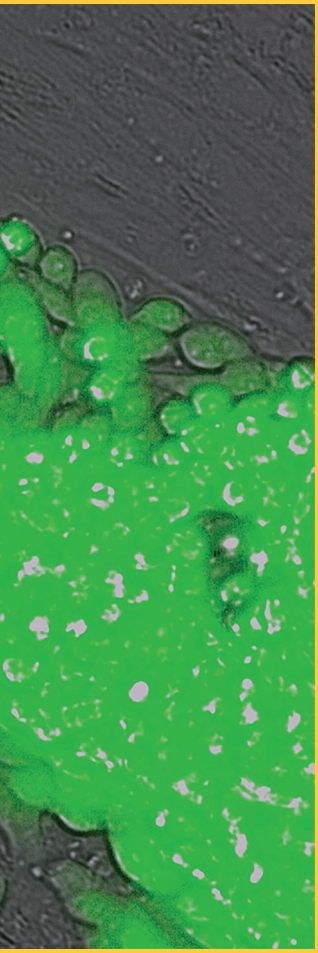
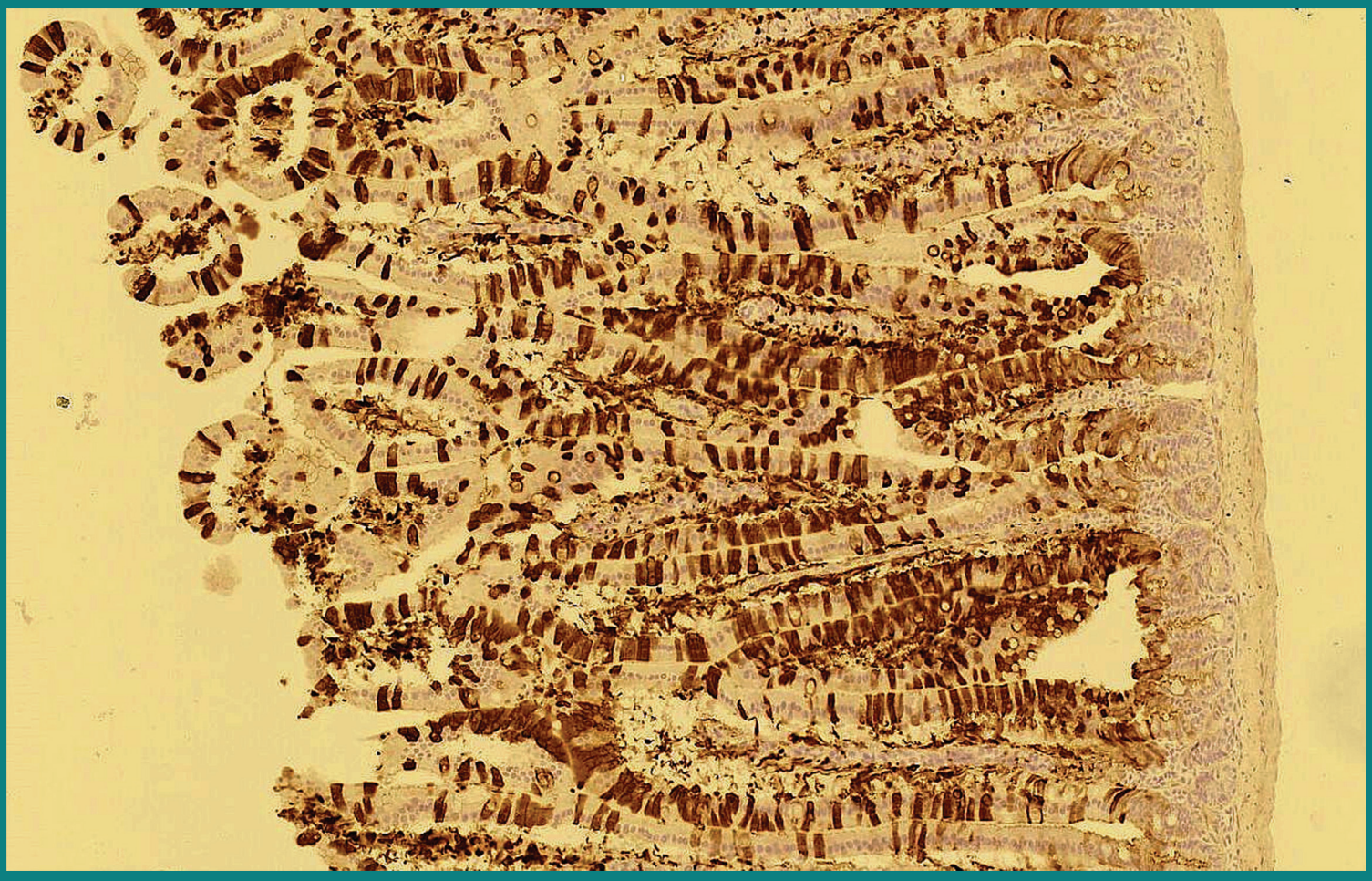


Scientific Report 2013/2014

DEPARTMENT OF MEDICINE

Faculty of Science
University of Fribourg
Switzerland



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Contents

This is the second edition of the biannual scientific report published by the **Department of Medicine,** covering the years *2013* and *2014*

The Department of Medicine is one of the seven departments forming the Science Faculty of the University of Fribourg (Biology, Chemistry, Earth Sciences, Informatics, Mathematics, **Medicine** and Physics), which also includes the Adolf Merkle Institute focused on soft nanomaterials. Capitalizing on a long tradition of teaching to medical students (though limited to the two first years), the Department of Medicine successfully introduced a third year of medical studies in 2009, corresponding to a full **Bachelor in Medicine** (BMed) at the University of Fribourg. In parallel, the Department of Medicine introduced two new teaching curricula, one in **Biomedical Sciences** (Bachelor level in 2006) and one in **Sport and Movement Sciences** (Bachelor level in 2007 and Master level in 2010). These new teaching developments were associated to the recruitment of 10 new professors, all active in research, thus strongly reinforcing the scientific pillar of the department, including the introduction of clinical research as well, in particular through the collaboration with the Fribourg Hospital Network.

The Rectorate of the University of Fribourg decided in 2013 to abandon teaching of Pharmacy (two first years were offered), to which the Department of Medicine contributed significantly in the past (without loss however of any professorship position). The drop of Pharmacy is compensated by the introduction of a new ***«Specialized Master in Experimental Biomedical Research (EBR)»*** which will be initiated in autumn 2015. The goal of this new EBR Specialized Master, with a limited number of students (up to 20), is to offer a solid and attractive training in the field of Experimental Biomedical Research, with emphasis on the three domains of scientific excellence at the Department of Medicine: 1) Neurosciences; 2) Cardiovascular, Metabolism and Endocrinology; 3) Cancer, Immunology and Microbiology. These domains actually correspond to the three clusters of research, on which the future structure of the Department of Medicine will be based, replacing the former structure based on teaching domains. The new research based structure of the Department of Medicine, as well as the introduction of this new Specialized EBR Master, reflect the strong inclination of the Department to strengthen its research activities to better face national and international competition in term of research output, external funding, visibility and attractivity for new faculty and students. Our long lasting tradition of excellence in teaching will be preserved and will directly benefit from these changes. The Department of Medicine comprises about half of the students (about 700 students) registered at the Faculty of Science.

Teaching and Research activities are conducted at the Department of Medicine by the groups of 20 Professors (one Professorship position vacant at the present time), capitalizing on the competences and motivation of scientific collaborators, didactic adjuncts, administrative and technical personal. The present scientific report is the opportunity to thank all collaborators for their outstanding engagement in order to reach the goals of the Department of Medicine, as defined in a recently elaborated «**strategic planning** (2015-2025)» available at: www.unifr.ch/med. In line with this strategic planning the Department of Medicine is member, the recently established **National Competence Center for Research (NCCR)** focused

on **bioinspired nanomaterials** (http://bioinspired-materials.ch/). Two professors of our Department, Prof. C. Bourquin and Prof. C. Rüegg (the latter also serving as deputy director of the NCCR) participate in this program. This is the first NCCR hosted by the University of Fribourg and thus represents a major achievement in order to boost science on our campus. In addition, the Department of Medicine will pursue its extension with access in autumn 2016 to a new building, which will host four research teams of our department (Profs. Bourquin, Rüegg, Nordmann and Wenger), a research team in Bioinformatics (Prof. Wegmann, Department of Biology), and the collaborators of the didactic unit and secretariat (GPS). On the technological point of view, the Department of Medicine collaborated closely in the field of **Life Sciences** with the Department of Biology to create technical platform in Microscopy (www3.unifr.ch/bioimage/) and in BioInformatics. Moreover, in the same field of Life Sciences, the Department of Medicine participated to the creation of a centralized technical facility in the form of a Faculty animal housing infrastructure (zebra fish, rodents, tupaia and macaque monkeys).

Also in line with the strategic planning of the Department of Medicine, in collaboration with the Fribourg Hospital Network, the Department of Medicine has been engaged in a working group with the mission to study the feasibility to introduce at the University of Fribourg a new **Master in Human Medicine** (MMed), which would thus offer the possibility to our medical students to follow the entire medical curriculum in Fribourg. A political decision on this MMed project is expected in 2015 or 2016. In case of acceptation by the Canton, the MMed project would represent a major challenge for our Department of Medicine and the Fribourg Hospital Network, again with the recruitment of several professors covering various clinical domains. Based on the successful implementation of the BMed in 2009, we are confident that the MMed project can be successfully achieved, in line with the effort expected at national level to train more medical doctors. On the long term the MMed would be highly beneficial to the Canton as it will improve the visibility of the University, strengthen the Fribourg Hospital Network and the health system of the Canton.

In summary, the Department of Medicine is determined at continuing its restructuration and development, both in the research and teaching domains, convinced that they are both complementary and feed each other. New and ambitious projects are ongoing or will be part of the near future, in which the strong engagement of all collaborators of the Department of Medicine will be needed, in a collegial and friendly atmosphere necessary to guarantee the success. All this is needed to face national and international competition in attracting excellent new faculty, students, scientific collaborators and external funding and maintain excellence in research and teaching in an ever changing academic landscape.

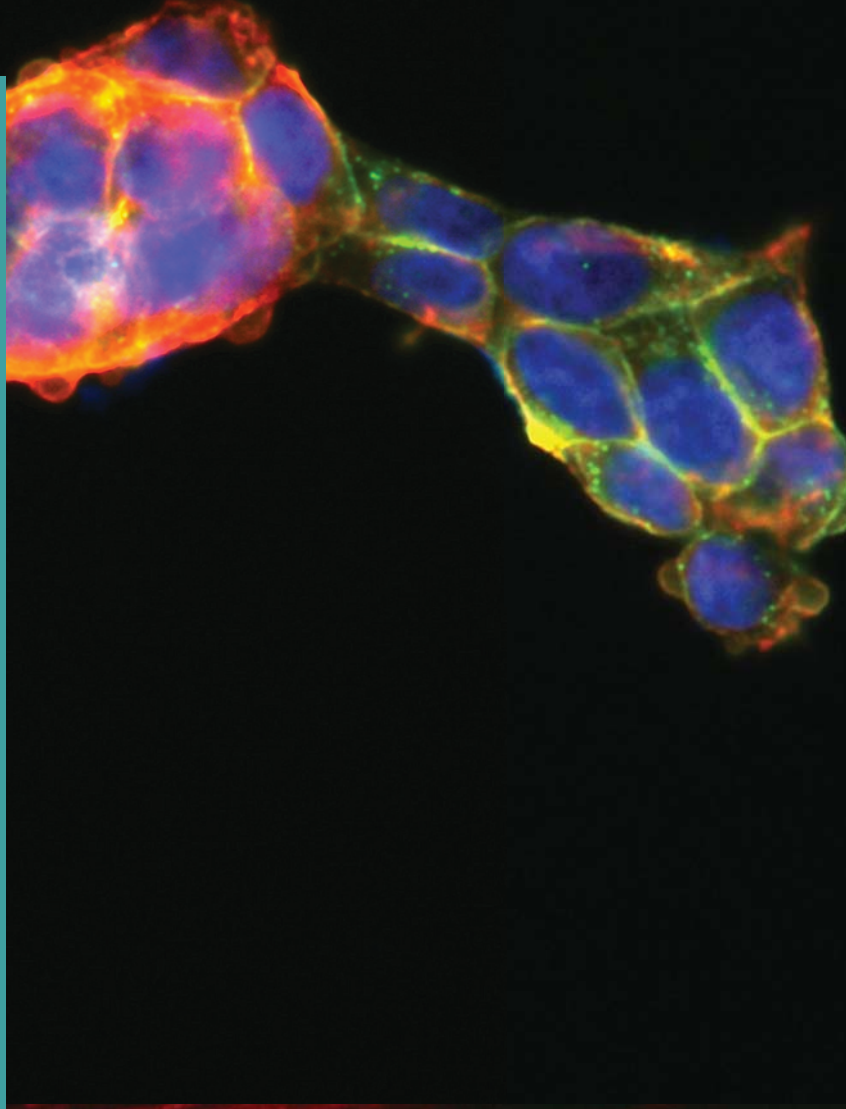
Warm thanks are deserved by all collaborators for their past contribution and their future motivation and engagement to pursue an exciting period of development.

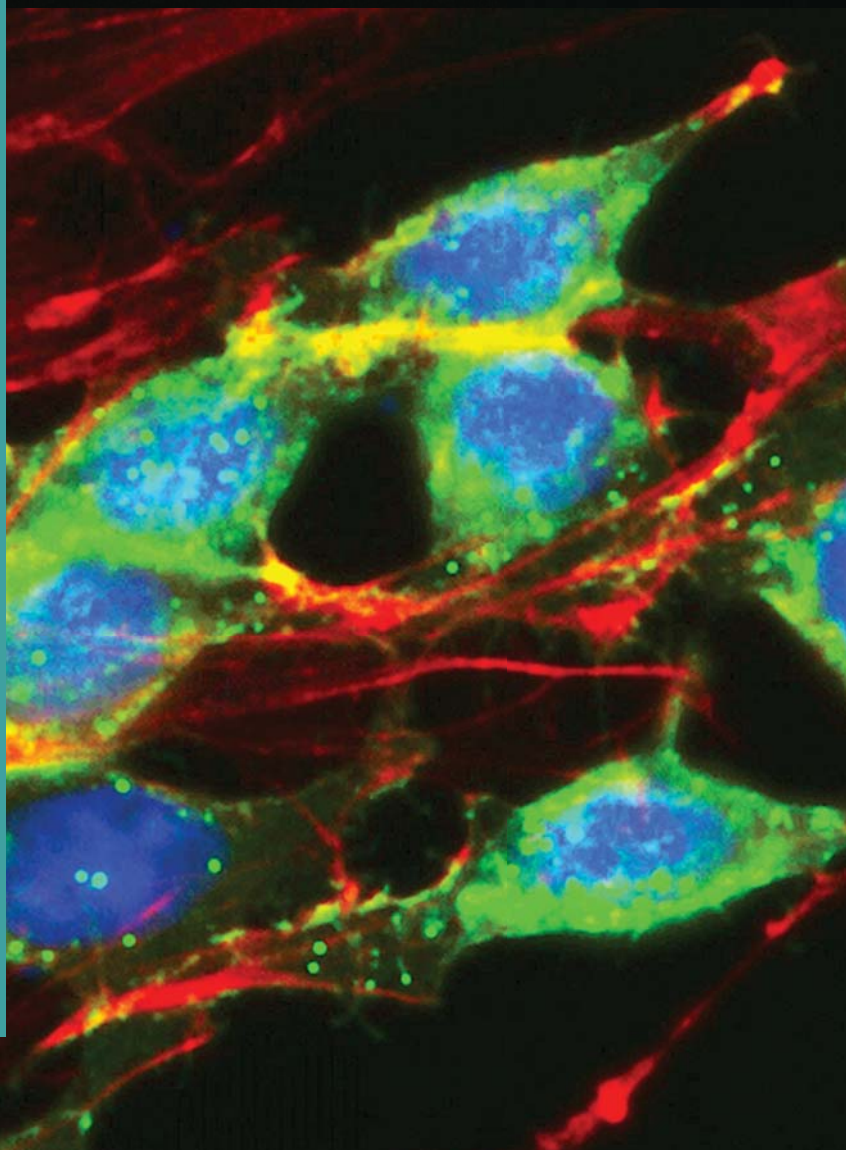
Professor Eric Rouiller
Department President

http://www.unifr.ch/med/

Infection, Immunology and Cancer

Infection, Immunology and Cancer are linked on many levels: pathological processes that were previously thought to be cell-autonomous, such as transformation of cancer cells, rely on the help of reprogrammed immune cells. In addition, infections are now known to be a contributing factor in inflammatory diseases and cancer. The research groups affiliated with the «Infection, Immunology and Cancer» cluster accommodate these commonalities by performing research in the fields of antibiotic resistance, viral infections, immunology, cancer biology as well as interactions of immune cells with tumors and infectious pathogens. These topics address global health concerns in both developed and developing countries. The study of the mechanisms and etiology of these linked pathologies is therefore essential to develop innovative diagnostic and therapeutic strategies for established and emerging threats to patients worldwide.





Carole Bourquin
Immunopharmacology of cancer

Luis Filgueira
Cell biology, immunology and clinical anatomy

Patrice Nordmann
Molecular and medical microbiology
Molecular and medical microbiology

Curzio Rüegg
Experimental and translational oncology

Carole Bourquin
Chair of Pharmacology

Immunopharmacology of cancer

INTRODUCTION

Cancer immunotherapy has reached a breakthrough in 2013 with the advent of drugs based on immune checkpoint blockade. However, even the most effective treatment options in immunotherapy result in an objective clinical response in only a minority of patients. One reason may be that many tumors lack the ability to recruit cytotoxic T cells, which can render them resistant to current immunotherapies. Strategies that reinforce the migration of T cells into tumors are therefore urgently needed to complement existing treatments. Our laboratory focuses on the development of pharmacological approaches to enhance antitumor immune responses, in particular by enhancing T-cell recruitment to tumors and by developing new strategies for drug delivery.

One approach for inducing antitumor immunity is to mimic the immune activation resulting from infectious agents by using synthetic ligands. Two receptor families of the innate immune system play a key role in the detection of microbial agents: the membrane-bound Toll-like receptors (TLRs) and the cytoplasmic RIG-I-like receptors (RLRs). The controlled pharmacological activation of these receptors to induce anticancer immune responses represents the major focus of our laboratory.

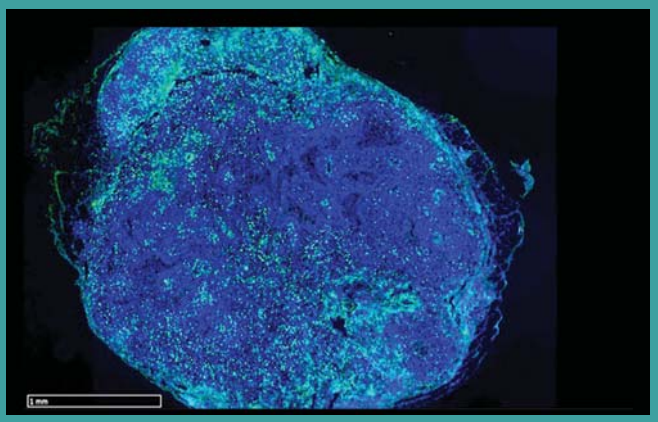


Fig.1 - T-cell recruitment in a gastric-derived tumor after TLR treatment. *(green: CD3-positive T cells, blue: nuclear staining - DAPI) (M. Treinies, 2014)*

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Immune cell recruitment to the tumor

We found that both T and B-lymphocyte trafficking to gut-associated lymphoid tissue (GALT) is profoundly modified by RLR/TLR stimulation, a point that is highly relevant for the TLR-based immunotherapy of gastric cancer. We found that the integrin α4β7, which is constitutively expressed on naïve lymphocytes and is essential for their entry into GALT, is downregulated on these cells following TLR activation. This downregulation of α4β7 prevents entry of naïve CD8 T cells and B cells into GALT. We hypothesize that the re-routing of naïve lymphocytes by the RLR/TLR signals associated with systemic infections may thus serve to redirect these cells to the systemic circulation to improve antiviral immunity (*Heidegger et al., J. Immunol. 2013; Heidegger et al., Blood 2013*). Our therapeutic aim is to control the immigration of lymphocytes into the gastrointestinal tract through immunostimulatory oligonucleotides and other immune modulators. This would enable the development of highly specific immunotherapeutic strategies to target gastrointestinal tumors.

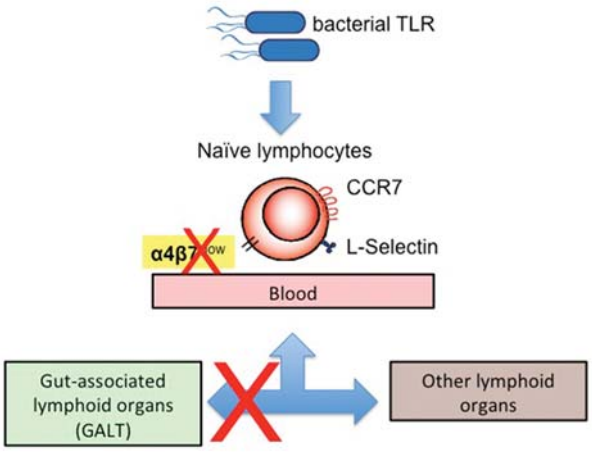

Fig.2 - TLR activation blocks trafficking of naïve lymphocytes to gut-associated lymphoid organs. *Upon stimulation of TLR, the integrin α4β7 is downregulated on naïve lymphocytes. This effectively prevents their entry into gut-associated lymphoid organs.*

In a translational study we examined the impact of a phage idiotype vaccine in both a preclinical model for lymphoma and in patients with advanced multiple myeloma in a phase I/II clinical study. We demonstrated that this vaccine leads to enhanced antitumoral T-cell responses in a subset of patients (*Roehnisch et al., J. Translational Medicine 2013 and Roehnisch et al., J. Translational Medicine 2014*). ▸▸

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Timing is everything: the importance of kinetics for immunotherapy

We have previously shown that repeated administration of ligands for TLR7 can lead to immune unresponsiveness and low efficacy of cancer therapy (*Bourquin et al., Cancer Research 2011*). Based on an extensive analysis of molecular signaling pathways, we have therefore developed a sequential treatment of RLR and TLR agonists that precludes unresponsiveness to immune stimulation and leads instead to enhanced immune responses (*Hotz et al., submitted*). We show that the sequence and interval between applications is essential for efficacy. We have also elucidated the molecular mechanisms responsible for the time-dependent effect. Using this stimulation sequence, we obtained for the first time a strong CD8 T-cell infiltration in gastric tumors. We thus contribute to the rational design of immunotherapy protocols based on molecular and cellular studies to improve the efficacy of cancer treatments.

