener ces recherches sans les macaques, je le ferais, Prof. Eric M.

Rouiller» article de C. Zurcher, *Le Matin Dimanche* du 11 février 2018.

Group Beat Schwaller

SFARI Explorer Grant Award. 2019-2020. 80,000\$.

Group Csaba Szabo

Thomson Reuter 2018, one of 5 scientists cited from the University of Fribourg

Council of the the Swiss Pharmacological Society

Group Michaël Walch

Founding member and vice-president of the Liechtenstein Academia of Sciences (M. Waldh, September 2018

Patent: Diagnosis of infection by detecting RNA in sample. Patents EP17209859.2

Group Zhihong Yang

Vigener Prize 2018 in Life Science for her PhD thesis, Yi Yu. Faculty of Science and Medicine, University of Fribourg, Switzerland.

Young Investigator Prize (Poster), Yi Yu. at the LS2-Swiss Physiology Meeting 2018.

President of LS2-Swiss Physiology Section (2018).

Member of the NCCR-Kidney network, Switzerland

Public outreach activities:

Uni-Press: New discovery of an age-related diabetes mechanism 2017.

<http://www.unifr.ch/news/en/17377/new-discovery-of-an-age-related-diabetes-mechanism?&p=1> and

Freiburger Nachrichten: <http://www.freiburger-nachrichten.ch/kanton/bahn-brechende-erkenntnisse-zur-altersdiabetes>

MEETINGS ORGANIZED BY DEPARTMENT MEMBERS

Group Jean-Marie Annoni

Research day, University and Hospital of Fribourg: 2017, 2018

Co-Organisation: Intensive Seminar Series on Interdisciplinary in Translation & Interpreting, Shanghai November, 2017.

Group Abdul Dulloo

4th International Conference on Recent Advances and Controversies in Measuring Energy Metabolism¹ (RACMEM-2017).

Fribourg, Oct 20-22, 2017.

<https://www.nature.com/articles/s41430-018-0137-7>

9th Fribourg Obesity Research Conference, FORC-2017, 2017 on theme: Targeting Lifestyle Energy Expenditure in Management of Obesity & Cardiometabolic risks: From Biology to Built environment;

Fribourg, October 19, 2017.

<https://onlinelibrary.wiley.com/toc/1467789x/2018/19/S1>

Group Luis Filgueira

80th Annual Conference of the Swiss Society of Anatomy, Histology and Embryology.

Fribourg, September 7, 2018.

Group Marie-Noëlle Giraud

LS2 cardiovascular section annual conference. Fribourg March 15-16, 2018.

Group Gregor Hasler

Annual Meeting, Swiss Society for Pharmacovigilance in Psychiatry (co-organizer).

Bern, October 25, 2018.

Psyche & Brain, national meeting on neuroscience in psychiatry and psychotherapy.

Bern, June 21, 2018.

Group Martina King

International conference La figure du poète-médecin, XXe-XXIe siècles. Organizers: Alexandre Wenger, Julien Knebusch, Martine Diaz, Thomas Augais.

Fribourg, March 30 – April 1, 2017.

Group Marco Merlo

La psycho-oncologie: origine, développement, méthodes. Co-organizer. Hôpital Riviera-Chablais (Switzerland), November 16, 2017.

Assessment of psychopathological symptoms: what is wrong and how much is it wrong? Co-organizer. March 8, 2018.

Group Jean-Pierre Montani

9th Fribourg Obesity Research Conference (FORC 2017), Targeting Lifestyle Energy Expenditure in Management of Obesity & Cardiometabolic Risks: from Biology to Built environment. Co-organizer. Fribourg, October 19, 2017.

Recent Advances & Controversies in the Measurement of Energy Metabolism (RACMEM 2017). Co-organizer.

Fribourg, October 20-22, 2017.

Group Patrice Nordmann

Rapid diagnostics of emerging antibiotic resistances: problems and solution. European Society for Clinical Microbiology and Infectious Diseases (ESCMID) Postgraduate technical workshop. Co-organizers: P. Nordmann and L. Poirel.

Fribourg, September 14-15, 2017.

37^{ème} Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI). P. Nordmann Co-organizer.

Paris, December 2017.

38^{ème} Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI). P. Nordmann Co-organizer.

Paris, December 2018.

17th European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Summer School. L. Poirel. Co-organizer.

Paris, July 1-7, 2018.

Group Eric Rouiller

Scientific Meeting, Inauguration of the platform of Neurosciences.

University of Fribourg, Fribourg. June 14th, 2018.

Group Eric Rüegg

7th International conference on tumor-host interaction and Angiogenesis. Co-organizer.

Monte Verità, Ascona (Switzerland), June 25-28, 2017.

Group Zhihong Yang

LS2 Annual Meeting-Symposium (co-organizer). Zürich, February 2, 2017.

Cardiovascular & Metabolic Reserch Meeting 2017. Co-organizer.

Fribourg, January 19, 2017

LS2-Swiss Physiological Annual Meeting. Bern, September 5, 2017.

LS2-Swiss Physiological Annual Meeting. Fribourg, September 4, 2018.

DISSERTATIONS

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PHD THESIS

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MASTER BIOMEDICAL ENGINEERING THESIS

Raphael
Wenger

Group Hasler

PHD THESIS

Reward and Relapse: Resolving the
Riddles of Bulimia Nervosa.

PHD THESES

Reward and Relapse: Resolving the
Riddles of Bulimia Nervosa.

MASTER MED THESIS

Default mode network connectivity
and trait rumination in adults with
major depressive disorder, remitted
MDD patients and healthy individuals

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Group Martina King

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LOCATION



FRIBOURG

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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

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Pédagogie médicale
Pédiatrie

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