Drug delivery systems for cancer immunotherapy

The application of pharmacological agents for cancer immunotherapy faces several challenges: the immune-activating drugs must be delivered either at the tumor site or at the site of induction of an immune response but must not lead to a generalized immune activation. They must be protected against degradation and, as we have shown, timing and sequence of release must be tighly controlled. We have initiated several collaborations to test different types of nanoparticles and their use as vehicles for drug delivery (*Schüller et al., ACS Nano 2011, Priebe et al., manuscript in preparation*). Our laboratory participates in the newly created NCCR in Bio-inspired Materials centered at the Adolf-Merkle Institute in Fribourg. Within this interdisciplinary network we are currently studying drug delivery in cancer immunotherapy by stimuli-responsive materials. ■

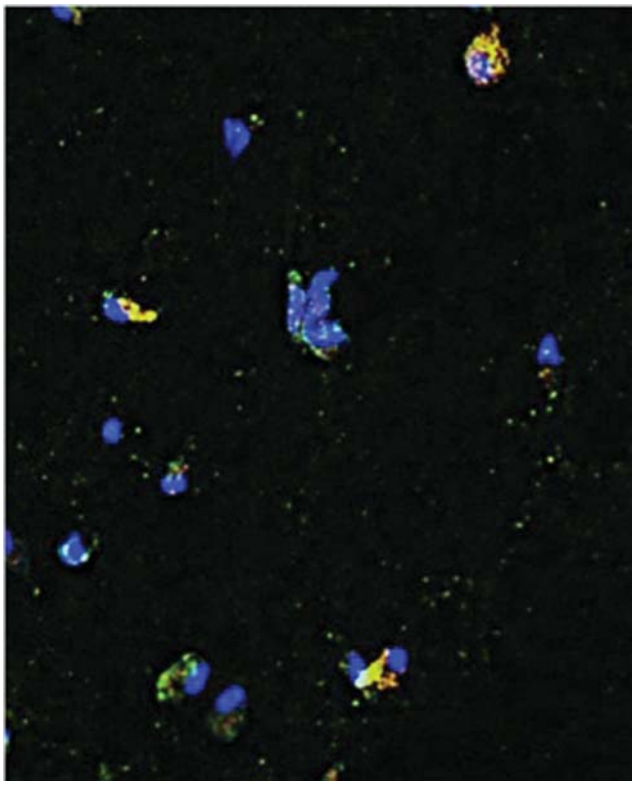

Fig.3 - PEG/PLGA nanoparticles are taken up by immune cells. *Green: fluorescently labeled PEG/PLGA nanoparticles; red: endosomal marker; yellow: colocalization of nano-particles in the endosome (J. Widmer, 2014).*

Selected Publications

Heidegger S, Anz D, Stephan N, Bohn B, Herbst T, Fendler WP, Suhartha N, Sandholzer N, Kobold S, Hotz C, Eisenächer K, Radtke-Schuller S, Endres S, ***Bourquin C***
Virus-associated activation of innate immunity induces rapid disruption of Peyer's patches in mice. Blood 2013, 122:2591-9. (JIF 9.0)

Heidegger S, Kirchner S, Stephan N, Bohn B, Suhartha N, Hotz C, Anz D, Sandholzer N, Stecher B, Rüssmann H, Endres S, ***Bourquin C***
TLR activation excludes circulating naive CD8+ T cells from gut-associated lymphoid organs in mice. J. Immunol., 2013, 190:5313-20 (JIF 5.6)

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Selective bispecific T-cell recruiting antibody enhances anti-tumor activity of adoptive T-cell transfer. J. Ntl. Canc. Inst., 2014, accepted for publication (JIF 14.3)

Luis Filgueira
Chair of Anatomy

Cell biology, immunology and clinical anatomy

INTRODUCTION

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

The first topic to be discussed covers the area of adult stem cells. In collaboration with the lactation research group (Peter Hartmann) at the University of Western Australia, a new population of breastmilk stem cells with pluripotent properties was discovered (Hassiotou et al.2012).

The second topic to be discussed covers the area of infectious immunology, where various infectious models are used, including Japanese encephalitis virus (Dr Lannes), Listeria (Dr Walch) and Malaria (Dr Mantel).

The third topic covers the area of clinical anatomy. Various projects are ongoing in collaboration with orthopaedic surgeons, including Dr G Kohut (Fribourg) and Dr. K Grob (St Gallen and University of Western Australia).

The following sections shall focus on the first and the second topic.

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Valerie Schwartz (2014)

Topic 1: Breastmilk stem cells with multipotent characteristics

It has been known for decades that human breastmilk contains cells. However, only recently we discovered that human breastmilk contains a population of stem cells with pluripotent properties. Those cells express corresponding markers usually expressed only by embryonic stem cells, including Oct4, Sox2, Nanog and SSEA-4, transcription factors that are essential for stemness and self-renewal. Upon exposure to specific culture conditions, the breastmilk stem cells differentiate along lineages of the 3 germinal layers, including stromal cells, liver and pancreatic cells, as well as keratinocytes and neuronal cells. These cells could be used for tissue engineering and future cell therapies. For that purpose, this approach has the advantage of breastmilk being an ethical and plentiful source of stem cells, as well as being able to apply autologous cells, which would reduce immune related side effects of cell transplants. We use these cells to develop a new cellular therapy to treat patients with diabetes mellitus type I. We take advantage of the development and differentiation pathways of stem cells towards pancreatic islet cells, including insulin producing beta cells (***Fig.1***). New protocols for the generation of pancreatic cells from breastmilk stem cells are established.

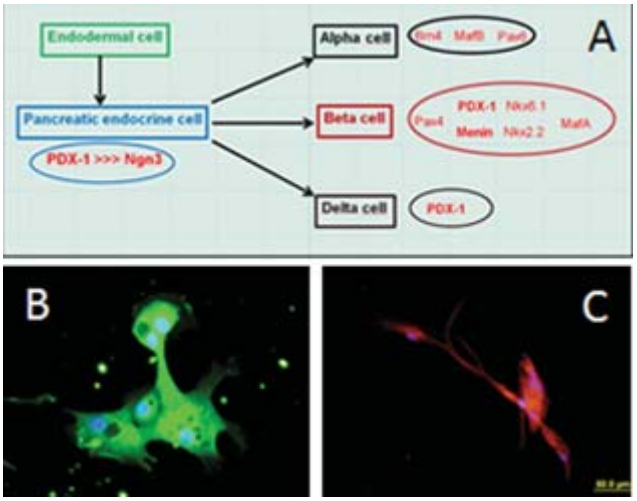

Fig.1 - A) Differentiation pathway of pancreatic cells from corresponding stem cells. *The different differentiation stages are characterized by the expression of certain transcription factor, e.g. PDX-1, Menin and Nkx6.1, that can be used as specific markers.* ***B)*** *and* ***C)*** *Breastmilk stem cells were cultured in pancreatic differentiation medium and stained for PDX-1 (B: green) or Insulin (C: red), as well as in blue nuclear stain with DAPI (Modified from Hassiotou et al. 2012).*

Topic 2: Infectious Immunology

Japanese encephalitis virus (JEV) is a neurotropic flavivirus causing mortality and morbidity in the humans. Infected patients exert strong inflammatory responses in the central nervous system with accumulation of viral particles in the hypothalamus and hippocampus. Microglia cells are the unique brain-resident immune cell population with potent migratory functions driven by the axis chemokine/chemokine receptor. Studies in rodent models suggest that microglia may act as reservoir for JEV. In the present study, we investigated how inactivated and live JEV regulates the expression of chemokines and corresponding receptors, using a novel model of human blood monocyte-derived microglia cells. Our new data suggest that certain JEV isolates possess particular mechanism to avoid inflammatory responses and immunity. Further research, also using electron microscopy (***Fig.2***), will elucidate the mechanisms used by the virus to manipulate the immune response.

Effector T lymphocytes are important in the control of intracellular bacterial pathogens, including Listeria, that evade many of the immune mechanisms. Upon bacterial antigen recognition, cytotoxic T lymphocytes release granule serine proteases, delivered into target cells by the pore forming protein perforin. However, the mechanisms of how bacteria are targeted are still not well understood. This research program, led by Dr Walch, investigates those mechanisms (***Fig.3***) with possibilities of future translational application to develop new antibiotic-like drugs (Walch et al. 2014, Cell 157(6), 1309-23). ■

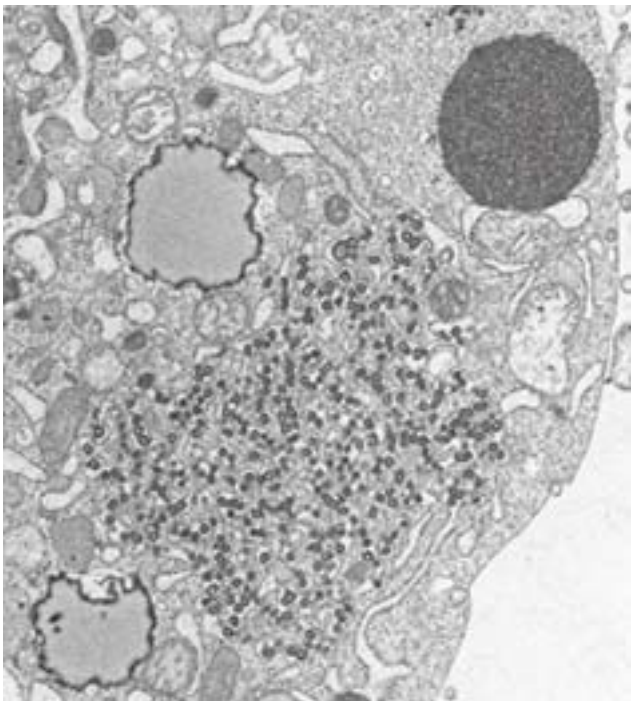

Fig.2 - Transmission electron microscopy of human dendritic cells infected with a retrovirus showing viral production and budding of viral particles *(Filgueira, unpublished).*

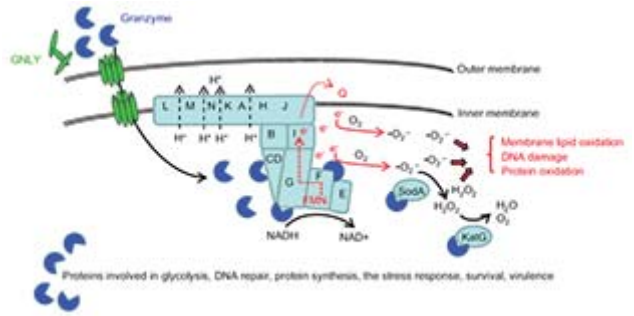

Fig.3 - Model of how granzyme B and granulysin mediates bacteriotoxic effects in bacteria *(for detailed description see Walch et al. 2014, Cell 157(6), 1309-23).*

Selected Publications

Hassiotou F, Hepworth A, Beltran A, Mathews M, Alison Stuebe, Hartmann P, ***Filgueira L****, Blancafort P*
Expression of the pluripotency transcription factor OCT4 in the normal and aberrant mammary gland. Frontiers in Women's Cancer 2013, 3:79. doi: 10.3389/fonc.2013

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Cisplatin induces differentiation of breast cancer cells. Frontiers in Oncology 2013, 3:134 doi: 10.3389/fonc.2013.00134

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Mantel PY*, Hoang AN, Goldowitz I, Potashnikova D, Hamza B, Vorobjev I, Ghiran I, Toner M, Irimia D, Ivanov AR, Barteneva N, Marti M*
Malaria-infected erythrocyte derived microvesicles mediate cellular communication within the parasite population and with the host immune system. Cell Host Microbe. 2013 May 15;13(5):521-34

Patrice Nordmann
Chair of Microbiology

Molecular and medical microbiology
Emerging antibiotic resistance unit

INTRODUCTION

Multidrug resistance is now emerging at an alarming rate worldwide. The rise of antibiotic-resistant bacterial strains represents a serious threat to public health and the economy. The severity of this menace is amplified by the fact that research for new antibiotic agents is currently stalled. The 20th century was the «century of antibiotics», marked by the discovery and the continuous development of new, more and more active antibiotics, but no new antibiotic family has been available for clinicians since 1987. In a world with few effective antibiotics, modern medical advances such as intensive care, transplant and chemotherapy (cancer treatment) may no longer be possible due to the threat of untreatable infections. It is estimated that 25,000 patients die each year in Europe due to multidrug resistant bacteria.

As underlined by the latest and important report from the White House in the US (September 29, 2014, National Strategy for Combating Antibiotic Resistant Bacteria) a multiple facet approach is needed. Basically, this strategy is intended to reach four synergistic goals:

1) Antibiotic stewardship from agriculture to human medicine

2) Surveying emerged and emerging resistance determinants

3) Accelerate basic and applied research and the development for new antibiotics, other therapeutics and vaccines

4) Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria

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Results

Our research is mostly on emerging resistance in gram negatives which are the main cause of infections for humans and for which very few therapeutic options are left. They are the source of community-acquired and hospital-acquired infections (urinary tract infections, septicemia, intra-abdominal infections...). The most clinically-significant gram negative species are the *Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae, Salmonella…), Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
Our research goals are the followings:

a) increase in the knowledge on the origin, the plasticity and diffusion of resistance genes

b) the prevention of their spread by implementing novel diagnostic tools, and

c) the discovery of novel antibiotic molecules.

Genetic and biochemistry of emerging antibiotic resistances

Our latest research focuses mostly on two emerging resistance determinants that are currently of utmost importance for humans, i.e. resistance to carbapenems and resistance to polymyxins (colistin).
Main results are as follows;

- Identification of *Acinetobacter baumannii* as an intermediate vector to transfer antibiotic resistance determinants from unknown bacterial reservoirs to *Enterobacteriaceae*. We have evidenced this novel paradigm of gene exchange for the *bla*NDM gene which protein (a carbapenemase) confers resistance to virtually all ß-lactams.

- Characterization of the molecular mechanism associated to the high level rate of interspecies diffusion of a very specific plasmid that contains the *bla*OXA-48 gene encoding one of the most prevalent carbapenemase gene in the world. Transposon-based inactivation of a repressor gene encoding for conjugative properties of this plasmid was the source of its high rate of diffusion ***(Fig.1)***.

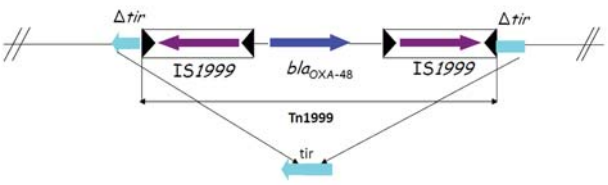

Fig.1 - Transposon inactivation of the tir gene encoding a protein that regulates negatively the cell-to-celle plasmid transfer of the IncL/M plasmid carrying the blaOXA-48 gene. *The bla OXA-48 gene encodes the carbapenemase OXA-48, the most prevalent carbapenemase in countries such as France and Germany.*

▸▸

• Identification of multidrug resistance determinants associating pandrug resistance to aminoglycosides, colistin, expanded-spectrum cephalosporins and carbapenems in clinical isolates of gram negatives from human and veterinary medicine from worldwide origin. Further identification of rapid spread of carbapenemase producers at the molecular and clonal levels and whole genome sequencing of pandrug resistance Enterobacteriacae with identification of novel resistance islands.

• Unravelling of the colistin resistance mechanisms in *Klebsiella pneumoniae*. Identification of modifications in regulatory proteins (in particular of the small transmembrane protein MgrB) of the lipopolysaccharide biosynthesis as the main source of colistin resistance in *Klebsiella pneumoniae*.

Rapid diagnostic techniques for identification of emerging antibiotic resistances and development of novel antibiotic strategies

The rapid diagnostic techniques may help to design an optimal strategy for a better antibiotic stewardship of each individualized infected patient and to promote the rapid isolation of colonized (non-infected) patients. They will contribute to initiate the implementation of companion diagnosis in the field of antibiotherapy. We have settled rapid diagnostic tests for identification of any carbapenemase producer in gram negatives (Carba NP and CarbAcineto NP test) in less than 1 h. The lately developed CarbaAcineto NP test identifies carbapenemases in *Acinetobacter baumannii* (a nosocomial pathogen as a source mostly of pneumonia and device-associated infections) that are systematically associated with multidrug resistance in this species. The developed test for the rapid identification of extended-spectrum ß-lactamases (the ESBL NDP test, ***[Fig.2]***) would be also particularly useful since up to 5-15% of *Escherichia coli* and 5-60% of *Klebsiella pneumoniae* express an ESBL in Europe. The ESBL NDP test may be used with bacterial colonies, blood and urines. Urine testing results are obtained within 15 min with 95-100% sensitivity and specificity. Those tests are cost efficient may be implemented easily and are becoming first line screening tests worldwide.

Fig.2 - The rapid test for identification of ESBL producers in gram negatives (ESBL NDP test). *The principle of the test is based on detection of acid production resulting from the hydrolysis of ß-lactam ring of an extended-spectrum cephalosporin, the cefotaxime molecule (pathway 1) and of the lack of acid production resulting from the inhibitory effect of cefotaxime hydrolysis by tazobactam addition (a ß-lactamase inhibitor) (pathway 2).*

We are contributing also to the identification of novel antibiotic targets and to the evaluation of the in-vitro and in-vivo antibiotic properties (animal model of infections) of novel antibiotic molecules using well-genetically defined bacterial strains and clinical isolates. ■

Selected Publications

Potron A, Poirel L, ***Nordmann P***
Derepressed transfer properties leading to the efficient spread of the plasmid encoding carbapenemase OXA-48. Antimicrob Agents Chemother. 2014, 58: 467-71

Poirel L, Jayol A, Bontron S, Villegas MV, Ozdamar M, Türkoglu S, ***Nordmann P***
The mgrB gene as a key target for acquired resistance to colistin in *Klebsiella pneumoniae*. J Antimicrob Chemother, 2015, 70:75-80

Dortet L, Poirel L, ***Nordmann P***
Rapid detection of extended-spectrum β-lactamase-producing *Enterobacteriaceae* from urine using the ESBL NDP test. J Clin Microbiol, 2014, 52:3701-6

Curzio Rüegg
Chair of Pathology

Experimental and translational oncology

INTRODUCTION

Emerging evidence indicates that carcinogenesis and tumor progression are not simply cell autonomous processes, but rather involve complex heterotypic multi-cellular interactions between cancer cells and cells present in their immediate surroundings. Hence, the concept of tumor microenvironment as an integrated part of the tumor tissue was coined. The tumor microenvironment contains many distinct cell types, including endothelial cells, pericytes, smooth muscle cells, fibroblasts. In addition, tumors and pre-tumoral lesions can recruite tumor-promoting inflammatory and immune cells from the bone marrow. Tumor-infiltrating immune and inflammatory cells play a dual role: one the one side they can repress tumor growth, yet, on the other side, they can promote tumor angiogenesis, tumor invasion and metastasis.

We are interested in understanding how the growing tumor interacts with the host and modifies normal tissues to its advantage, how this modified tissue contributes to tumorigenesis and how therapeutic interventions modify this cross-talk. We are interested in developing tools to improve early cancer detection and monitoring and to prevent or inhibit metastasis formation.

Specifically, we are addressing the following questions:

1) How do brain metastases form?

2) How do immune cells control cancer dormancy?

3) How do inflammation promote tumor progression?

4) What are the local and systemic effects of radiotherapy?

5) How do fibroblasts promote cancer progression?

6) How can we exploit tumor-host interactions for early cancer detection?

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A novel gene expression signature in peripheral blood mononuclear cells for early detection of colorectal cancer

Colorectal cancer (CRC) is the second-leading cause of cancer-related death in Europe. CRC is often curable, when diagnosed at early stages. Moreover, adenomatous polyps (AP) detection and removal prevents CRC formation and decreases mortality rates. It is recommend that average risk individuals begin regular CRC screening at age of 50. Colonoscopy is the «gold standard» for CRC detection; however it is not the preferred method for screening because of its cost, invasiveness, low compliance and limited accessibility.
Non-invasive methods for mass-screening include immunochemical and fecal occult blood testing.

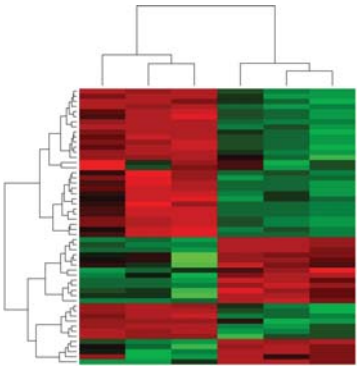


Fig.1 - Heat map representation *of the unsupervised clustering of genes expression in peripheral blood circulating mononulclear cells of tumor-bearing vs non tumor-bearing mice that served as a preclinical model for the development of the COLOX test.*

A blood-based screening test is highly attractive due to its minimal invasiveness and high acceptance among patients.
We identified gene expression signatures in the peripheral blood mononuclear cells able to detect the presence of AP and early stages CRC. A 42-gene panel for CRC and AP discrimination was identified by RNASeq profiling of PBMC and including previously reported genes. Logistic regression analysis followed by bootstrap validation determined CRC- and AP-specific classifiers, to discriminate patients with CRC and AP from controls. The CRC and AP classifiers detect CRC with a sensitivity of 78% and AP with a sensitivity of 46%, respectively, and a specificity of 92%. The false discovery rate is lower than 0.2%. The test was developed in collaboration with Diagnoplex and is commercialized since March 2014.

Fibroblasts induce cell contact-dependent colon cancer cell migration and invasion through a FGF-2, Src and integrin dependent mechanism

Carcinoma-associated fibroblasts are known to promote colorectal cancer (CRC) invasion by secreting motility factors and modification of the extracellular matrix. Less is known about whether fibroblast-induced CRC cell motility and invasion might also involve direct cell-cell contact.

We characterized the interaction between fibroblasts and

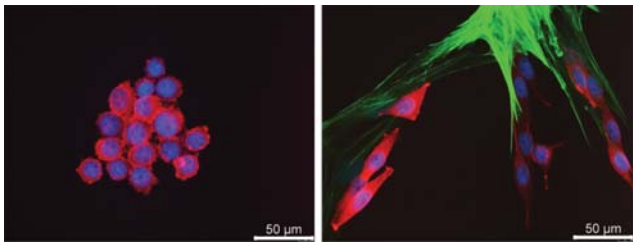


Fig.2 - Elongation of tumor SW620 CRC cells (red) in contact with fibroblasts (green). *SW620 cells alone have a rounded morphology.*

CRC cells in 2D and 3D in vitro co-culture models. We observed that fibroblasts induce CRC cell elongation, motility and invasiveness in a contact-dependent manner. We demonstrate that FGF2 present on the fibroblast surface as well as FGF-Receptors (FGFR) and integrins expressed by CRC cells are essential mediators of elongation, motility and invasion of co-cultured CRC cells. Pharmacological inhibition of FGFR, Src kinase or αVβ5 integrin prevented CRC cells adhesion to

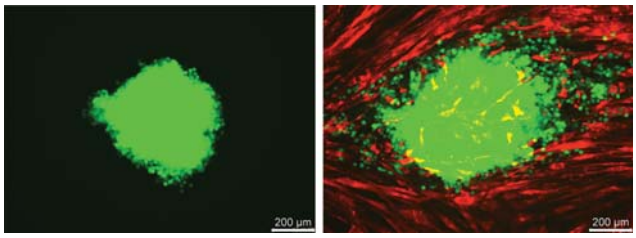


Fig.3 - Induction of SW602 cell (green) scattering and invasion by a monolayer of fibroblasts (red).

fibroblasts, and fibroblast-induced CRC cell elongation, motility and invasiveness. These results demonstrate that fibroblasts induce CRC cell migration and invasion through direct cell-cell contact and identify FGFR, Src and αVβ5 integrin molecules as candidate targets for preventive or therapeutic purposes.

CYR61 promotes tumor growth, invasion and angiogenesis in the Rip1Tag2 pancreatic neuroendocrine tumor model

Cysteine Rich Protein 61 (CYR61) is a secreted matricellular protein implicated in the regulation of angiogenesis, fibrosis, wound healing and cancer. Experimental and clinical studies suggest that CYR61 might promote

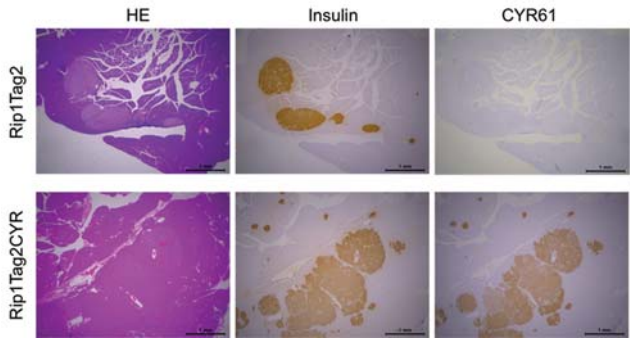


Fig.4 - CYR61 promotes tumor growth and invasion in Rip1Tag2 mice. *Insulin and CYR61 IHC staining (IHC) demonstrate larger and more invasive tumors*

cancer progression. To elucidate the function of CYR61 in multistep tumorigenesis we adopted the Rip1Tag2 transgenic mouse model. Firstly, we generated Rip1CYR mice expressing CYR61 in the β-cells of the Langerhans islets. Rip1CYR mice had irregularly shaped islets while the size or number of the islets and the density or morphology of their vasculature were not altered. Secondly, we crossed Rip1CYR mice with Rip1Tag2 transgenic mice to obtain double-transgenic offspring expressing CYR61 in pancreatic β-tumors. Double-transgenic Rip1Tag2CYR mice had larger and more invasive, high-grade tumors compared to

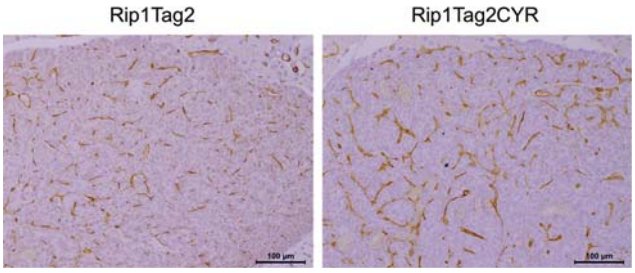


Fig. 5 - CYR61 promotes tumor angiogenesis in Rip1Tag2 mice. *CRY61 enhances vascular density, length, area and bifurcation points in Rip1Tag2 mice.*

Rip1Tag2 mice. Tumors in Rip1Tag2CYR mice were more vascularized than those in Rip1Tag2 mice.
These results demonstrate for the first time in a transgenic model of multistep tumor progression that CYR61 promotes tumor growth, invasion and angiogenesis. CYR61 has no impact on the size or vascularization of normal islets. These observations are consistent with a tumor promoting rather than a tumor-initiating role of CYR61. ■

Selected Publications

Nichita C, Ciarloni L, Monnier-Benoit S, Hosseinian S, Dorta G, ***Rüegg C***
A novel gene expression signature inperipheral blood mononuclear cells for early detection of colorectal cancer. Aliment Pharmacol Ther. 2014;39(5):507-17

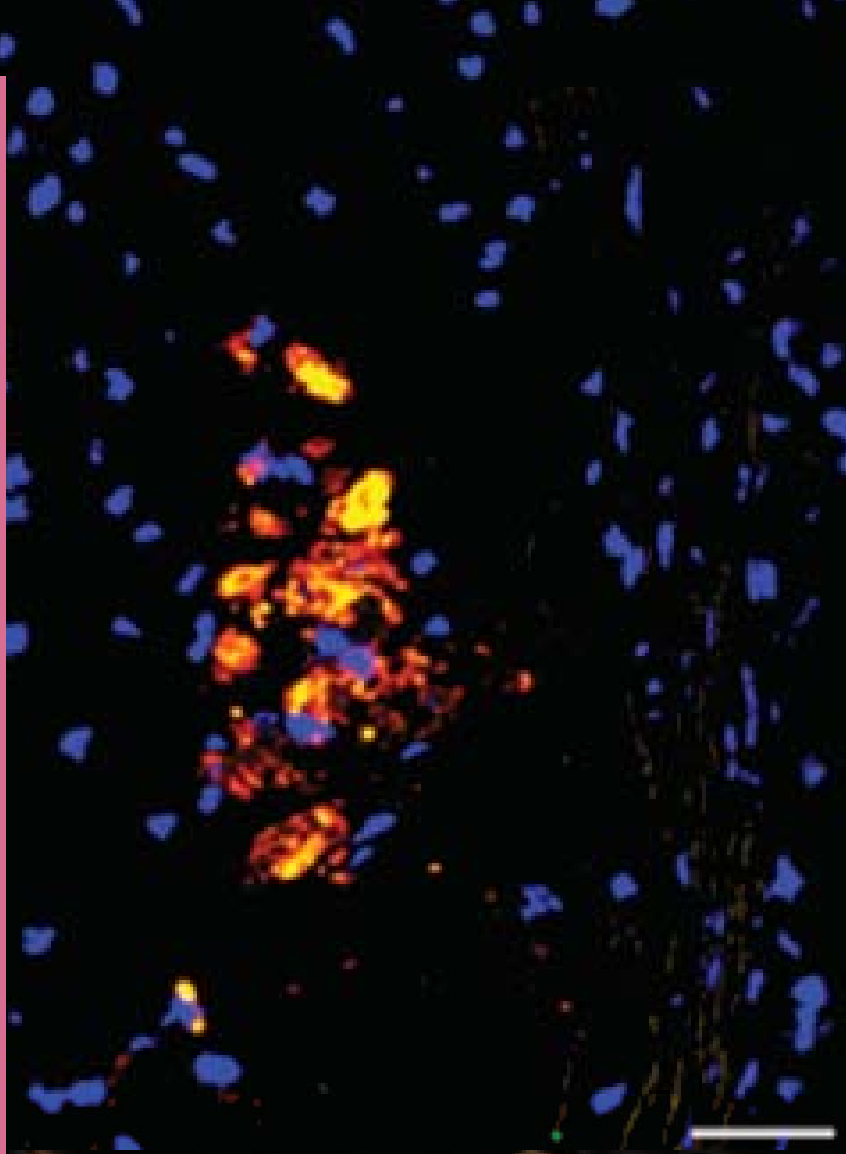
Barras D, Lorusso G, ***Rüegg C****, Widman C*
Inhibition of cell migration and invasion mediated by the TAT-RasGAP317-326 peptide requires the DLC1 tumor suppressor. Oncogene. 2014;33(44):5163-72

Barras D, Lorusso G, Lhermitte B, ***Rüegg C****, Widmann C*
Fragment N2, a caspase-3 generated RasGAP fragment, inhibits breast cancer metastatic progression. Int. J. Cancer, 2014, 1;135(1):242-7

Cardiovascular, Metabolism and Endocrinology

Cardiovascular, Metabolism and Endocrinology is the second deep-rooted thematic cluster. The already established cardiometabolic research groups (Dulloo, Montani and Yang) were complemented with the new Chair of Cardiology (Cook and Togni), active in translational and clinical research on atherosclerosis and coronary disease, and by research in the renal field (Theilig). Furthermore, basic and translational research in endocrinology in the field of sexual differentiation and genetics of diabetes joined this cluster through the appointment of the Chair of Endocrinology (Lauber-Biason).

Cardiovascular, metabolic and endocrine dysfunctions are closely interlinked, sharing many common pathways to diseases. Metabolic disorders, such as diabetes and obesity, lead to cardiovascular diseases, which in turn promote physical inactivity, further worsening metabolic disorders. The prevalence of obesity has now reached epidemic proportions, touching younger people and bringing type 2 diabetes, its major complication, to steadily younger populations, exposing thus the ageing population to many more years of cardiovascular, metabolic and renal injuries. However, there is a large variability in the susceptibility to cardiovascular disorders and to weight gain, influenced already in the womb by the nutritional status of the mother and the genetic background. The challenges of this century will be to understand the causes of this susceptibility to diseases, to dissect the mechanisms of pathogenesis and complications and to harness the therapeutic pathways to alleviate and prevent cardiovascular, metabolic, renal and endocrine dysfunctions.



Stéphane Cook & Mario Togni
Translational and clinical cardiology

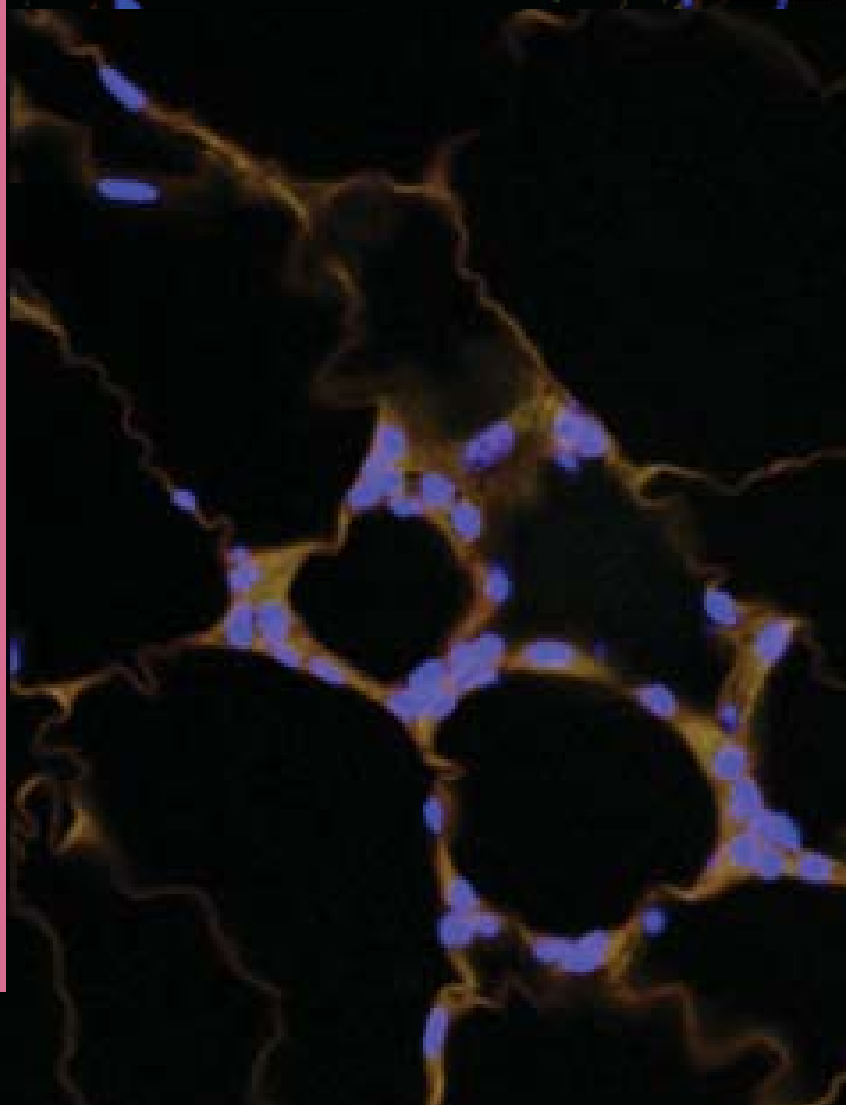
Abdul Dulloo
Nutritional energetics and body composition regulation

Anna Lauber-Biason
Molecular endocrinology

Jean-Pierre Montani
Cardiovascular and metabolic physiology

Franziska Theilig
The importance of renal proximal tubular function

Zhihong Yang
Cardiovascular and aging research



Stéphane Cook
Mario Togni
Chair of Cardiology
Translational and clinical cardiology

INTRODUCTION

Since its inception in the late 1970's, treatment by interventional cardiologic procedures constitutes the main reason for the decline in mortality from cardiovascular causes and, more specifically, from coronary artery disease. 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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Preclinical Research

In 2013 and 2014, our group has successfully submitted two projects to the SNF and further developed its research in the cardiovascular field following two major axes:

1. Myocardial cell therapy

Our predominant findings established that functional recovery following the treatment of myocardial infarction with cell administration was consistently superior when using hydrogel matrices compared with the recovery obtained with solid patches for cell delivery. Fascinatingly, myocardial regeneration was improved for epicedial delivery of mesenchymal stem cell together with a gel type matrix. Though, cell tracking using bioluminescence showed a low retention rate of implanted cells.
In addition, we have developed and improved experimental tools for in vivo evaluation of therapies' efficacy. For examples, quality of myocardial infarct and prediction of its extension is now under the control of specific biomarkers. In addition, we have developed a minimally invasive microsurgery based on a double thoracotomy for myocardial infarction induction and treatment administration that efficiency reduced postoperative animal mortality.

2. New treatments for atherosclerosis plaques

Photodynamic therapy (PDT) and Femtolaser therapy are been actually investigating for the destruction of vulnerable atherosclerotic plaques in collaboration with two groups at EPFL. Ex vivo evaluation of both approaches have been investigated.
• Proof of concept investigation has been carry out for the destruction of atherosclerotic plaque with focused high-energy, ultrafast pulses using a newly developed femtolaser.
• Screenings of the drugs for PDT have currently been initiated ex vivo using an arterial perfusion system perfused (EVASS).
Our group has also an interest in developing new bioresorbable stents. Our objective is to design, develop and validate a new generation of drug eluting stents with a bioresorbable platform that will both prevent restenosis and promote re-endothelialisation and arterial healing. To fulfill our goal, we established solid multidisciplinary collaborations in particular with the i-printing institute (Prof. Fritz Bircher, Fribourg).
In addition our group maintained and analyze a bank of histological characterization of thrombi harvested from occluded coronary during primary percutaneous coronary intervention. ▸▸

CLINICAL RESEARCH

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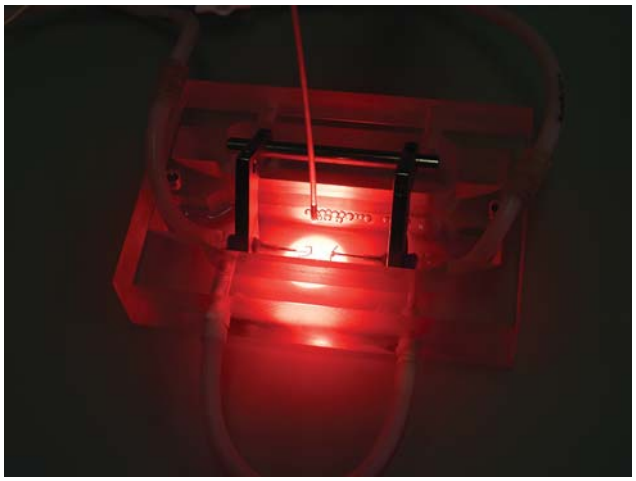

Fig.1 - Ex vivo administration of photodynamic therapy (PDT) on an aorta harvested from genetically modified mouse (ApoE-/-) that developed atherosclerotic plaques. *PDT involves administration of a photosensitizing agent, followed by activation of the agent by light of a specific wavelength. Resulting generated reactive oxygen species induce nearby cell death. Local administration of the treatment allows advantageous high effectiveness/side-effect ratio.*

Clinical Research

Throughout the years 2013 and 2014 the unit has conducted the first superiority trial in the world that compared a fully bioresorbable coronary stent to the best-in-class metallic stents (EVERBIO II). Results have been presented at the prestigious TCT-Conference in Washington, D.C. in September 2014. Analysis and Interpretation of a sub-study that assessed vascular healing by optical coherence tomography in the studied devices is currently on-going. Fully bioresorbable coronary stents are the latest innovation in the field and harbour the potential to revolutionize Interventional Cardiology. The unit has a particular interest for these devices and is part of a multi-national collaboration that scrutinizes the pathophysiologic mechanisms behind thrombosis in these fully bioresorbable stents.

Other single-centre trials conducted during 2013/2014 were vasomotor and imaging studies comparing the vasomotion of everolimus-eluting vs. biolimus-eluting coronary stents (COMPARE Vasomotion Trial) as well as everolimus-eluting stents with biodegradable polymer vs. fully bioresorbable stents (MOVES Trial).

With regard to multicentre collaborations, our unit is participating in some landmark clinical trials in interventional cardiology. Fribourg University & Hospital is, e.g., one of the recruitment centres for the DAPT-STEMI trial, which addresses the question whether a dual antiplatelet therapy of 6 months for 2nd generation drug-eluting stents is non-inferior to the currently recommended 12-months duration. Other multi-centre comparative coronary stent trials in which our research unit is partaking are COMPARE II, BIOMARIX, BIOSCIENCE and SENIOR. Furthermore, the unit participates in large multicentre registries such as the Swiss National Registry of myocardial infarction (AMIS-PLUS) or the international registry on renal denervation (GLOBAL SIMPLICITY).

The research group has the lead on several multicentre clinical registries that assess clinical outcome in patients according to the type of device implanted. One of the currently on-going registries is SWEET, which evaluates the 1-year outcome of patients treated with the SYNERGY stent. In 2014, propensity-score matched analyses of this type of data have led to several publications such as EVERBIO (head-to-head comparison of the latest everolimus-eluting and biolimus-eluting stents) or SOLUTION (Comparison of the most frequently used percutaneous foramen ovale closure devices). A registry for the evaluation of the treatment of ST-Elevation Myocardial Infarction at Fribourg Hospital (EVALFAST) and the evaluation of post-traumatic stress syndrome after myocardial Infarction (ESPOIR) are currently on-going. A registry for quality control and the assessment of clinical follow-up in all patients undergoing percutaneous coronary intervention at Fribourg Hospital has been created in 2014 (CARdIO-FR). ■

Selected Publications

Puricel S, Arroyo D, Corpataux N, Baeriswyl G, Lehmann S, Kallinikou Z, Muller O, Allard L, Stauffer JC, ***Togni M****, Goy JJ,* ***Cook S***
Comparison of Everolimus- and Biolimus-Eluting Coronary Stents with Everolimus-Eluting Bioresorbable Vascular Scaffolds - A Randomized Controlled Trial, Journal of the American College of Cardiology. 2015 Mar 3;65(8):791-801

Pilgrim T, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, ***Cook S****, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S*
Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularization (BIOSCIENCE): a randomised, multicentre, non-inferiority trial. Lancet. 2014 Dec 13;384(9960):2111-22.

Puricel S, Arroyo D, Goy JJ, Praz F, Palhais N, Wahl A, Stauffer JC, ***Togni M****, Berger A, Meier B,* ***Cook S***
A propensity score-matched comparison between Cardia and Amplatzer PFO closure devices - insights from the SOLUTION registry (Swiss percutaneOus patent foramen ovale cLosUre in recurrent clinical events prevenTION). EuroIntervention. *2014 May 20*

Abdul G. Dulloo
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Nutritional energetics and body composition regulation

INTRODUCTION

Energy expenditure (EE) associated with everyday life physical activities, often referred to as non-exercise activity thermogenesis, plays an important role in the regulation of body weight and in contributing to human variability in proness to obesity and cardiometabolic diseases. To study such low-intensity physical activities, however, is a challenging task as they include not only voluntary occupational and leisure activities but also subconscious spontaneous physical activity such as muscle tone and posture maintenance and fidgeting (***Fig.1***).

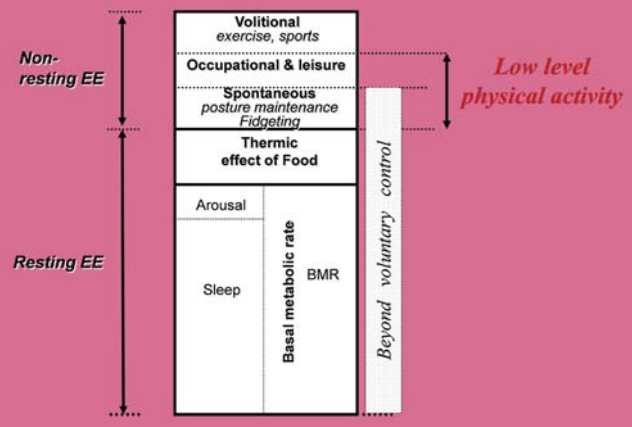

Fig.1 - The various compartments and sub-compartments of human energy expenditure (EE). Note that «spontaneous» physical activity is essentially beyond voluntary control (subconscious). From Dulloo et al. *Obesity Reviews* (2012) 13 (suppl.2.): 105-21

In addition to the development of accelerometers and activity monitors for the detection and quantification of these low-intensity activities, approaches have been developed and validated for assessing EE variability in response to standardized «dynamic» exercise at low power outputs. However, because movements comprise not only dynamic work but also static (isometric) work, and that intermittent isometric thermogenesis is an important component of EE associated with spontaneous physical activity, there is also a need to develop standardized tests for assessing human variability in the energy cost of isometric work of low intensity (energetically comparable to daily life physical activities) - and hence to extend the capacity for metabolic and EE phenotyping beyond those conducted at resting or during dynamic exercise.

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Exploring novel approaches in human phenotyping for susceptibility to obesity: Focus on isometric thermogenesis

During the last few years, our laboratory has developed and validated two approaches to study human variability in isometric thermogenesis: (I.) using posture-adapted ventilated hood indirect calorimetry to study EE response to standing posture maintenance and (II.) by incorporating a standardized protocol of intermittent leg press of low intensity in a protocol of indirect calorimetry for measuring EE in a comfortable seated position. The context, main results, and the significance of these findings are outlined below.

I. Energy cost of standing: energy savers vs energy spenders

The disease risks associated with sedentary behavior are now firmly established, and consequently there is much interest in methods of increasing low-intensity physical activity. In this context, it is a widely-held belief that altering posture allocation can modify EE to impact upon body weight regulation and health. However, using posture-adapted, ventilated-hood indirect calorimetry to monitor min-by-min EE in healthy young adults during a 10 min steady-state standing period (***Fig.2***), we showed that the vast majority of adults (> 75%) showed either no increase or no sustained increase in EE during the standing period compared to sitting comfortably (1). Furthermore, no differences in EE were observed during sitting compared to lying in the supine position (2). The mechanisms by which the large majority of individuals appear to maintain supine, sitting and standing postures at the same energetic cost (hence showing an energy-saving phenotype) remains to be elucidated but is of considerable importance to our understanding of the spontaneous physical activity compartment of EE.

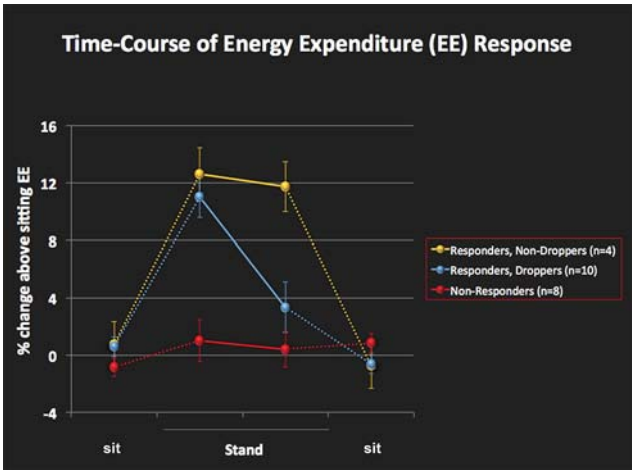

Fig.2 - Energy expenditure (EE) in response to standing in young adults (n=22). *The two values for standing refer the change in EE during the 1st and 2nd five min periods during 10 min standing. The «Non-Responders» and the «Responders-Droppers» are the «energy savers», while the «Responders Non-Droppers» are «energy-spenders». From Miles-Chang et al. (1)*

II. Energy cost of leg-press exercise: large (mass-independent) inter-individual variability

In another approach to study human variability in isometric thermogenesis, the isometric work was performed by intermittent leg press (30 sec press & 30 sec rest in every min for 8 min) at low-intensity isometric loads (range 5-25 kg force) (***Fig.3***), and performed in the seated position in an ergonomic and adjustable car seat with measurements of EE by ventilated-hood indirect calorimetry in young healthy men and women. A strong linearity was observed in the relationship between EE vs leg press isometric exercise in the range of 5-25 kg force. The slope (i.e. the energy

cost per kg force applied intermittently) was found to show good repeatability; the low intra-individual coefficient of variability (CV) of ~10% contrasted with the much higher inter-individual CV of 35%; the latter being mass-independent but partly explained by height (3). Given reports from large epidemiological studies for an association between adult short stature and increased risks for cardiovascular diseases, type 2 diabetes and obesity, the hypothesis is put forward that low isometric thermogenesis could constitute a metabolic link in the inverse association between stature and cardiometabolic risks.

Perspectives

These two novel standardized and validated approaches to study human variability in isometric thermogenesis extend the capacity for metabolic and EE phenotyping beyond those conducted in the resting state or during dynamic exercise, and hence open new avenues for research in human energy metabolism in general, and in proness to obesity and cardiometabolic risks in particular. ■

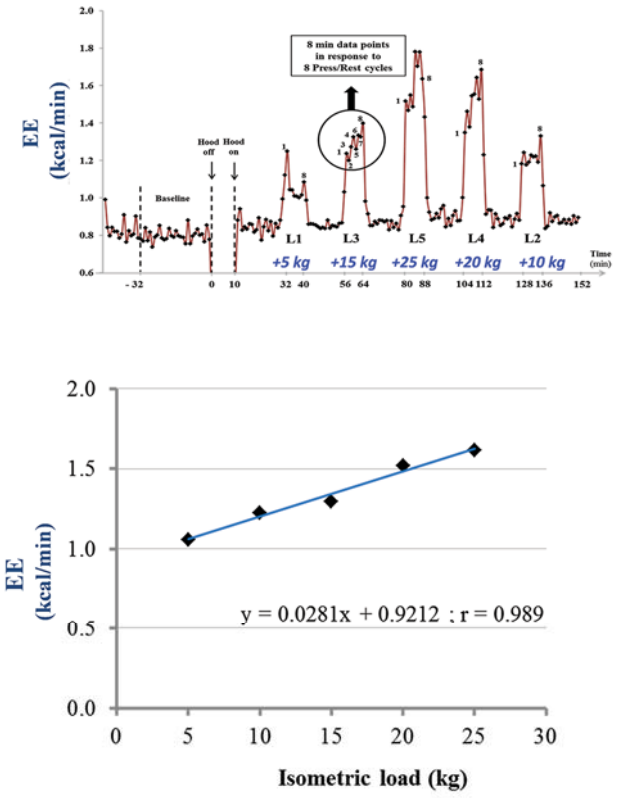

Fig. 3 - Energy expenditure (EE) at rest and in response to intermittent leg press exercise of low intensity. *The upper panel is an example of the EE (kcal/min) profile in a young woman at rest (Baseline) and in response to five isometric active loads (+5, +10, +15, +20, +25 kg) recorded minute by minute by indirect calorimetry. The lower panel is the linear regression analysis from the above EE data as a function of the 5 isometric active loads. The slope, which characterizes the energy cost of this intermittent isometric exercise, shows a 3-fold variability between individuals. From Sarafian et al. (3)*

Selected Publications

Miles-Chan JL, Sarafian D, Montani JP, Schutz Y, ***Dulloo AG***
Heterogeneity in the energy cost of posture Maintenance during standing relative to sitting: Phenotyping according to magnitude and time-Course. *PLoS One*, 8: e65827, 2013

Miles-Chan JL, Sarafian D, Montani JP, Schutz Y, ***Dulloo AG***
Sitting comfortably versus lying down: is there really a difference in energy expenditure? *Clinical Nutrition* 33:175-8, 2014

Sarafian D, Miles-Chan JL, Yepuri G, Montani JP, Schutz Y, ***Dulloo AG***
A standardized approach to study human variability in isometric thermogenesis during low-intensity physical activity. *Frontiers in Physiology* 201;4:155 : 1-15, 2013

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Molecular endocrinology

INTRODUCTION

The process of sexual differentiation is central for reproduction of almost all metazoan, therefore for maintenance of practically all multicellular organisms. In sex development we can distinguish two different processes: **sex determination** and **sex differentiation** (***Fig.1***). The former is the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual and it is regulated by several factors, including SRY in man (***Fig.1***). The second process, sex differentiation, takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. Still, much of this process is unknown, as demonstrated by the failure in finding a cause in many patients with disorders/differences of sex development (DSD). DSD are diseases of childhood with a prevalence of 1:3500-1:5000. We are one of the few centers in Switzerland dedicated to research these cases. Although the understanding of these conditions advanced, a precise etiology is unknown in about 50% of the patients. The birth of a DSD child prompts a long-term management strategy that involves a significant number of professionals working with the families. Initial gender uncertainty is stressful for families. A prompt thorough assessment and decision is required. One of the key factors that influence gender assignment is the diagnosis, together with genital appearance, surgical options, need for life-long replacement therapy, the potential for fertility, and psychosocial issues such as view of the family and cultural practices. Collecting as much data as possible in DSD is as important as in other conditions with life-long consequences. Considerable progress has been made with understanding the genetic basis of human sexual development, yet a specific molecular diagnosis is identified in only a part of cases of DSD. It is therefore mandatory to maintain the momentum for research in this field. This work gives the opportunity to identify the underlying pathophysiological and genetic mechanisms of DSD, to determine new causes of DSD, and translate these into evidence-based diagnostic tools. This will lead to structured diagnostic and management procedures and ultimately benefit all patients with DSD to alleviate health care problems, advice appropriate therapies, and foster their integration into society. It will also broaden concepts of sex and gender in our changing societies.
The recently published statement of Swiss National Advisory Board on Biomedical Ethics (NEK, http://www.bag.admin.ch/nek-cne/04229/04232/index.html?lang=de) further confirms the cultural relevance of this topic in our Country.

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1. Sex Development

Background

Sexual differentiation is a complex developmental process involving various genes and hormones. Most of the knowledge on the mechanisms regulating sexual development in mammals derives from knock-out experiments in animals or studies of disorders of sex development (DSD) in human patients. These diseases are not as rare as previously thought: it is estimated that genital anomalies occur in 1:3500-5000 births. Considerable progress has been made in the understanding the genetic basis of human sexual development, yet a specific molecular diagnosis is identified in only 50% of DSD cases. It is therefore mandatory to maintain the momentum for research in this field. For these reasons and given our longstanding experience in identifying such diseases, we plan study them and to focus on two fields: the steroidogenic enzymes AKR1Cs and the polycomb protein CBX2.

Project A - AKR1Cs in human sex development

Following development of the fetal bipotential gonad into a testis, male genital differentiation requires testicular androgens. Fetal Leydig cells produce testosterone that is converted to dihydrotestosterone (DHT) in genital skin, resulting in labio-scrotal fusion. An alternative «backdoor» pathway of DHT synthesis that bypasses testosterone has been described in marsupials, but its relevance to human biology has been uncertain. The classic and backdoor pathways share many enzymes, but a 3α-reductase, AKR1C2, is unique to the backdoor pathway. We identified human AKR1C2 mutations in 46, XY DSD patients, lending weight to the idea that both pathways are required for normal human male sex development.
We perform mutation- and functional analysis of patients with DSD using standard methods to clarify the role of the proposed alternative pathway in humans. We also want to study the role of a second isoform of AKR1C2 in the backdoor pathway in DHT synthesis with the ultimate goal to potentially identify another cause of DSD. Furthermore, we will analyze AKR1C1-4 in CAH patients with CYP21 deficiency, where the backdoor pathway seems to be activated after birth.

Relevance:

Deficiencies in AKR1Cs could explain some cases of apparent androgen insensitivity lacking identifiable androgen receptor mutations, who are still a significant quote of patients with DSD. The study of the role of the backdoor pathway to androgens may provide new targets for pharmacological intervention for states of androgen excess, such as 21-hydroxylase deficiency but also polycystic ovary syndrome and for androgen-dependent malignancies.

Project B - CBX2 isoforms in male and female sex development

CBX2 (Chromobox homolog 2) is a chromatin modifier that plays an important role in sexual development and its disorders (disorders of of sex development, DSD), yet the exact rank and function of human CBX2 in this pathway remains unclear. Here, we performed large-scale mapping and analysis of in vivo target loci of the protein CBX2 in Sertoli-like NT-2D1cells, using the DNA adenine methyltransferase (DamID) technique. We identified close to 1600 direct targets for CBX2. Intriguingly, validation of selected candidate genes using qRT-PCR in cells overexpressing CBX2 or in which CBX2 has been knocked down indicated that several CBX2-responsive genes encode proteins that are involved in DSD. We further validated these effects on the candidate genes using a mutated CBX2 causing DSD in human patient. Overall, our findings suggest that CBX2 role in the sex development cascade is to stimulate the male pathway and concurrently inhibit the female pathway (***Fig.1***). These data provide fundamental insights into potential etiology of DSD.

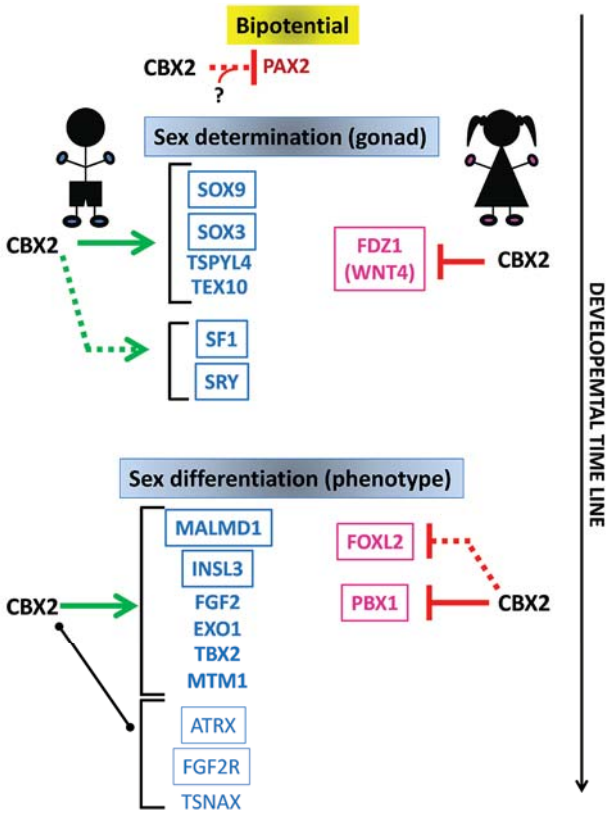

Fig.1 - Potential role of CBX2.1 in the regulation of sex development. *The developmental stages listed in relation to time, are indicated as bipotential, sex determination as the decision determined by several factors to develop into a male or a female gonad, and sex differentiation, the step determining the actual sexually dimorphic phenotype. In blue the male and in pink the female factors. The framed factors were found to be related to human disease. PAX2, which is important for the development of the bipotential gonad is in ocra. Solid lines between CBX2 and its targets* ▸▸

indicate a direct interaction (binding of CBX2 on target's DNA sequences). Green arrows indicate stimulatory effects of CBX2 on the indicated target, red «t» indicate inhibitory effects. The broken line indicates a functional but not physical interaction (changes in expression without direct binding). A black line indicate direct binding of CBX2 on the target without any effect on expression.

To rank more precisely CBX2 isoform 2 in the sex developmental cascade and to establish the role of both CBX2 isoforms in ovarian development, we plan to recognize DNA sequences that are target for CXB2 binding using the novel DamID-Seq technique. The validation of such high through-put experiments is performed using standard methods, e.g. siRNA, overexpression followed by RNA-Seq, and transactivation and complementation studies.

Relevance:

One of the defining moments of human lives occurs early during embryonic development, when individuals sexually differentiate into either male or female.. Although there have been a considerable advance in our understanding of the genetic factors involved in sex development, the fact remains that in most patients the underlying genetic cause is unknown. CBX2 is a protein which acts as a chromatin modifier and is required for normal human sex development; however its exact rank in the sex development cascade is still unclear. Here, we were able to identify numerous novel and direct targets of CBX2. Moreover, we validated a subset of these genes and found that their expression is CBX2-dependent. These results contribute to our understanding of the pathological mechanisms underlying disorders of sex development and improve diagnosis management of these complex clinical cases. Studies on CBX2 will shed more light on testicular and, most interestingly, on ovarian development, a terrain still relatively unexplored. Similarly to the next generation sequencing whole exome approaches, our approach will identify new factors and networks important for development. Thus, our studies will advance our knowledge of the biology of sex development in humans, but also help identifying novel and potential pathological mechanisms that could be involved in DSD: further characterization of how these new targets fit into an expanding CBX2-regulated network should reveal how CBX2 activation and suppression can impact our understanding of DSD pathogenesis and ultimately DSD diagnosis and management (***Fig.2***, in collaboration with the Bioinformatic Division, UniFR).

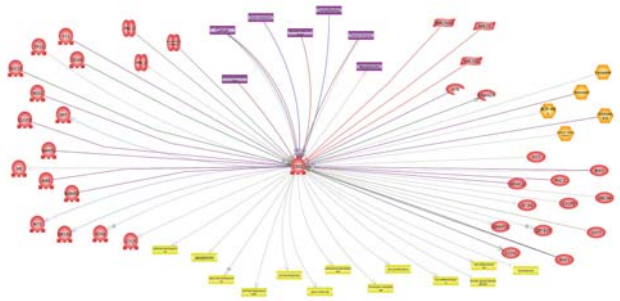

Fig.2 - CBX2: Interactions and pathways in health and disease *(created by P. Sproll using Pathway Studio software)*

2. Role of Sirtuin 1 (SIRT1) in onset of diabetes and autoimmunity

In collaboration with the group of Prof. Marc Donath (University of Basel) we took advantage of our expertise in the diagnosis of human genetic diseases to study a family with several cases of type 1 diabetes. Direct and exome sequencing identified a mutation in SIRT1 leading to overproduction of nitric oxide, cytokines and chemokines in β-cells. These observations identify a novel role for SIRT1 in human autoimmunity and unveil a monogenic form of type 1 diabetes. We are currently analysing other patients/families with phenotypes similar to that identified in ref. 3 to find novel SIRT1 mutations. We also collaborate with Marc Donath in the characterization of the SIRT1 knock-in mouse model that his group has created. ■

Selected Publications

***Biason-Lauber A**, Böni-Schnetzler M, Hubbard BP, Meyer-Böni M et al.*
Mutation in SIRT1 in a family with Type 1 diabetes. Mutation of SIRT1 in a family with Type 1 Diabetes. Cell Metab 2013, 17: 448-455 (Impact Factor 13.668)

***Biason-Lauber A**, Miller WL, Pandey A, Flueck CE*
Of Marsupials and Men : «Backdoor» Dihydrotestosterone Synthesis In Male Sexual Differentiation. Mol Cell Endocrinol 2013, 371: 124-132 (Impact factor 4.19)

*Eid W, Opitz L, **Biason-Lauber A***
Genome-wide identification of CBX2 targets: insights in the human sex development network. Mol Endocrinol 2014, (Impact Factor 4.746) (in press).

Jean-Pierre Montani
Chair of Systemic Physiology

Cardiovascular and metabolic physiology

INTRODUCTION

Cardiovascular diseases are promoted by many risk factors such as hypertension and metabolic disorders (obesity, diabetes, dyslipidemias,…). Our aims are to better understand the pathogenesis of those risks factors and how they impact on the cardiovascular system and on metabolic regulation.

In particular, our interests focus on the importance of the diet (fats and sugars), ranging from animal studies (chronic high fat or sugary diets) to human studies (acute cardiovascular monitoring on a beat-per-beat basis after the ingestion of various drinks or meals). We are particularly interested in the cardiovascular, cerebrovascular and metabolic effects of the ingestion of caffeinated soft drinks, including energy drinks.

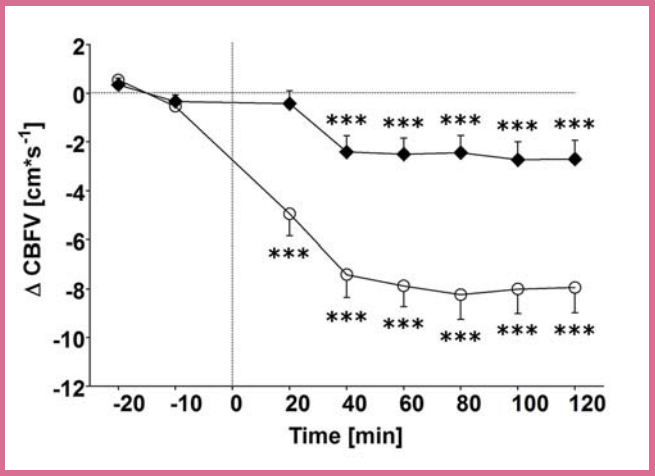

Fig.1 - Effect of the energy drink Red Bull on cerebral blood flow velocity (CBFV). *Ingestion of 355 mL water (black symbol) led to a marginal decrease in CBFV whereas the ingestion of an equivalent volume of the energy drink Red Bull (open circle) decreased CBFV by more than 12% (n=25).*

Additional interest touches the pathogenesis of postprandial and orthostatic hypotension and the countermeasures to prevent it. Finally, we aimed to understand the mechanisms by which a primary reduction in renal function may alter glucose and lipid homeostasis.

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Cardiovascular and cerebrovascular effects of energy drink consumption

Consumption of sugary drinks is associated with an increased cardiovascular risk. Energy drinks represent an important subcategory of caffeinated soft drinks and their popularity have increased substantially in the last 20 years, particularly among high school and university students.
In young healthy subjects, we tested whether the acute consumption of an energy drink (Red Bull) would affect hemodynamic variables and potentiate the cardiovascular responses to a mental stress test. Our results show that ingestion of a single can (355 mL) increases the workload to the heart and decreases cerebral blood flow velocity. Performing a mental arithmetic task imposes an additional cardiovascular load with higher absolute values of blood pressure and heart rate. Mental performance during the arithmetic test was not improved by the prior ingestion of the energy drink. Taken together, our data suggest that the acute ingestion of an energy drink results in an unfavourable cardiovascular profile, which could affect adversely people suffering from hypertension, heart failure and cerebrovascular diseases.

Effects of drinking temperature on the cardiovascular effects of water

Although humans prefer to drink water or soft drinks at colder temperatures, studies addressing the role of water temperature on cardiovascular and metabolic changes are scarce. To test the effects of cold drinks, we compared the cardiovascular and autonomic variables in response to cold- (3°C), room- (22°C) and body-tempered (37°C) tap water, and evaluated their potentially differential impacts on skin blood flow and resting energy expenditure (EE).

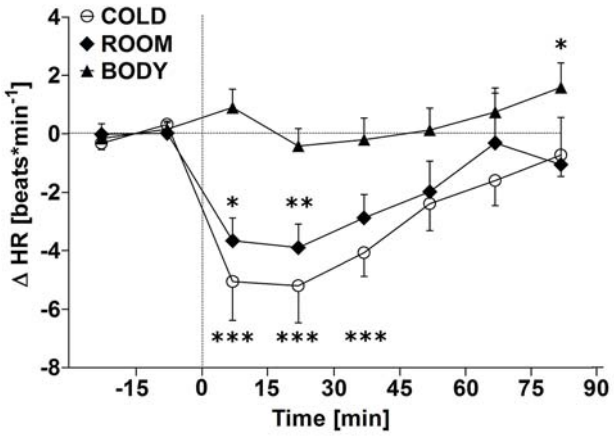

Fig.2 - Effect of water drinking temperature on heart rate (HR). *Cold water, and to some extent room-temperature water, led a significant decrease in HR.*

Ingestion of cold- and room-tempered water decreased heart rate (***Fig.2***) and increased stroke volume, heart rate variability and baroreflex sensitivity; these effects were not observed with body-tempered water. In addition, cold water increased EE over 90 min by ~3% accompanied by a diminished skin blood flow, thereby suggesting that both small increases in heat production together with decreased heat loss contribute to warming up the ingested water to intra-abdominal temperature levels. Overall, ingestion of cold- and room-, but not body-tempered water, reduced the workload to the heart through a reduction in heart rate, which could be mediated by an augmented cardiac vagal tone.

Mechanisms of postprandial hypotension and countermeasures to prevent it

An important consequence of ageing is the tendency for blood pressure (BP) to fall after eating a meal, often with a drop of more than 20 mmHg within 2 hours after the meal (postprandial hypotension). The most common symptoms of postprandial hypotension are dizziness and lightheadedness but syncope may also occur. We investigated in elderly individuals whether the prior ingestion of water before a breakfast would attenuate the decrease in BP.
After a stable cardiovascular baseline, twelve elderly (67 ± 1y) subjects ingested, in a crossover study design, either 100 mL or 500 mL of tap water, which was followed by a light breakfast meal (400 kcal). Eleven young (25 ± 1y) and healthy subjects served as a control group. In the elderly, but not in the young group, systolic and diastolic BP started to decline around 30 min after the meal, with the lowest values around 60 min. Drinking 500 mL of water attenuated significantly the drop in BP, and could thus serve as a useful countermeasure to attenuate postprandial hypotension.

Metabolic consequences of experimental uninephrectomy (NCCR project)

It is well known that metabolic diseases, obesity and diabetes lead to a progressive reduction in kidney function. Our aim is to test the converse, whereas a primary decrease in kidney function (as induced by uninephrectomy, UniNX) can alter whole body metabolism, leading to a potential vicious cycle in metabolic diseases. To that purpose, we studied rats before and after UniNx, analyzing body composition, plasma and tissue levels of metabolic and inflammatory markers, several weeks after surgery.
Compared to sham-operated animals, UniNX resulted in decreased body fat associated with evidence of increased lipolysis rather than with decreased fat synthesis. The increase in lipolysis could be related to mild fat sympathetic stimulation and to a low-grade inflammation of circulating cytokines such as interferon-gamma (IFNy) and granulocyte and macrophage colony stimulating factor (GM-CSF) from splenic origin. Since we can show increased IFNy-Receptor, GM-CSF-Receptor, and melanocortin 4 receptor (MC4R) mRNA levels in the hypothalamus, we hypothesize that IFNy and GM-CSF may act on brain areas to stimulate the MC4-R, which in turn may activate the sympathetic nervous system to promote lipolysis. ■

Selected Publications

Grasser EK, Yepuri G, Dulloo AG, ***Montani JP***
Cardio- and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. European Journal of Nutrition, 53(7):1561-1571, 2014

Grasser EK, Dulloo AG, ***Montani JP***
Cardiovascular responses to ingestion of sugary drinks using a randomised cross-over study design: does glucose attenuate the blood pressure-elevating effect of fructose? British Journal of Nutrition, 112(2):183-192, 2014

Girona M, Grasser EK, Dulloo AG, ***Montani JP***
Cardiovascular and metabolic responses to tap water ingestion in young humans: does the water temperature matter? Acta Physiologica (Oxford), 211(2):358-370, 2014

Grobéty B, Grasser EK, Yepuri G, Dulloo AG, ***Montani JP***
Postprandial hypotension in older adults: Can it be prevented by drinking water before the meal? Clinical Nutrition, 2014 doi: 10.1016/j.clnu.2014.09.009

Grasser EK, Dulloo AG, ***Montani JP***
Cardio- and Cerebrovascular Effects in Response to Red Bull Consumption Combined with Mental Stress. American Journal of Cardiology, 2014 doi: 10.1016/j.amjcard.2014.10.017

Franziska Theilig
Anatomy

The importance of renal proximal tubular function

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Proximal tubular water reabsorption

In the kidney, a huge amount of water and soluble substances pass the glomerular filtration barrier to subsequently being reduced to approximately one per cent by the tubular epithelium for urinary excretion. To maintain volume and blood pressure homeostasis the proximal tubule reabsorbs the highest amount of the primary ultrafiltrate of all nephron segments. The latter is established by a polarized transport system mirroring the terminal differentiation of epithelial cells. Aquaporins are small integral membrane proteins that function as molecular water channels in plasma membranes. Their permeability depends on the properties of the pore formed by the different channel isoforms and on their abundance within the cell membrane. Aquaporin-1 (AQP1) is expressed in various cell types including renal epithelial cells. In the proximal nephron, fluid reabsorption is primarily driven by transcellular transport of solutes, basolateral cycling of Na+, and the secondary movement of water via transcellular and paracellular pathways. High proximal tubular water permeability is thus tightly coupled to solute fluxes which make up approximately 60% of the reabsorption along the nephron. AQP1 is the major water channel of the proximal tubule. It is densely expressed in the brush border membrane (BBM) and also lines the basolateral membrane. Its exclusive role for transcellular osmotic water permeability has been demonstrated in AQP1-deficient mice. The high abundance of AQP1 in the BBM and especially its insensitivity to vasopressin indicated a constitutive expression mode. It has, however, been established that the proximal tubule adapts rapidly to changes in electrolyte and fluid reabsorption to either prevent loss or retain sodium and water during variations of glomerular filtration rate (GFR). The direct positive effect of tubular flow rate on tubular reabsorption at short term has been referred to as the glomerulo-tubular balance (GTB). Based on studies using micropuncture and microperfused proximal tubules, GTB has been defined as part of a feedback system that maintains a constant fractional reabsorption. GTB is in part related with the major luminal sodium transporter of the proximal tubule, Na+/H+-exchanger- 3 (NHE3). Tubular fluid shear stress (FSS), caused by increased flow, was shown to augment transport activity of NHE3 at short term. Less is known about the regulation of AQP1.

We hypothesized that the surface expression of AQP1 is regulated by fluid shear stress, contributing to GTB. Consistent with this, we found that the abundance of AQP1 in brush border and apical membranes was augmented >2 fold, after 15 minutes, by increasing luminal perfusion rates in isolated, microperfused proximal tubules. This implied rapid adaptation in AQP1 surface expression, involving changes in trafficking, endocytosis, protein stability, and transmembrane water permeability. We found that AQP1 surface expression was dependent on an intact endocytic apparatus, as kidneys with a conditional deletion of megalin or the choride channel, ClC-5, had constitutively enhanced AQP1 abundance in the proximal tubule brush border membrane. In AQP1-transfected, cultured proximal tubule cells, fluid shear stress as well as the addition of cyclic nucleotides enhanced AQP1 surface expression and concomitantly diminished its ubiquitination, pointing to increased protein stability. These effects were also associated with an elevated osmotic water permeability. In sum, we have demonstrated that luminal surface expression of AQP1 in the proximal tubule brush border membrane is regulated in response to flow. Cellular trafficking, endocytosis, an intact endosomal compartment, and controlled stability are the likely prerequisites for AQP1's activation by enhanced tubular fluid shear stress, serving to maintain glomerulotubular balance.

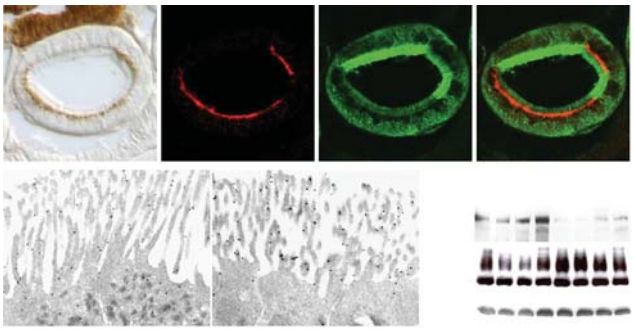

Fig.1 - Renal AQP1 distribution in mice with partial deficiency of megalin. *(A) Triple-labeling immunohistochemistry showing complementary patterns of AQP1 BBM signal and endocytosis in the S2 proximal tubule with mosaic deficiency of megalin ($Lrp2^{fl/fl}$; $apoE^{Cre}$ conditional megalin knockout), with HRP marking intact endocytosis (dark brown signal; 5 minutes after injection), megalin (red immunofluorescence), AQP1 (green immunofluorescence), and the respective merge image. Boundaries between megalin-positive and megalin-deficient cells are indicated by black and white bars. (B) AQP1 immunogold staining shows balanced expression in the BBM and subapical compartment of megalin-expressing cells identified by an intact endosomal apparatus. (C) AQP1 signal is absent from the subapical compartment but enhanced in the BBM of megalin-deficient cells, displaying a reduced endosomal apparatus. (D) Representative Western blots of megalin, AQP1, and b-actin as loading controls in BBM preparations from control versus conditional megalin knockout mouse kidneys.*

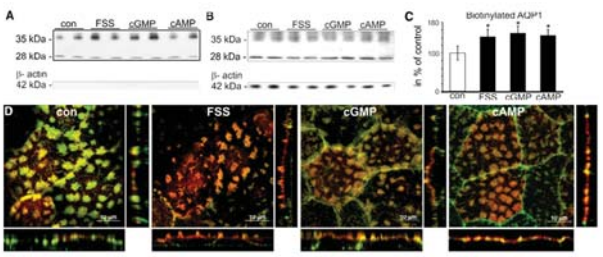

Fig.2 - Experimentally induced redistribution of AQP1 in cultured proximal tubule cells. *OKC cells stably transfected with rat AQP1 cDNA (AQP1-OKC) were evaluated. (A–C) To show cell luminal expression of AQP1 by surface* ▸▸

*biotinylation and streptavidin-based immunoprecipitation techniques, immunoblotting of (A) biotinylated and (B) nonbiotinylated fractions is shown in controls (con), on induction of FSS (1 hour; <2 dynes/cm²), and after addition of cGMP or cAMP (8-bromo-cGMP and 8-bromo-cAMP, respectively; each 100 mmol for 1 hour); b-actin bands serve as loading controls. Representative duplicates are shown. (C) Densitometric evaluation of the biotinylated fractions shows increases of cell surface-expressed AQP1 in the experimental conditions; the nonbiotinylated intracellular fractions reveal no changes. (D) Immunohistochemical analysis of AQP1-OKC showing AQP1 (red signal) and actin (green signal) immunofluorescence; apical microvilli, typically occurring as clusters, display merged signals with a red shift in the experimental conditions. Values are means ±SDs from n=12 independent experiments. *P<0.001.*

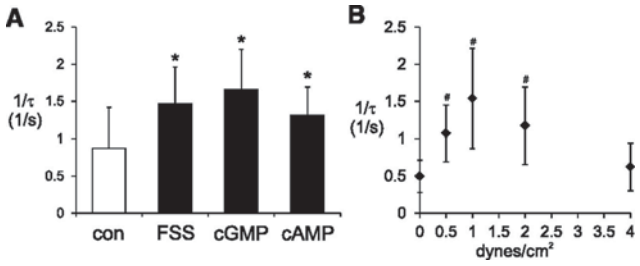

Fig.3 - Osmotic water permeability in cultured proximal tubule cells. *Osmotic cell swelling rates of AQP1-OKCs are shown in response to orbital FSS (1 hour; <2 dynes/cm²) or addition of cGMP or cAMP (8-bromo-cGMP and 8-bromo-cAMP, respectively; each 100 mmol for 1 hour) to show changes in osmotic water permeability. The calcein fluorescence quenching method was applied; the magnitude of change in calcein fluorescence is presented as reciprocal exponential time constants (1/t) and corresponds to cell expansion in response to reduced solution osmolality. (A) Calcein loaded cells show changes in calcein fluorescence on all three experimental conditions. (B) Cells grown in flow chambers were calcein loaded, and increasing intensities of laminar FSS were applied for 1 hour. Controls: no treatment (con) or 0 dyne/cm²; values are means±SDs from n=6 and n=5 independent experiments in each condition, respectively. *P<0.05 versus #P<0.005.*

Proximal tubular endocytosis

The proximal tubule is also the main localization for the reabsorption of filtered proteins. This central function is almost exclusively accomplished by the receptor-mediated endocytosis for maintaining serum protein concentration and to impede urinary loss of important body proteins. More than 80 per cent of all plasma proteins, including albumin or low molecular weight proteins, f.e. vitamin binding proteins and hormones, are reabsorbed by receptor-mediated endocytosis and delivered to the body circulation to maintain extracellular body homeostasis and vitamin- and hormone metabolism. A global dysfunction of all proximal tubular transport processes are described as renal Fanconi-Syndrom, which can lead to dehydration, rachitis, amyosthenia, growth retardation and finally also to progressive renal failure. The receptor-mediated endocytosis uses multi-ligand receptors such as megalin and cubilin, which are abundantly expressed in the brush border membrane of the proximal tubule. Both can interact and partly function as co-receptors. Megalin is a glycoprotein of ~600 kDa belonging to the low-density lipoprotein (LDL)-receptor family. In the proximal tubule it is predominantly encountered in clathrin-coated pits, endosomes and in microvilli of the brush border membrane. Megalin possesses a large extracellular domain consisting of 4 agglomerations of ligand binding domains, followed by a transmembrane segment and an intracellular cytoplasmic portion of 209 amino acids. The cytoplasmic portion contains two motifs for endocytosis, one motif for apical sorting and several phosphorylation sites.4 Mutation in the megalin gene is known to lead to the Donnai-Barrow/ Facio-Oculo-Acustico-renal syndrome. Megalin interacts with several molecules of the apical membrane and in the cytoplasm. Cubilin, a ~460 kDa large glycoprotein without a transmembrane domain, is interacting with megalin to ensure its own endocytosis. It is responsible for the reabsorption of various proteins, including intrinsic factor, albumin and transferrin. A genetic defect within the gene encoding for cubilin is leading to hereditary megaloblastic anemia or Immerslund-Graesbeck syndrome. Binding of a ligand to megalin and/ or cubilin results in internalization of the ligand-receptor-complex into clathrin-coated vesicles. For delivery to the endosomal-lysosomal pathway and further processing, recycling or degradation of proteins, clathrin-coated vesicles are transported anterograde along microtubules to fuse with early endosomes. Luminal acidification of endosomes facilitates the dissociation of ligands from its receptor, ligand processing, receptor recycling or degradation and vesicles trafficking and fusion to late endosomes and lysosomes. In proximal tubular cells endosomal acidification is accomplished by the vacuolar H+-ATPase (V-ATPase) and the counter current for the establishment of electron neutrality by the chloride channel-5, ClC-5. Loss of function of ClC-5 by a mutation in the CLCN5 gene is leading to the Dent's disease with renal tubular dysfunction which is characterized by a low-molecular weight proteinuria, hypercalcuria and nephrolithiasis. Additionally, hyperphosphaturia and consecutive hypophosphatemia followed by rachitis formation is frequently observed. Finally, this may induce renal failure. Additionally to the pathological changes occurring in genetic defects of endocytosis components, systemic and renal diseases, such as sepsis, diabetes, acute renal failure and proteinuric kidney diseases affect proximal tubular endocytosis. In a rat model for type 1 diabetes mellitus is was shown that the early occurring microalbuminuria does not result from increased glomerular permeability but is rather connected to proximal tubular endocytosis dysfunction. Similarly, lipopolysaccharide (LPS)-induced sepsis is leading to reduced megalin and cubilin mRNA with consecutively diminished proximal tubular albumin endocytosis which seems to be partially responsible for the appearance of hypoalbuminemia. The acute renal

failure is taking a double-tracked position. On the one hand, acute renal failure can be induced by the megalin-mediated exceeding uptake of nephrotoxins and heme complexes known to lead to cell stress and apoptosis, on the other hand megalin mediates the endocytosis of reno-protective proteins, such as neutrophil-gelatinase-associated Lipocalin, L-FABP, clusterin and surviving. In acute renal failure megalin mRNA expression was demonstrated to be reduced protecting thereby the proximal tubule for nephrotoxin-induced cell stress. In the later phase of acute renal failure, megalin expression increases which helps cells to recover by the uptake of proteins inducing an antiapoptotic or proliferative pathway. Although it is now widely established that the megalin expression level and therefore the endocytosis rate changes upon various diseases, less is known about the control of its expression level and its cell surface abundance. Possible regulation points include the regulation of transcription, protein synthesis and stability and trafficking towards and from the cell surface.

mTORC1 und -2 induced effects on proximal tubular endocytosis

Inducible conditional transgenic mice Raptor$^{fl/fl}$; Pax8^{Cre}, Rictor$^{fl/fl}$; Pax8^{Cre}, and Raptor$^{fl/fl}$/Rictor$^{fl/fl}$; Pax8^{Cre} for a tubular deletion of raptor (a component of the mTORC1 complex), rictor (component of the mTORC2 complex) and both proteins together were analyzed. We could demonstrate a reduced albumin endocytosis occurring in the Raptor$^{fl/fl}$; Pax8^{Cre} and Raptor$^{fl/fl}$/Rictor$^{fl/fl}$; Pax8^{Cre}, which may result from impaired membrane trafficking. This work is still in progress and more details will be presented in future. ■

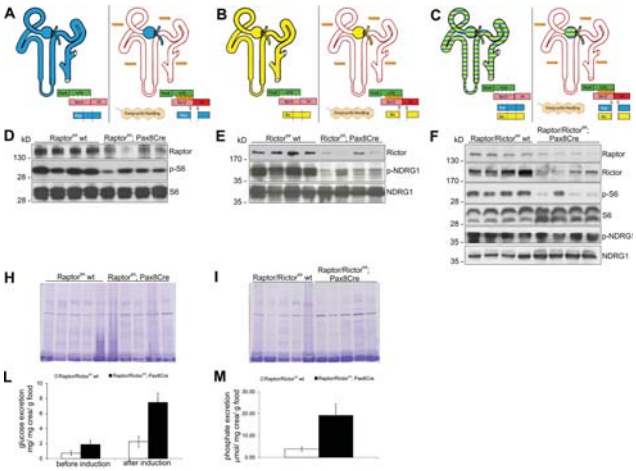

Fig.4 - Tubular cell-specific mTORC1 and mTORC1 and -2 deletions lead to albuminuria and mTORC1 and -2 deletions to glucosuria and phosphaturia. *(A - C) Schematic of the recombination strategy and site of the Pax8^{Cre}-mediated Raptor (A), Rictor (B) and double (C) knockout within the tubular system. (D – F) Proof of knockout by western blot of raptor and downstream target p-S6P in mTORC1 knockout (Raptor$^{fl/fl}$; Pax8^{Cre}, D), of rictor and the downstream target p-NDRG1 in mTORC2 knockout (Rictor$^{fl/fl}$; Pax8^{Cre}, E) and of raptor, rictor and downstream targets p-S6P and p-NDRG1 in mTORC1 and -2 double mutants (Raptor/Rictor$^{fl/fl}$; Pax8^{Cre}, F). (H – I) Coomassie staining of SDS-Page prepared from urine samples from mTORC1 knockout (H) and double mutants (I). (L – M) Urinary glucose and phosphate excretion from double mutants.*

Selected Publications

Pohl M, Shan Q, Petsch T, Styp-Rekowska B, Matthey P, Bleich M, Bachmann S, ***Theilig F***
Short-Term Functional Adaptation of Aquaporin-1 Surface Expression in the Proximal Tubule, a Component of Glomerulotubular Balance. J Am Soc Nephrol. Sep 30, 2014

Zhihong Yang
Physiology

Cardiovascular and aging research

INTRODUCTION

Aging and age-associated diseases including cardiovascular disease, type-II diabetes, chronic kidney disease, and cancer represent the great challenge in our society, due to the global accelerating aging population. Oxidative stress, vascular endothelial dysfunction, and inflammation have been evidently shown to be the important mechanisms underlying organism aging and age-associated diseases. Our previous research demonstrated the importance of the enzyme arginase-II (Arg-II) and a crosstalk of this enzyme with mTORC1/S6K signaling pathway in vascular dysfunctions and macrophage pro-inflammatory responses in atherosclerosis, diet-induced obesity, and aging. Our research in 2013 and 2014 further explored the function of these enzymes in vascular cell dysfunction, including senescence, apoptosis, and impairment of autophagy functions.

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L-arginine-ureahydrolase activity-independent functions of Arg-II in activation of mTORC1-S6K1 in vascular smooth muscle cells (SMCs), contributing to vulnerability of atherosclerotic plaque.

As mentioned, our previous study demonstrated a positive crosstalk between mTORC1/S6K1 and Arg-II in vascular aging. To further investigate whether Arg-II exerts certain biological effects independently of eNOS, human umbilical vein smooth muscle cells (SMCs) were used. Western blot analysis reveals no expression of eNOS or iNOS in the SMCs. No NO production is detectable in these cells. The effect of ectopically expressed Arg-II in the SMCs is thus attributable to its effects independently of NOS. With SMCs, we for the first time provide firm evidence showing that Arg-II has dual opposing functions, i.e., Arg-II on one hand promotes SMC proliferation which is dependent on its L-arginine-ureahydrolase activity, most likely due to polyamine generation. On the other hand, Arg-II also promotes mitochondrial H2O2 generation through parallel activation of S6K1-p66Shc and p53, which is independent on its enzymatic activity. This latter mechanism involves a positive and complex crosstalk between Arg-II, S6K1, JNK, ERK and p66Shc in senescent cells, leading to SMC senescence and apoptosis in atherosclerotic plaques in mouse models. The mechanisms are illustrated in ***Fig.1*** shown below.

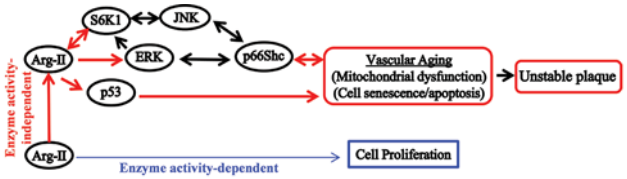

Fig.1 - Enzyme activity-dependent and -independent functions of Arg-II in VSMC. *Elevated Arg-II under pathological conditions exhibits dual opposing functions in promoting SMC proliferation and senescence/apoptosis through different mechanisms. While it promotes SMC proliferation in an enzymatic activity-dependent manner (in blue), it induces H2O2 generation, mitochondrial dysfunction and senescence/apoptosis through activation of the parallel pathways consisting of Arg-II–S6K1–JNK-p66Shc, Arg-II-ERK-p66Shc and Arg-II-p53 independently of its L-arginine ureahydrolase activity (in red), contributing to atherosclerotic plaque instability. Moreover, in senescent SMC, Arg-II, S6K1, JNK, ERK and p66Shc form a complex positive crosstalk network resulting in acceleration of SMC aging.*

L-arginine-ureahydrolase activity-independent functions of Arg-II impairs endothelial autophagy through regulation of mTORC2-Akt-mTORC1-S6K1 and AMPK signaling in advanced atherosclerosis

The L-arginine-ureahydrolase activity-independent function of Arg-II is also observed in endothelial cells in atherosclerotic mouse models. Impaired function of autophagy, a self-cleaning and repairing mechanism of cells under ▸▸

stress conditions, is believed to be implicated in vascular aging and atherosclerosis. Given that mTORC1 suppresses autophagy and that Arg-II-mTORC1 form a positive regulatory circuit, we investigated the role of Arg-II and the potential underlying mechanism(s) in modulation of endothelial autophagy. Using human non-senescent «young» and replicative senescent endothelial cells as well as ApoE$^{-/-}$Ar-II$^{+/+}$ and ApoE$^{-/-}$Arg-II$^{-/-}$ mice fed high fat diet for 10 weeks as the atherosclerotic animal model, we demonstrate that Arg-II impairs endothelial autophagy independently of the L-arginine ureahydrolase activity through activation of S6K1 signaling and inhibition of AMPK, which is implicated in advanced atherosclerotic lesion formation. Moreover, we show in this study that Arg-II positively regulate mTORC1-S6K1 at least in part through activation of mTORC2-Akt (***Fig.2***).

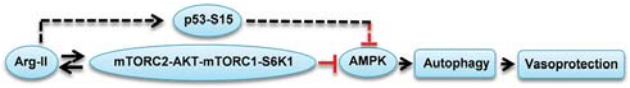

Fig.2 - Schematic summary of the endothelial autophagy inhibition by Arg-II. *A feed-forward crosstalk between elevated Arg-II expression and rictor activates mTORC2-Akt-mTORC1-S6K1 signaling cascade which leads to inhibition of AMPK and subsequently inhibition of endothelial autophagy in senescent endothelial cells. Arg-II can also activate p53 pathway in parallel with mTOR signaling, resulting in inhibition of AMPK and suppression of autophagy. Arg-II exerts these effects independently of its L-arginine ureahydrolase activity. The reduced AMPK activation by Arg-II results in impairment of endothelial autophagy and acceleration of endothelial senescence and atherosclerosis.*

Long term exposure to L-arginine accelerates endothelial senescence through Arg-II and S6K1 signaling.

Acute L-arginine supplementation has shown to be able to increase endothelial NO production. Chronic L-arginine supplementation in patients with cardiovascular disease, however, causes decreased endothelial function and even enhanced mortality rate. The underlying mechanisms are not known. Our most recent study has provided evidence in vitro demonstrating that chronic L-arginine supplementation in cultured endothelial cells causes cell senescence associated with eNOS-uncoupling through up-regulation of Arg-II, which involves activation of mTORC-S6K1 signaling. This finding of in vitro experiments may provide the mechanistic explanation for the adverse effects of chronic L-arginine supplementation therapy in patients and will also alert our society being cautious of using L-arginine as food supplementation to boost health status. ■

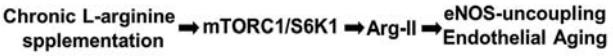

Fig.3 - Chronic L-arginine supplementation activates mTORC1/S6K1-Arg-II, leading to eNOS-uncoupling and endothelial aging

Selected Publications

*Xiong Y, Yu Y, Montani JP, **Yang Z**, Ming XF*
Arginase-II Induces Vascular Smooth Muscle Cell Senescence and Apoptosis Through p66Shc and p53 Independently of Its L-Arginine Ureahydrolase Activity: Implications for Atherosclerotic Plaque Vulnerability. J Am Heart Assoc. 2013 Jul 5;2(4):e000096. doi: 10.1161/JAHA.113.000096

*Xiong Y, Forbiteh Fru M, Yu Y, Montani J-P, Ming X-F, **Yang Z***
Long term exposure to L-arginine accelerates endothelial cell senescence through arginase-II and S6K1 signaling. Aging. 2014;6:369-379

*Xiong Y, Yepuri G, Forbiteh M, Yu Y, Montani J-P, **Yang Z**, Ming X-F*
ARG2 impairs endothelial autophagy through regulation of MTOR and PRKAA/AMPK signaling in advanced atherosclerosis. Autophagy 2014;10(12):2223-38

Neurosciences Understanding the brain requires the integration of theoretical and experimental approaches at many different level of analysis, ranging from molecular approaches focusing on the role of particular signaling pathways to sophisticated analyses of behavior and underlying brain processes using neuroimaging methods. This diversity is reflected in the research of the Neuroscience cluster. Work is conducted in both humans and relevant animal models, with particular effort also being expended for translating findings from animal models to improve understanding of mental and degenerative disorders in humans. The neuroscience cluster is fostering collaborative work between research groups within the department of medicine, but also with other departments through the Fribourg Center for Cognition. It is noteworthy that several newly established groups are now beginning to produce exciting scientific output, substantially expanding the scope of research topics and methods in the neuroscience cluster. Capitalizing and reinforcing existing strengths of the Neuroscience cluster, as well as intensifying interdisciplinary and collaborative work are expected to further improve the visibility of Neuroscience research at the national and international levels.

Lavinia Albéri
Notch signaling in neuronal plasticity and neurodegeneration

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Laboratory for cognitive and neurological sciences

Jean-Pierre Bresciani
Perception and control of movement

Marco Celio
Prof. Celio declined to contribute to the scientific report

Pierre Lavenex
Laboratory of brain and cognitive development

Marco Merlo
Neurophysiology of cognitive and emotional functions as well as decision-taking in normal subjects and psychiatric patients

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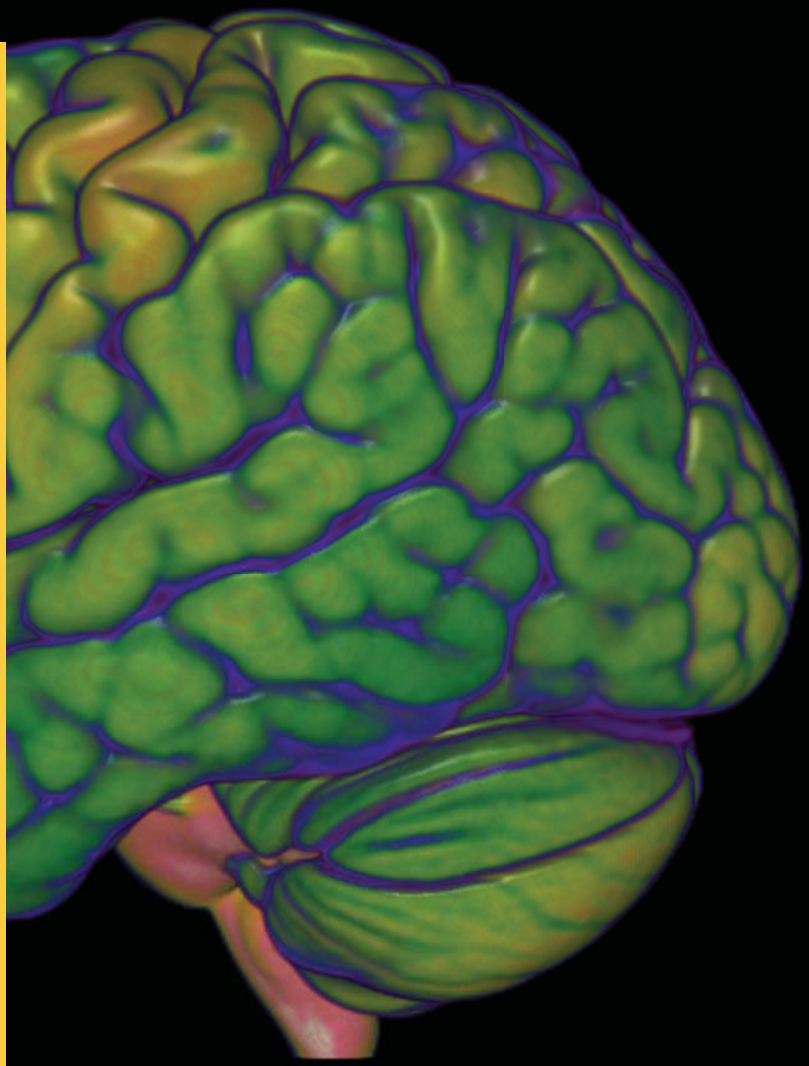
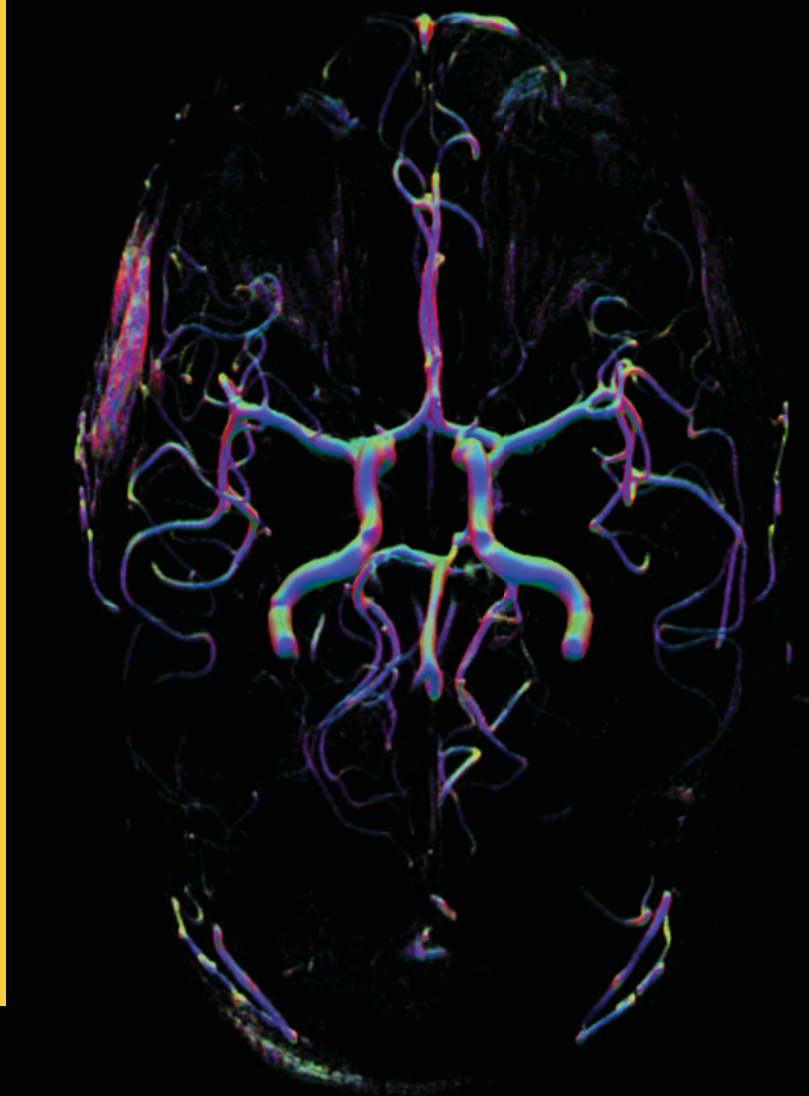
Beat Schwaller
Calcium signaling in health and disease

Wolfgang Taube
Motor control and motor learning





Lavinia Albéri
Neuroanatomy and Electrophysiology
Notch signaling in neuronal plasticity and neurodegeneration

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INTRODUCTION

The research in our group focuses on understanding the molecular mechanisms underlying Notch signaling in the mature brain in memory/sensory processing as well as in neurodegeneration. Our research focuses on molecular/cellular and signaling neuroscience, but takes advantage also of behavioral, *in vivo* viral injections (***Fig.1***) and neurophysiological techniques. In addition, we have developed several unique mouse models to address the implication of different Notch signaling components in the mature brain.

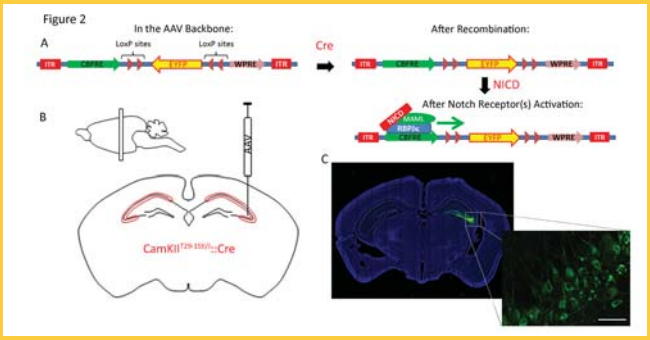

Fig.1 - Intrahippocampal viral injection of a cell specific Notch responsive construct. *A) Strategy of the cre/flox recombination used to obtain a cell specific Notch reporter. B) Drawing of mouse brain section at which the injection is performed. The red lining indicates the CA region where cre is expressed in the CamKIIT29-1Stl/J.::Cre mouse line. C) One week after injection, in response to endogenous Notch activity, EYFP is expressed specifically in hippocampal CA3. Scale bar in C is 25 µm. From Marathe et al., Methods Mol Biol. 2014*

In the past year, we have focused on five main projects:

1) Notch and Reelin crosstalk in neurons

2) Nuclear Notch/RBPJK signaling in brain injury

3) Role of Notch signaling in olfactory behavior

4) Jagged1: is it a novel synaptic modulator?

5) Genome-wide screen of Notch targets in neurons

1. Notch and Reelin crosstalk in neurons

In this project, we aim to understand whether Notch, APP& Reelin represent a molecular complex that synergize in modulating synaptic plasticity. We have recently observed that the Reelin receptor, ApoER2, is functionally associated with Notch and, in Notch1cKO hippocampi, Reelin signaling is reduced. More recent experiments have assessed that Reelin signals through Notch to regulate synaptic plasticity. This project is carried out in collaboration with Dr. Simone Astori at the University of Lausanne.

2. Nuclear Notch/RBPJK signaling in brain injury

Erroneous cell cycle reentry is hypothesized to play a causative role in neurodegeneration. We show that forcing S-phase reentry in cultured hippocampal neurons is sufficient to induce neurodegeneration. We found that kainic-acid treatment in vivo induces erroneous cell cycle reentry and neuronal death through a Notch-dependent mechanism. Ablating transcriptional Notch-signaling in neurons provides neuroprotection against kainic-acid induced neuronal death (***Fig.2***). We further observed that kainic-acid treatment activates Notch signaling, which increases bioavailability of CyclinD1 through Akt/GSK3β pathway, leading to aberrant cell cycle reentry via activation of CyclinD1-Rb-E2F1 axis. In addition, pharmacological blockade of this pathway at critical steps is sufficient to confer resistance to kainic-acid induced neurotoxicity in mice. Taken together, our results demonstrate that excitotoxicity leads to neuronal death in a Notch dependent manner through erroneous cell cycle reentry. This project has been carried out in collaboration with Dr. Shuxi Liu at the National Institute of Heath, Bethesda (USA).

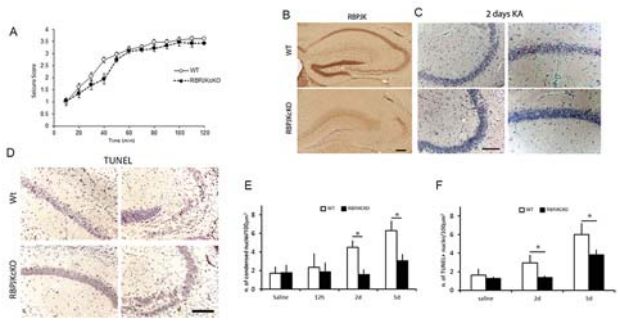

Fig.2 - RBPJKcKO mice display significant neuroprotection in response to KA. *A) Graph summarizing the time course of seizure in WT and RBPJKcKO mice within the 120 minutes of observation (n=15 mice per genotype). B) Immunohistochemistry for RBPJK shows targeted ablation of RBPJK expression in CA1, CA3 fields in the RBPJKcKO as compared to WT. C) Representative Hematoxylin Eosin staining on hippocampal sections from WT and RBPJKcKO mice in CA1 and CA3 layers. D) Representative images of TUNEL staining in WT and RBPJkcKO CA1 and CA3 fields. E) Graph summarizing counts of condensed cells, on HE stainings, in Wt and RBPJKcKO at 12 hours, 2 and 5 days following KA systemic challenge as compared to Saline controls (n=5 mice per genotype per condition). F) Graph summarizing counts of TUNEL positive nuclei in WT and RBPJKcKO 2 and 5 days following KA administration as compared to Saline controls (n=3 mice per genotype per condition). Asterisks indicate significant differences. Error bars represent ± SEM. Scale bar in B-D is 200 µm.*

3. Role of Notch signaling in olfactory behavior

Notch signaling plays an important role in synaptic plasticity, learning and memory functions both in Drosophila and rodents. In this paper, we report that this feature is not restricted to hippocampal networks but also interests the olfactory bulb (OB). Odor discrimination and olfactory learning in rodents are essential for survival. Notch1 expression is enriched in mitral cells of the mouse OB. These principal neurons are responsive to specific input odorants and relay the signal to the olfactory cortex. Olfactory stimulation activates a subset of mitral cells, which show increase in Notch activity. In Notch1cKOKln mice, the loss of Notch1 in mitral cells affects the magnitude of the neuronal response to olfactory stimuli (***Fig.3***). In addition, Notch1cKOKln mice display reduced olfactory aversion to propionic acid as compared to wildtype controls. This indicates, for the first time, that Notch1 is involved in olfactory processing and may contribute to olfactory behavior (Brai et al. 2014). This project has been carried out in collaboration with Dr. Lorena Zentilin and Prof. Mauro Giacca at the ICGEB in Trieste (Italy) and Prof. Johannes Nimpf at Max Perutz Laboratories in Vienna (Austria).

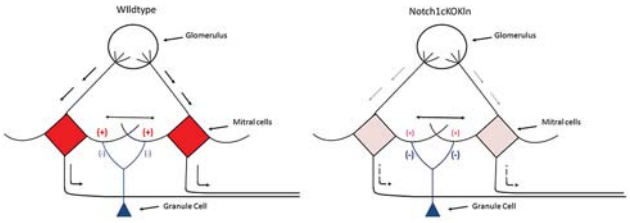

Fig.3 - Schematic illustration of the effect of Notch1 loss on olfactory processing. Notch1 positive mitral cells (red) project their primary dendrites to a glomerulus, their long axon to cortical structures. Their secondary dendrites are contacted by reciprocal synapses of granule cells (blue), in addition mitral cells are connected via gap junctions (mitral neurites junction).In wildtypes, when an odor is applied, odorant input is transmitted to mitral cells (descending arrows) and Notch activity is induced. In response to the strong depolarization, mitral cells activate (bold positive signs) granule cells which, in turn, by feedback inhibition (light negative signs), synchronize mitral cells firing (bidirectional arrow) and determine signal discrimination and olfactory behavior (arrows along the mitral cell axon). When Notch1 expression is strongly reduced (pale red), as in the Notch1cKOKln, the spontaneous as well as the evoked activity of mitral cells is reduced (light positive signs). In the same model, feedback ▸▸

inhibition is increased (negative signs) leading to increase in synchronous firing (thicker bidirectional arrow) and dampening the odor - evoked responses. This may result in a compensatory effect on the outgoing signal which can lead to a partial olfactory defect (broken arrows along the mitral cell axon). From Brai et al., Eur J Neurosci. 2014.

4. Jagged1: is it a novel synaptic modulator?

Jagged1 is a cognate ligand of Notch and it is essential for proper signaling. We have observed that Jagged is expressed both in neurons and in glia cells and that it can be released to interact with Notch. We have obtained two loss of function mouse models for Jagged1 in neurons and glia to address whether glial or neuronal-born can act as a synaptic modulator through Notch signaling. This project is carried out in collaboration with Prof. Jozsef Csicsvari at the Institute for Science and Technology, Vienna (Austria).

5. Genome-wide screen of Notch targets in neurons

Notch signaling is a highly conserved molecular cascade, which plays an essential role in neuronal development. Growing evidence indicates that the same cascade is crucial also in mature brain function. Notch-mediated signaling pathways have been implicated in several brain dysfunctions such as Alzheimer's disease and Stroke. This functional dichotomy indicates a critical and complex balance between physiological and non-physiological signaling that might be instrumental in neurodegenerative diseases. Nevertheless, at present, the relevant targets of Notch in neurons remain largely unexplored. We have collected the hippocampus from wildtype and Notch mutant mice exposed to enriched environment, which strengthen synaptic connections, mice, which underwent kainate injury, and cage control animals. The tissue has been employed to perform a genome-wide screen of Notch gene targets in neurons. We believe that this research will bring to light relevant Notch targets in neurons that may determine the balance between physiological and pathological signaling. This project is carried out in collaboration with the Genome facility of the University of Bern, the EMBL Heidelberg (Germany) and Dr. Kyuson Yu at the Jackson Laboratories (USA). ■

Selected Publications

***Albéri L**, Hoey S, Brai E, Scotti A, Marathe S*
Notch signaling in the brain: In good and bad times. Ageing Res Rev. 2013 Jun; 12(3):801-14

Alberi L
Asthma a clinical condition for brain health. Exp Neurol. 2013 Oct; 248:338-42

*Schnell A, Chappuis S, Schmutz I, Brai E, Ripperger JA, Schaad O, Welzl H, Descombes P, **Albéri L**, Albrecht U*
The nuclear receptor REV-ERBα regulates Fabp7 and modulates adult hippocampal neurogenesis. PLoS One. 2014 Jun 16;9(6):e99883

*Brai E, Marathe S, Zentilin L, Giacca M, Nimpf J, Klein R, Kretz R, Scotti A, **Albéri L***
Notch1 activity in mitral cells is odor dependent and contributes to olfactory behavior. Eur J Neurosci. 2014 Sep 19. doi: 10.1111/ejn.12719

*Marathe S, **Albéri L***
Monitoring notch activity in the mouse. Methods Mol Biol. 2014;1187:115-29. doi: 10.1007/978-1-4939-1139-4_9

Jean-Marie Annoni
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Laboratory for cognitive and neurological sciences

INTRODUCTION

Jean-Marie ANNONI

The healthy bilingual brain (JM Annoni & L Spierer)

After having examined how the bilingual brain selects one or another language, our current research on the bilingual brain focuses on how the linguistic constrains of each language modulate eye movement patterns and electrical brain activity, as biomarkers of language strategies. This line of research aims at demonstrating the adaptive abilities of the brain to the language mode in which we are engaged.

The clinical bilingual brain (JM Annoni)

In our clinical studies, we had two major focuses:

1) To identify how first and second languages resist to neurological diseases (essentially neurodegenerative disorders and strokes) and to develop predictors of language recovery of the first and second language, whether spontaneously or through therapy -this having a direct impact on rehabilitation strategies

2) To understand how cognitive and affective changes, as well as other factors such as fatigue, associated with neurological diseases (mainly multiple sclerosis and stroke) modify patients' behaviour, particularly decision-making patterns, capacity of initiating activities and social cognition, in order to improve the follow-up and outcomes of neurological patients.

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▸▸

INTRODUCTION

Lucas SPIERER

1) Can executive functions training reshape the functional and structural architecture of the frontal lobe?

In our previous research we have established the optimal training parameters to improve frontal executive functions. On this basis, we have now focused on the functional and microstructural effects of extensive executive function training on the brain. We have shown that i) weeks of training not only improves the functional efficiency of the brain networks involved in our ability to supress ongoing actions or thoughts (namely, inhibitory control), but also modify grey and white matter structure; ii) years of intensive practice of complex daily activities relying strongly on inhibitory control indirectly yields functional and structural changes in frontal executive networks matching those induced by our training regimens; and iii) specific patterns of training-induced plasticity manifest within the 'hot' executive function system, i.e. when the training involves the reward and motivational systems. Plastic changes are indeed hindered when participants are trained to inhibit their responses to rewarding stimuli such as hedonic food.

2) Do variations in the difficulty levels of executive tasks induce qualitative changes in the supporting brain networks?

With electrical neuroimaging and anatomo-clinical correlations in brain-damaged patients, we have respectively examined whether qualitatively different brain networks are involved in inhibitory control tasks differ when the difficulty of the tasks increases. Resolving these issues we eventually help optimizing the diagnosis and the rehabilitation of frontal patients.

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▶ Jean-Marie ANNONI

Using behavioural, ERP and fMRI studies on bilinguals, we have demonstrated the following points: 1) Language selection is achieved through a neural network involving areas supporting both general cognitive processes and language processing; 2) Language control processes recruit specific parts of the left caudate and the anterior cingulate cortex (ACC); 3) Switching into a less-proficient language necessitates controlled processing resources and irregular switches engage brain structures involved in syntactic and phonological processing; 4) Second language proficiency influences the selection of the first language; 5) The neural substrates involved in the processing of semantic information are independent on the second language proficiency; 6) Reading strategies depend on language proficiency and on the orthographic depth of the used language.

Concerning the last finding, recent studies from our group have brought insights into the neural underpinnings of orthographic regularity processing. Our findings on measures of brain electrical activity and eye movements patterns of bilingual readers in each language complement current literature on reading processing and support the orthographic depth hypothesis (Katz and Feldman, 1983), by showing that not only the lexicality/familiarity of a stimulus, but also its orthographic regularity may modulate the engagement of different reading routes.
In a second clinical work, we analyzed the effect of Phonological therapy in a bilingual aphasic patient with distant languages (Farsi /French) and showed that phonological training in the second language did not transfer to the untreated language, but participated in the global improvement of the language performances and that the therapy modified the brain networks engaged during the phonological processing steps during naming only in the trained language.

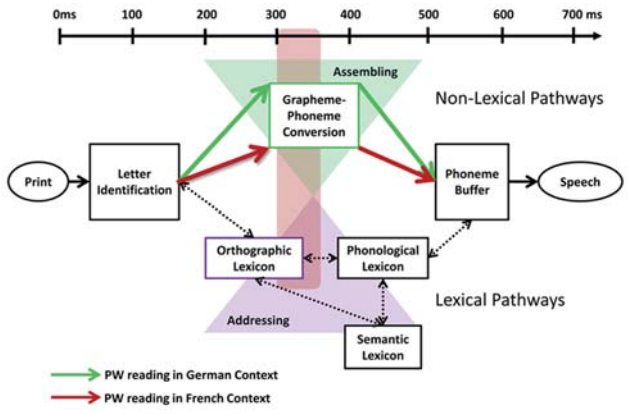

Fig.1

The other clinical studies investigated the pattern of movement impairment and its recovery after disconnection on SMA-basal ganglia following a minor stroke. Our published results suggest that SMA-basal ganglia disconnection decreases contralateral movement initiation and maintenance and this effect is partly compensated by visual cues. Extending our data in a general initiation behavior, Apathy, a motivational disorder defined as a reduction of goal-directed behaviors, we investigate the relationships between self-reported apathy, reward sensitivity and neuroanatomical substrates of 55 minor stroke patients. We found that poor reward sensitivity in stroke patients with damage to the right basal ganglia and the thalamus constitutes a core feature of apathy.

Decision making (DM) was tested in relapsing-remitting and progressive Multiple Sclerosis under explicit risk conditions (in which decisions have to be made in the presence of explicit information about the potential consequences of the choice). We found that the reduction in the expression of regret resembles previous results observed after orbitofrontal lesions, but coexisted with an absence of risk taking and an increased risk aversion. Such results suggest that MS may modify the quality of DM by decreasing implicit and explicit response. ■

Fig.1 - The orthographic depth hypothesis by Katz and Feldman (1983) posits that different reading routes are engaged depending on the type of grapheme/phoneme correspondence of the language being read. *Shallow orthographies with consistent grapheme/phoneme correspondences favor encoding via non-lexical pathways (assembled reading; green triangle), where each phoneme is sequentially mapped to its corresponding grapheme. In contrast, deep orthographies with inconsistent grapheme/phoneme correspondences favor lexical pathways (addressed reading; violet triangle), where phonemes are retrieved from memory structures. With regard to this framework, we propose that the topographic effects 300–360 ms after stimulus onset (red square) reflect a modulation of the routine non-lexical pathways in PW reading by the stronger recruitment of lexical pathways in the deep than shallow language context. Reading in a shallow context activates the non-lexical pathways more strongly than reading in the deep context, which reinforces the non-lexical processing routinely recruited in pseudoword (PW) reading (green arrows). In contrast, reading in a deep context activates the lexical pathways more strongly than the shallow context, which reduces the engagement of the non-lexical pathways routinely recruited in PW reading (red arrows).* ▸▸

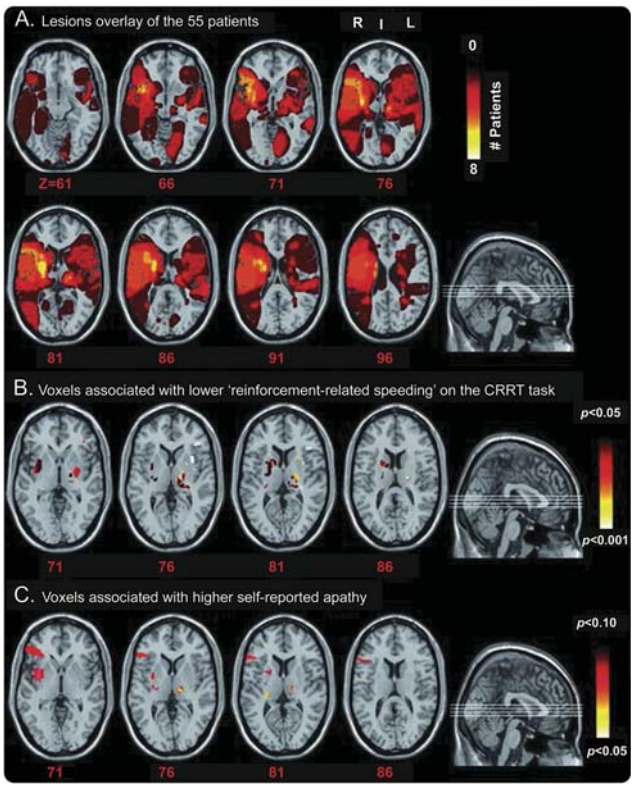

Fig.2 - Brain slices are displayed from z-coordinates (labelled under each template) of the Montreal Neurological Institute space, with the left hemisphere on the right side. *CRRT = Cued Reinforcement Reaction Time.*

▶ Lucas SPIERER

Inhibitory control, a key aspect of executive functions, refers to the ability to cancel ongoing cognitive or motor processes and allows adapting to changing environments. Inhibitory control deficits have been advanced to characterize or even to constitute a causal factor in the emergence of several prominent brain-related disorders including e.g. addiction or ADHD. Functional and structural deficits of frontal executive brain networks have indeed been identified as biomarkers of inhibition-related conditions.

A normalisation of the functions and structure of frontal cortices via training-based behavioural interventions might thus help the rehabilitation of these pathologies. However, the development of efficient inhibitory control training regimens first requires demonstrating in healthy participants that the frontal executive brain network can be modified with training. To this aim, our recent research focused on: A) whether and how inhibitory control can be trained and the underlying plastic mechanisms B) whether and how the level of difficulty of the inhibitory control tasks modulates the involved brain mechanisms.

Using electrical neuroimaging, functional MRI, voxel-based morphometric analyses of grey matter structure and diffusion tensor imaging of white matter tracts, as well as voxel-based lesion-symptom mapping, we addressed the neural underpinnings of inhibitory control and the brain mechanisms of training-induced plasticity of inhibitory control.

A) Can executive functions training reshape the functional and structural architecture of the frontal lobe?

We used functional and structural magnetic resonance imaging to measure the effects of two weeks of training with a Go/NoGo task specifically designed to improve frontal top-down inhibitory control mechanisms. Our combined anatomical and functional findings revealed for the first time that differential patterns of functional and structural plasticity between and within inferior frontal gyri enhanced the speed of top-down inhibition processes and in turn inhibitory control proficiency. Our results suggest that training-based interventions might help overcoming the anatomic and functional deficits of inferior frontal gyri manifesting in inhibition-related clinical conditions.

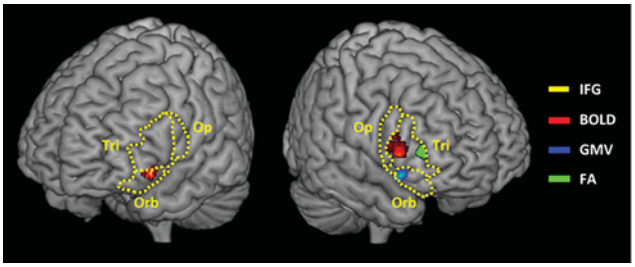

Fig.3 - Cluster maxima of the plastic modifications *induced by the inhibitory control training in magnetic resonance imaging blood oxygen level dependent signal (BOLD, red), grey matter volume (GMV, blue) and white matter fractional anisotropy (FA, green). The left and right inferior frontal gyri (IFG, dotted yellow lines), pars opercularis (Op.), triangularis (Tri.) and orbitalis (Orb.) are represented.*

Chavan et al., 2014

B) Do variations in the difficulty levels of executive tasks modify qualitatively the involved brain networks?

With electrical neuroimaging and the study of anatomo-clinical correlations in brain-damaged patients, we demonstrated that varying the difficulty level of inhibitory control tasks actually modify qualitatively the brain networks engaged in the task. This finding in important since it reveals that difference in difficulty can account for the discrepancies between the results of studies on inhibitory control. Moreover, it points out that the difficulty level should be carefully controlled in neuropsychological tests used for diagnostic purposes. ■

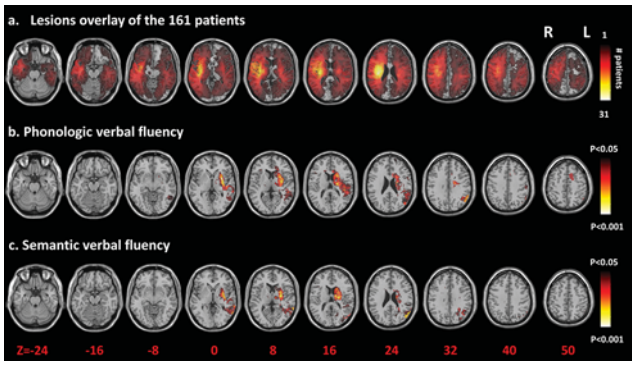

Fig.4

Fig.4 - Voxel-based lesion–symptom mapping on the 161 patients shows the relationship between performance in the verbal fluency tasks and brain lesions. *A. Overlap plot of the lesion of the 161 patients. The number of overlapping lesions is coded with colors ranging from dark red (n=1) to light yellow (n=31 patients). B. «Difficult fluency» impairments were associated with lesions to a network centered on left putamen, caudate nucleus and pallidum and left dorsal temporal regions. C. «Easy fluency» impairments were associated with lesions of the left putamen, caudate nucleus and pallidum and left ventral temporal regions. Only voxels significant at p<.05 uncorrected are color-coded from red (p<0.05) to white (p<0.001). Brain slices are displayed with the left hemisphere on the right side.*

Chouiter et al., 2014

Selected Publications

Jean-Marie ANNONI

Radman N, Cacioppo S, Spierer L, Schmidlin E, Mayer E, ***Annoni JM***
Posterior SMA Syndrome following subcortical stroke: contralateral akinesia reversed by visual feedback. Neuropsychologia. 2013 Nov; 51(13):2605-10.

Rochat L, Van der Linden M, Renaud O, Epiney JB, Michel P, Sztajzel R, Spierer L, ***Annoni JM***
Poor reward sensitivity and apathy after stroke: implication of basal ganglia. Neurology 2013 Nov 5; 81(19):1674-80.

Battistella G, Fornari E, ***Annoni JM****, Chtioui H, Dao K, Fabritius M, Bernard Favrat B, Mall JF, Maeder P and Giroud Ch*
Long-term effects of cannabis on brain structure Neuropsychopharmachology 2014 Aug; 39(9):2041-8.

Lucas SPIERER

Chavan C, Mouthon M, Van Der Zwaag W, Draganski B, ***Spierer L***
Differential patterns of functional and structural plasticity within and between inferior frontal gyri support training-induced improvements in inhibitory control proficiency. Human Brain Mapping, 2014

Chouiter L, Holmberg J, Manuel A, Colombo F, Clarke S, Annoni JM, ***Spierer L***
«Shared subcortical but distinct cortical left hemispheric structures support phonologic and semantic verbal fluencies: a brain lesion study». Neuropsychologia, 2014

Chouiter L, Dieguez S, Annoni JM, ***Spierer L***
High and low stimulus-driven conflict engage segregated brain networks, not quantitatively different resources. Brain Topography, 2014

Jean-Pierre Bresciani
Sport and Motricity

Perception and control 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 the speed and amplitude of motion, 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 mechanically stable and highly-adaptive behaviors in different contexts. Combining psychophysics methods and virtual reality technology, we investigate how the signals provided by different sensory systems are integrated to ensure perceptual stability. Through the analyses of movements at multiple levels (e.g., 3D kinematics, EMG or kinetic measurements, video-ocular recordings), we also try to understand better how humans implement efficient motor strategies in normal situations or in reaction to unexpected perturbations.

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Effect of color on perceived performance in ballet dancing

Color has been shown to affect athletes' behavior and performance in various sports. We tested whether the color of the costume worn by the dancer in ballet dancing can alter the perception / evaluation of the performance by persons watching / judging it. An expert dancer wearing a full-body second skin costume including a hood performed the same forty-second choreography in three slightly different ways. The three productions were video-recorded and the color of the costume selectively modified using chroma-keying technique. Three different costume colors were used (cyan, red and green), for a total of nine performance-color combinations / footages. Participants were presented with the footages and asked to evaluate how much passion was expressed in the dancer's performance. Two different methods were used for the evaluation, namely a Likert scale and two-alternative forced choices using paired-comparisons. Irrespective of the costume color, the three executions of the choreography were «ranked» according to the passion expressed, and the ranking was consistent across the two evaluation methods. This shows that the participants were able to evaluate the dancing performance and that the evaluation methods were reliable. Importantly, both evaluation methods indicated that the performance was 'perceived' as expressing significantly less passion when the costume of the dancer was cyan as compared to red and green. The results suggest that in artistic sports such as dance, rhythmic gymnastics or figure skating, the color of the costume worn by the athletes is likely to influence the evaluation of the performance.

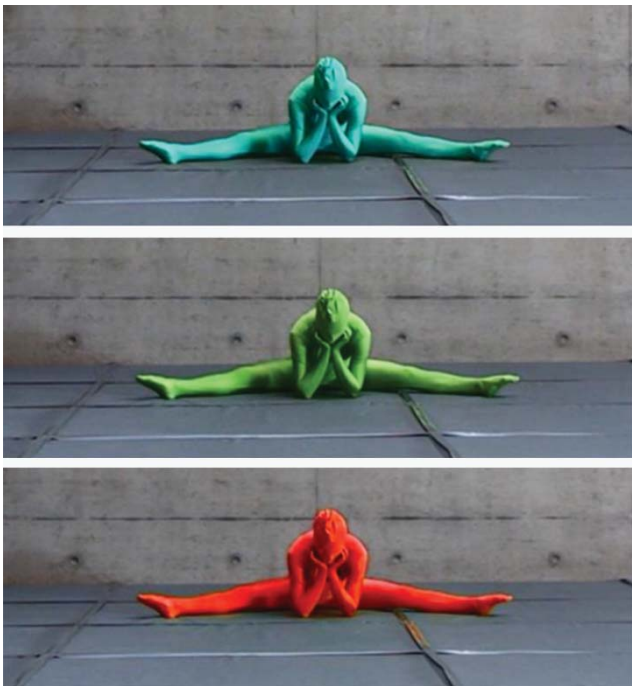

Fig.1 - First image of one of the 40-seconds footages after chroma-keying modification. *In all three images, the original image (i.e., footage) is the same. The color of the costume was selectively changed, but the remaining of the visual scene remained unaltered*

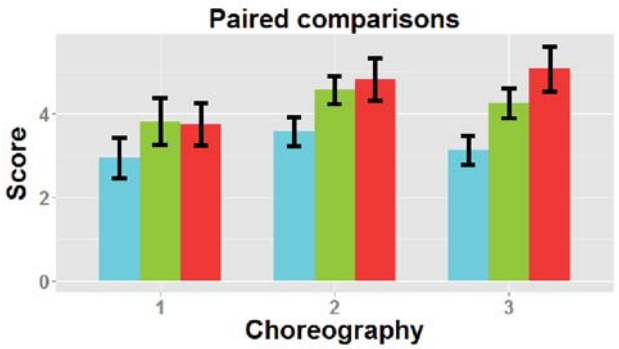

Fig.2 - Paired-comparisons between footages indicated that performance was «perceived» as expressing significantly less passion when the costume of the dancer was cyan as compared to red and green

Effect of bioceramic fabrics on postural stability

Bioceramic fabrics have been claimed to improve blood circulation, thermoregulation and muscle relaxation, thereby also improving muscular activity. We assessed whether bioceramic fabrics have an effect of postural control and contribute to improve postural stability. Specifically, we measured the effects of bioceramic fabrics on body-sway when maintaining standard standing posture, as well as when maintaining a more instable posture, namely a handstand hold. In all experiments, postural oscillations were measured using a force platform with four strain gauges that recorded the displacements of the center of pressure (CoP) in the horizontal plane. Participants wore either a full-body second skin suit containing a bioceramic layer or a «placebo» second skin suit that had the same cut, appearance and elasticity as the bioceramic suit but did not contain the bioceramic layer. Whether standing on the feet or on the hands, the surface of displacement of the CoP was significantly smaller when participants were wearing the bioceramic suit than when they were wearing the placebo suit. Our results suggest that bioceramic fabrics do have an effect on postural control and improve postural stability. ■

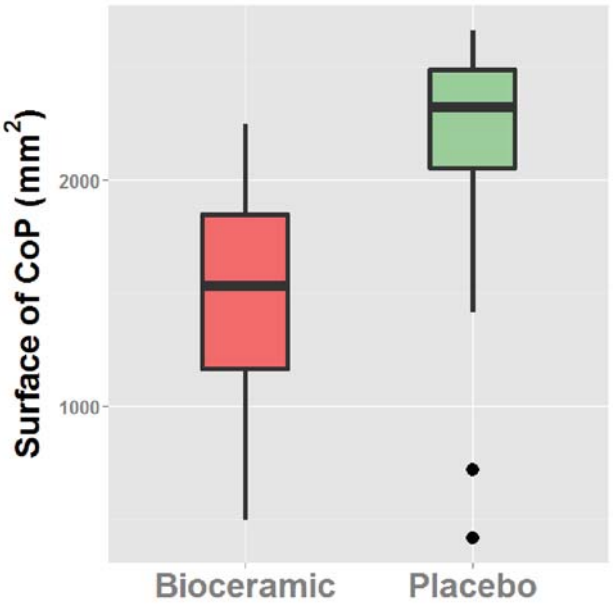

Fig.3 - The mean surface of displacement of the center of pressure was larger when wearing the placebo suit (green box) than when wearing the bioceramic suit (red box)

Selected Publications

Reichenbach A, Thielscher A, Peer A, Bülthoff HH, ***Bresciani JP***
A key region in the human parietal cortex for processing proprioceptive hand feedback during reaching movements. NeuroImage, 2014, 84:615-625

Metral M, Guinot M, ***Bresciani JP****, Luyat M, Roulin JL, Guerraz M*
Bimanual coordination with three hands: Is the mirror hand of any help? Neuropsychologia, 2014, 52:11-18

Cian C, Gianocca V, Barraud PA, Guerraz M, ***Bresciani JP***
Bioceramic fabrics improve quiet standing posture and handstand stability in expert gymnasts. Submitted

Pierre Lavenex
Neurophysiology

Laboratory of brain and cognitive development

INTRODUCTION

How does one build a brain to learn and remember?

One particularly pertinent conundrum regarding human memory is the fact that until 2-3 years of age children do not have the ability to remember specific episodes of their life. Although this phenomenon, known as infantile amnesia, has been the focus of intensive psychological investigation, its neurobiological basis is not understood. In adults, it is well known that the hippocampal formation is the center of a brain network critical for episodic memory, and damage to the hippocampus results in amnesia, a total loss of episodic and semantic memory. Is it possible, then, that the emergence of episodic memory depends on the structural and functional maturation of these brain areas? And, if so, how does one build a brain to learn and remember? In order to answer these questions, our multidisciplinary, systems neuroscience research program focuses on the role of the hippocampal formation in memory processes, with special emphasis on early postnatal development and the relationship between structure and function.

Current research in our laboratory is aimed at determining the molecular and cellular changes underlying the development of the different regions of the primate hippocampal formation, and at identifying which specific memory functions are capable of being expressed at different points during early postnatal development. This knowledge is imperative in order to understand the neurobiological basis of the emergence of episodic memory, and provides critical insight into the functions of the medial temporal lobe structures across the lifespan.

Understanding the postnatal development of the primate hippocampal formation is equally pertinent for understanding the root of neurodevelopmental and genetic disorders, such as autism and schizophrenia, in which developmental abnormalities in these structures are implicated. Although the structures of the primate hippocampal formation are easily recognizable at birth, they undergo substantial postnatal maturation throughout infant and juvenile life. It is therefore logical that during this critical maturational period, these structures are particularly sensitive to intrinsic and environmental factors capable of modulating the expression of particular genes, thus affecting normal brain development and cognition. Data from our research program elucidating the normal development of the primate hippocampal formation are therefore essential to defining processes, substrates and critical periods of maturation that are sensitive to perturbation and contribute to the etiology of neurodevelopmental disorders.

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The human hippocampus beyond the cognitive map: evidence from a densely amnesic patient

Banta Lavenex P, Colombo F, Ribordy Lambert F and Lavenex P; Front Hum Neurosci 8:711 (2014)

We tested a densely amnesic patient (P9), with bilateral hippocampal damage resulting from an autoimmune disorder, and 12 age- and sex-matched controls on a series of memory tasks designed to characterize allocentric spatial learning and memory abilities. We compared P9's ability to perform spatial memory tasks with her ability to perform non-spatial, color memory tasks. First, P9's performance was impaired as compared to controls even in the simplest versions of an allocentric spatial memory task, in which she had to find repeatedly over 10 trials the same location(s) of one, two or three illuminating foot pad(s) among 23 pads distributed in an open-field arena. In contrast, she performed as well as controls when she had to find repeatedly over 10 trials the same one, two or three pad(s) marked by color cue(s), whose locations varied between trials. Second, P9's performance was severely impaired in working memory tasks, when she had to learn on a trial-unique basis and remember the location(s) or the color(s) of one, two or three pad(s), while performing an interfering task during the 1-min interval separating encoding and retrieval. Without interference during the retention interval of the trial-unique tasks, P9's performance was partially preserved in the color tasks, whereas it remained severely impaired in the allocentric spatial tasks. Detailed behavioral analyses indicate that P9's memory representations are more limited than those of controls both in their precision (metric coding) and in the number of items that can be maintained in memory (capacity). These findings are consistent with the theory that the hippocampus contributes to the integration or binding of multiple items, in order to produce high-resolution/high-capacity representations of spatial and non-spatial information in the service of short-term/working and long-term memory.

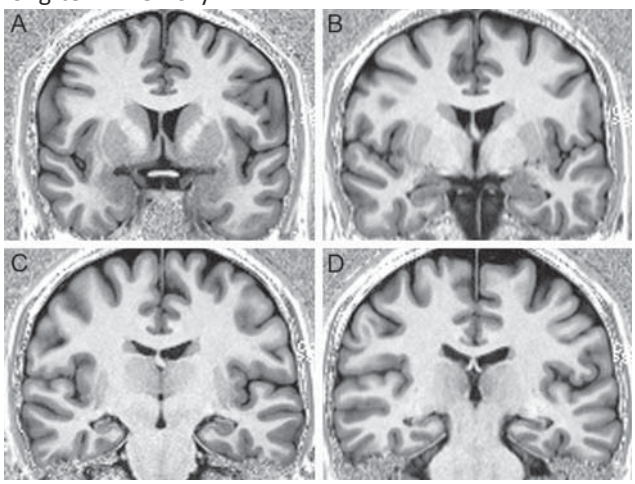

Fig.1 - T1-weighted MRI images of P9's brain performed 3 years after the onset of pathology showing bilateral hippocampal atrophy, and no obvious signs of pathology in the surrounding cortical areas, from rostral (A) to caudal (D).

Building hippocampal circuits to learn and remember: insights into the development of human memory

Lavenex P and Banta Lavenex P; Behav Brain Res 254:8-21 (2013)

The hippocampal formation is essential for the processing of episodic memories for autobiographical events that happen in unique spatiotemporal contexts. Interestingly, before 2 years of age, children are unable to form or store episodic memories for recall later in life, a phenomenon known as infantile amnesia. From 2 to 7 years of age, there are fewer memories than predicted based on a forgetting function alone, a phenomenon known as childhood amnesia. Here, we discuss the postnatal maturation of the primate hippocampal formation with the goal of characterizing the development of the neurobiological substrates thought to subserve the emergence of episodic memory. Distinct regions, layers and cells of the hippocampal formation exhibit different profiles of structural and molecular development during early postnatal life. The protracted period of neuronal addition and maturation in the dentate gyrus is accompanied by the late maturation of specific layers in different hippocampal regions that are located downstream from the dentate gyrus, particularly CA3. In contrast, distinct layers in several hippocampal regions, particularly CA1, which receive direct projections from the entorhinal cortex, exhibit an early maturation. In addition, hippocampal regions that are more highly interconnected with subcortical structures, including the subiculum, presubiculum, parasubiculum and CA2, mature even earlier. These findings, together with our studies of the development of human spatial memory, support the hypothesis that the differential maturation of distinct hippocampal circuits might underlie the differential emergence of specific „hippocampus-dependent" memory processes, culminating in the emergence of episodic memory concomitant with the maturation of all hippocampal circuits.

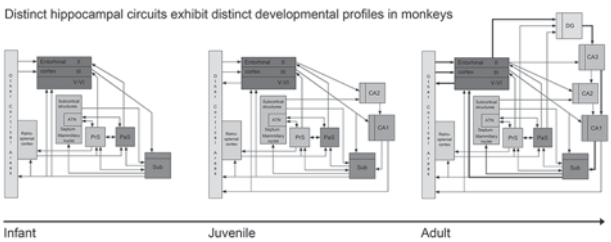

Fig.2 - Hierarchical model of the postnatal maturation of the primate hippocampal formation. *The maturation of hippocampal circuits involving the subiculum, presubiculum and parasubiculum might support path integration abilities before 1 year of age in children. The maturation of hippocampal circuits involving the direct projections from the superficial layers of the entorhinal cortex to CA1 (and CA2) might support basic allocentric spatial memory abilities at 2 years of age in children. The protracted maturation of hippocampal circuits involving the dentate gyrus and CA3 might support high-resolution allocentric spatial memory abilities after 3 years of age in children.*

The complete maturation of all hippocampal circuits might support episodic memory abilities after 7 years of age in children. The dentate gyrus is thought to contribute to pattern separation. Neurogenesis in the dentate gyrus is thought to contribute to the encoding of temporal associations. CA3 is thought to contribute to pattern completion and the rapid and flexible acquisition of spatial memories. CA1 is thought to contribute to the integration of all sensory and memory inputs; it might enable slow and gradual learning of allocentric spatial memory. The subiculum, presubiculum and parasubiculum are thought to contribute to the integration of self-generated movement information, enabling path integration. Abbreviations: ATN: anterior thalamic nuclei; DG: dentate gyrus; CA3, CA2, CA1: fields of the hippocampus proper; Sub: subiculum; PrS: presubiculum; PaS: parasubiculum; II, III, V–VI: layers of the entorhinal cortex.

An analysis of entorhinal cortex projections to the dentate gyrus, hippocampus, and subiculum of the neonatal macaque monkey

Amaral DG, Kondo H, Lavenex P; J Comp Neurol 522:1485-1505 (2014)

The entorhinal cortex is the primary interface between the hippocampal formation and neocortical sources of sensory information. Although much is known about the cells of origin, termination patterns, and topography of the entorhinal projections to other fields of the adult hippocampal formation, very little is known about the development of these pathways, particularly in the human or nonhuman primate. We have carried out experiments in which the anterograde tracers ^{3}H-amino acids, biotinylated dextran amine, and *Phaseolus vulgaris* leucoagglutinin were injected into the entorhinal cortex in 2-week-old rhesus monkeys (*Macaca mulatta*). We found that the three fiber bundles originating from the entorhinal cortex (the perforant path, the alvear pathway, and the commissural connection) are all established by 2 weeks of age. Fundamental features of the laminar and topographic distribution of these pathways are also similar to those in adults. There is evidence, however, that some of these projections may be more extensive in the neonate than in the mature brain. The homotopic commissural projections from the entorhinal cortex, for example, originate from a larger region within the entorhinal cortex and terminate much more densely in layer I of the contralateral entorhinal cortex than in the adult. These findings indicate that the overall topographical organization of the main cortical afferent pathways to the dentate gyrus and hippocampus are established by birth. These findings add to the growing body of literature on the development of the primate hippocampal formation and will facilitate further investigations on the development of episodic memory. ■

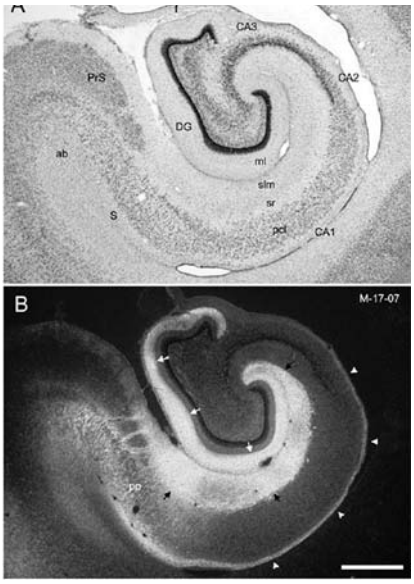

Fig.3 - Overview of the entorhinal cortex projections to the dentate gyrus, hippocampus, and subiculum in the 2-week-old infant monkey. **A:** *Bright-field photomicrograph of a Nissl-stained coronal section of the hippocampal formation at a midrostrocaudal level.* **B:** *Dark-field photomicrograph of a coronal section adjacent to the one in A showing anterograde labeling following an injection in the lateral part of Ec (case M-17-07; see the injection site in Fig. 5A). Note that labeling is present in the outer two-thirds of the molecular layer of the dentate gyrus (white arrows), the stratum lucunosum-moleculare of CA1, CA2, and CA3, and the molecular layer of the subiculum (black arrows). Projections from the entorhinal cortex perforate the subiculum (pp) to terminate in the hippocampal formation. Arrowheads indicate labeled fibers in the alveus that continue into the fimbria at more caudal levels and contribute to the commissural projections to the contralateral entorhinal cortex. Abbreviations: ab, angular bundle; ml, molecular layer; pcl, pyramidal cell layer; pp, perforant path; slm, stratum lacunosum-moleculare; sr, stratum radiatum. Scale bar = 1 mm in B (applies to A,B).*

Selected Publications

Banta Lavenex P, Colombo F, Ribordy Lambert F and ***Lavenex P***
The human hippocampus beyond the cognitive map: evidence from a densely amnesic patient. Frontiers in Human Neuroscience, 8:711. 2014. doi: 10.3389/fnhum.2014.00711

Lavenex P *and Banta Lavenex P*
Building hippocampal circuits to learn and remember: insight into the development of human memory. Behavioural Brain Research, 254: 8-21, 2013. doi: 10.1016/j.bbr.2013.02.007

Amaral DG, Kondo H and ***Lavenex P***
An analysis of entorhinal cortex projections to the dentate gyrus, hippocampus, and subiculum of the neonatal macaque monkey. Journal of Comparative Neurology, 522: 1485-1505, 2014. doi: 10.1002/cne.23469

Marco C.G. Merlo
Chair of Psychiatry and Psychotherapy

Neurophysiology of cognitive and emotional functions as well as decision-taking in normal subjects and psychiatric patients

INTRODUCTION

Modern psychiatry aims at early detection of psychiatric disorders and emphasizes the importance of avoiding their social impairment. Patients, who develop major psychiatric disorders, show -during adolescence and young adulthood- cognitive and emotional dysfunctions linked to difficulties in role and social functioning. Therefore therapeutic interventions integrate pharmacological and psychotherapeutic strategies with in real live coaching for formation or employment («supported education/employment model»). Up to date, research still needs better understanding of cognitive and emotional mechanisms («stress-coping model») in order to understand why these patients fail in their effort to be integrated in the community. Our research applies neurophysiological methods to measure attention, memory, emotional and decision making functions in normal subjects and psychiatric patients. Three projects have been accepted by ethical committee and started in 2013 by our research group:

1) Measuring auditory *Event-Related Potentials* (ERPs) in psychiatric patients to calculate a *Time Index of Neural Network Variation* (TINNV) to assess mental workload

2) Developing paradigms for psychosocial intervention in early psychosis by studying decision-taking and false memory with delusions

3) Reducing stress by a program of *Mindfulness-Based Stress Reduction* (MBSR) evaluating components mechanisms regulation of attention and emotions

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Utility of auditory Event-Related Potentials (ERPs) as clinical tool in psychiatry

Normal subjects and psychiatric patients perform an auditory oddball task with an easy memory task and a more constraining one. P2 and P3 auditory ERP components are measured by computing electrophysiological indexes. Applying a new averaging ERP method, we will analyze values of ERP parameters for target auditory stimuli in the two memory conditions. This method allows elaborating a *Time Index of Neural Network Variation* (TINNV).

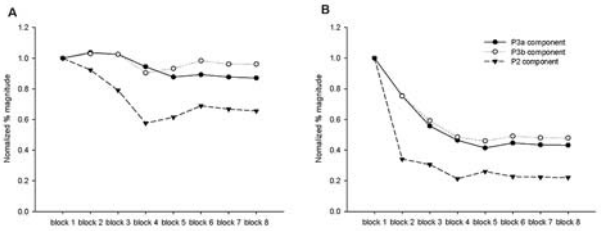

Fig.1 - P2, P3a and P3b components for Time Index of Neural Networks Variability (TINNV). *For each component, amplitude was averaged in a height consecutive blocks differentiating between easy (A) and more constraining (B) memory task. Amplitudes of each block were compared to amplitude of first block. This parameter informs on networks reactivity and it is referred to as TINNV. Note the linear decrement of P3a and P3b magnitude in strong (B) task only (data of controls).*

We hypothesize variations due to task difficulty and to time course for the P2, P3a and P3b components (i.e. TINNV) which will discriminate normal subjects from psychiatric patients. As decision-making and/or attentional disturbances differ between psychiatric disorders, we are also interested to find neurophysiological parameters to differentiate between psychiatric syndromes.

Study of paradigms for psychosocial intervention in early psychosis: difficulties in decision-taking and memory

Recent studies have shown social impairment based on difficulties in social decision-taking in patients suffering from first-episode psychosis (FEP). With *Ultimatum Game* (UG) paradigm, we evaluate cognitive and emotional functioning in the position as «proposer», who offers a portion of money to a «responder», who decides to either accept or reject the offer and vice versa. As these patients also experience delusions which are linked to an exaggerated trend to produce false memories, we also apply *Deese-Roediger-McDermott* (DRM) paradigm. DRM consists of a memory task where subjects have to memorize a list words and then are confronted with another list with some words similar to the first list. The «lure» is falsely recognized as having been studied, especially in psychotic patients. During both tasks, we will compare brain activities and cortisol level between FEP patients and healthy controls.

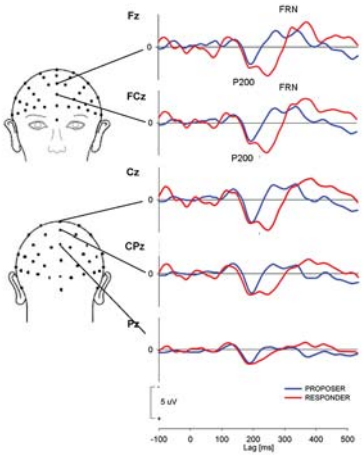

Fig.2 - ERPs changes during Ultimatum Game (UG). *Grand-average ERPs at electrode sites Pz, CPz, Cz, FCz, Fz following responder (red line) and proposer (blue line) decision-making during the Ultimatum Game for all outcomes (both acceptance and refusal of the offer). The labels show the main positive component (P200) and the main negative component (Feedback-Related Negativity; FRN). Note the increase of FRN latency for responder condition (data of controls).*

▸▸

We hypothesize that brain activity will differ between FEP and healthy controls especially in the proposer task of UG. According to the emotional involvement, required during this task, higher cortisol levels are expected. Furthermore, we believe that FEP experiencing delusions will produce more false memories in DRM than controls and that these differences can be observed in the patterns of brain activities. Both results will help us to elaborate new rehabilitation strategies for FEP.

Mindfulness-Based Stress Reduction (MBSR) - Evaluation of subjective and neurophysiological effects of an eight weeks group program

The MBSR group program aims at developing several specific capacities: directed attention, self-regulation of attention and acceptance of one's own experiences. Its therapeutic effect has been shown for reducing stress reactions, chronic pain and symptoms in several psychiatric disorders. Its common mode of action may be an impact on auto-regulation of attention and emotions. In this study, we combine subjective evaluation with neurophysiological measures. We perform the *Attentional Network Test* (ANT) to measure three components of the attention system: orientation, arousal, executive control and an affective paradigm to collect data on spontaneous and voluntarily controlled reactions to emotionally positive and negative visual stimuli. Cortisol level is also measured. We hypothesize that it is possible to objectivize changes in regulation of attention and emotion by MBSR and that there are differences between healthy subjects and anxious patients in processing emotionally stressful visual stimuli. ■

Selected Publications

Missonnier P, Herrmann FR, Zanello A, Badan Bâ M, Curtis L, Canovas D, Chantraine F, Richiardi J, Giannakopoulos P, ***Merlo MCG***
Event-related potentials and changes of brain rhythm oscillations during working memory activation in patients with first-episode psychosis. J Psychiatry Neurosci, 2012; 37(2): 95-105

Tettamanti M, Badan Bâ M, Zbinden E, Giannakopoulos P, Rey-Bellet Ph, Curtis L, ***Merlo MCG***
Short-term effect of supported employment/education on negative symptoms changes in first-episode psychosis. Early Interv Psychiatry, submitted

Missonnier P, Hasler R, Perroud N, Herrmann FR, Millet P, Richiardi J, Malafosse A, Giannakopoulos P, Baud
EEG anomalies in adult ADHD subjects performing a working memory task. Neuroscience, 2013, 241: 135-146

Gregor Rainer
Neurophysiology

Visual cognition laboratory

INTRODUCTION

The general aim of the Visual Cognition laboratory is to contribute to understanding how visual information is represented in cortical brain regions, how these representations are modified by learning and how they are used in higher cognitive functions such as perceptual decision making. Currently, we are particularly interested in how the neuromodulator Acetylcholine affects various aspects related to the brain processing of visual information. We use a variety of methods including multi-channel electrophysiological extracellular recordings, electrical deep brain stimulation of the basal forebrain and iontophoretic drug application. We perform behavioral experiments to test the visual and cognitive capacities of animals using video tracking as well as custom-built automated behavioral setups. Finally, in addition to the electrophysiological and behavioral work, we are also working actively to study neurochemical modulations that accompany different behavioral or pharmacological manipulations. This work encompasses both microdialysis based monitoring of small molecule neurotransmitters and neuromodulators, as well as identification and quantification work related to neuropeptides that are important signaling molecules often co-released with traditional neurotransmitters.

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Basal forebrain deep brain stimulation exerts a strong influence on neural activity in the visual cortex

The basal forebrain (BF) regulates cortical activity by the action of cholinergic projections to the cortex. At the same time, it also sends substantial inhibitory projections to both cortex and thalamus, whose functional role has received far less attention. We used deep brain stimulation (DBS) in the BF, which activates both projections, to investigate the impact of BF activation on neural activity in primary visual cortex (V1). BF acitvation increased V1 single and multi-unit activity, decreased orientation selectivity and remarkably increased contrast sensitivity as demonstrated by lowered semi-saturation contrast values. The spontaneous V1 local field potential generally exhibited spectral peaks centered at 40 and 70 Hz as well as a broad γ-band (30-90 Hz) enhancement following BF stimulation, whereas effects in a low frequency band (1-10 Hz) were less consistent. The broad γ-band was the best predictor of both the firing rate increase and contrast sensitivity increase of V1 unit activity. BF activation has a strong influence on contrast sensitivity in V1. We suggest that in addition to cholinergic modulation, the BF inhibitory projections play a crucial role in the impact of BF DBS on cortical activity.

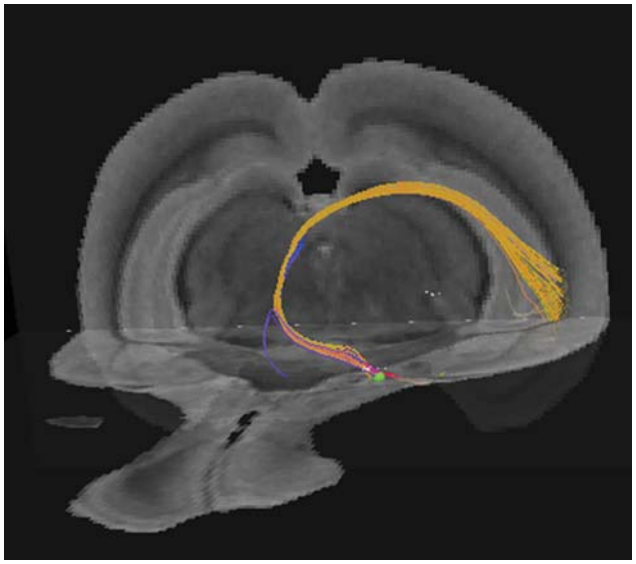

Fig.1 - Axonal projections from the basal forebrain to the visual cortex, mediating long range cholinergic and GABAergic influence on cortical function, visualized using diffusion tensor imaging.

Visual cortex in the tree shrew exhibits virtual absence of simple cells

It is widely assumed that simple cells in the visual cortex, defined by spatial as well as temporal aspects of the neural response, represent the elementary functional units from which more complex responses are constructed in the cortex. Here, we present quantitative data on receptive field (RF) structure, response modulation, and orientation tuning for single neurons in V1 of the tree shrew, a close relative of primates. We find that spatial RF subfield segregation, a criterion for identifying simple cells, was virtually absent in the tree shrew V1. In contrast, many neurons exhibited elevated F1/F0 modulation that is often used as a simple cell marker. This apparent discrepancy can be explained by the robust black dominance in tree shrew V1, which inflates F1/F0 ratio values. RF structure mapped with sparse-noise-which is spatially restricted and emphasizes thalamo-cortical feed-forward inputs-appeared unrelated to orientation selectivity. However, RF structure mapped using the Hartley subspace stimulus-which covers a large area of the visual field and recruits considerable intracortical processing-did predict orientation preference. Our findings reveal a number of striking similarities in V1 functional organization between tree shrews and primates, emphasizing the important role of intracortical recurrent processing in shaping V1 response properties in these species.

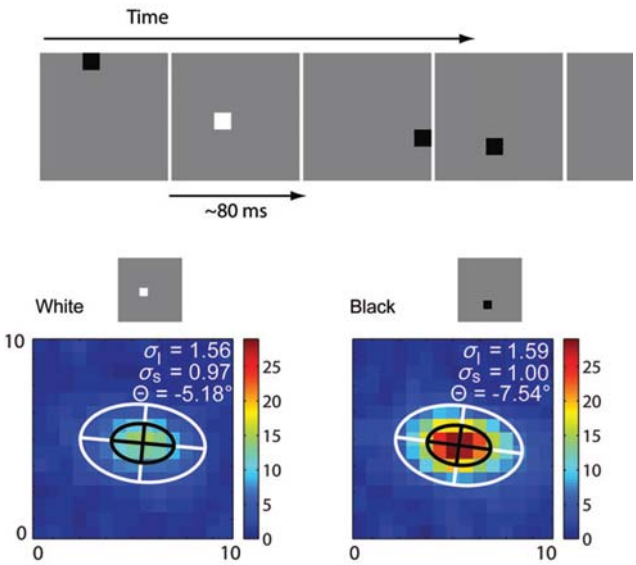

***Fig.2 top** - The sparse noise stimulus, used for receptive field (RF) mapping, consisted of briefly flashed white or black spots on a grey background.*
***bottom** - Single neuron example showing firing rate as heat map as a function of visual space, demonstrating large RF overlap and dominance of black responses.*

Mass spectrometry studies reveal that several novel families of neuropeptides are upregulated after chronic use of nicotine

To understand the impact of chronic nicotine on neuropeptides, which are potential molecules associated with dependence, we conducted neuropeptidomics on the rat dorsal striatum, an important brain region implicated in the preoccupation/craving phase of drug dependence. We used extensive LC-FT-MS/MS analyses for neuropeptide identification and LC-FT-MS in conjunction with stable isotope addition for relative quantification. Five enkephalin opioid peptides were up-regulated, although no change was observed for dynorphin peptides. Specially, nicotine altered levels of nine non-opioid peptides derived from precursors, including somatostatin and cerebellin, which potentially modulate neurotransmitter release and energy metabolism. This broad but selective impact on the multiple peptidergic systems suggests that apart from the opioid peptides, several other peptidergic systems are involved in the preoccupation/craving phase of drug dependence. Our finding permits future evaluation of the neurochemical circuits modulated by chronic nicotine exposure and provides a number of novel molecules that could serve as potential therapeutic targets for treating drug dependence. ■

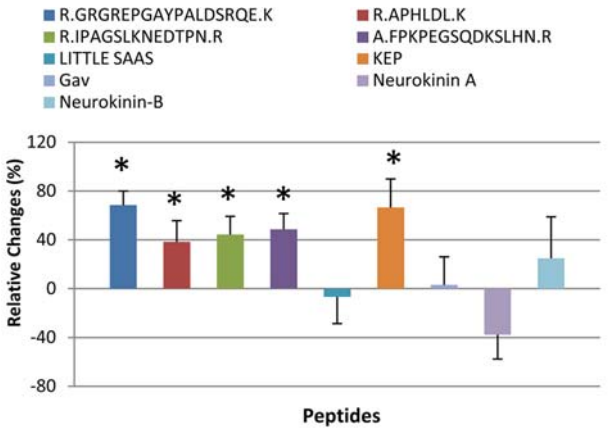

Fig.3 - Neuropeptides derived from granin or granin-like precursors as well as from protachykinin, that were upregulated in the dorsal striatum by chronic nicotine administration.

Selected Publications

Bhattacharyya A, Veit J, Bondar I, Kretz R, ***Rainer G***
Basal forebrain activation controls contrast sensitivity in primary visual cortex BMC Neuroscience 14:55, 2013

Veit J, Bhattacharyya A, Kretz R, ***Rainer G***
On the relation between receptive field structure and stimulus selectivity in the tree shrew primary visual cortex. Cerebral Cortex 24(10):2761-71, 2014

Petruzziello F, Falasca S, Andren P, Rainer G, Zhang X
Chronic nicotine treatment impacts the regulation of opioid and non-opioid peptides in the rat dorsal striatum. Mol Cell Prot 12(6):1553-62, 2013

Eric M. Rouiller
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INTRODUCTION

As compared to other mammals, the order of primates (human, monkey) exhibits an outstanding and exquisite capability to optimally and quickly adapt behaviours in a constantly changing world, based on a multitude of sensory inputs of different modalities (vision, hearing, proprioception, etc), integrated with the goal to quickly generate the most sophisticated and appropriate actions in order to efficiently interact with the external world as well as with other individuals. The laboratory is engaged in elucidating some of the complex neural mechanisms involved in such overall sensorimotor integration process. Furthermore, in case of brain pathology (lesion, disease like Parkinson), our goal is to establish brain plasticity mechanisms underlying spontaneous functional recovery (most often incomplete) and generate therapeutic strategies aimed at enhancing rehabilitation.

1) How and where different senses (vision, hearing, touch, etc) merge in order to form a quick and unified percept, as well as increasing the performance (better detection and decreased reaction time) in comparison to presentation of the individual (unimodal) stimuli?

2) How cortical representations of body parts are modified by practice or following a lesion of the central nervous system?

3) How does the motor system control fine movements executed with the fingers, which is a prerogative of primates, involving the corticomotoneuronal system?

4) What is the extent, the time course and the mechanisms involved in the functional recovery of manual dexterity following a lesion of the central nervous system, at spinal or cortical level or in case of neurodegenerative disease (e.g. Parkinson)?

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These questions are currently under investigation in macaque monkeys, an animal model whose central nervous system has anatomical and functional properties close to human subjects, optimal to study such advanced functions in the field of integrative and cognitive neurosciences. Some of these investigations are extended to human subjects, for instance the representation in the brain of tactile information from fingers in the context of specific hand use (e.g. smartphone).

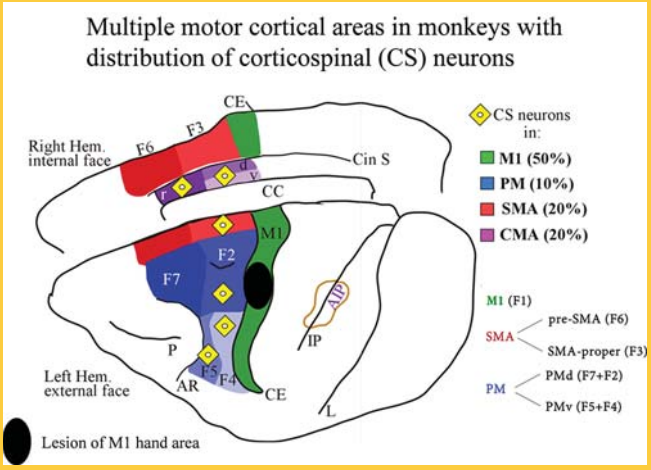

Fig.1 - Schematic representation of the two brain hemispheres of the macaque monkey (external face of the left hemisphere in foreground and internal face of the right hemisphere in background) with emphasis on the nomenclature identifying the multiple motor cortical areas in the frontal lobe (rostral to the central sulcus=CE). *M1=primary motor cortex; PM=premotor cortex; SMA=supplementary motor cortex; CMA=cingulate motor cortex. AR=arcuate sulcus; CC=corpus callosum; CinS=cingulate sulcus; CS=corticospinal; IP=intraparietal sulcus; L=lateral sulcus; P=principal sulcus. The black area represents the location of a restricted lesion in the hand area of M1, representing our model to investigate the mechanisms involved in the functional recovery from unilateral motor cortex lesion.*

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Multisensory and sensorimotor integration

Simultaneous presentation of sounds **and** visual stimuli generate a more reliable and faster detection of the stimuli, as compared to separate presentation of the same auditory stimulus **or** visual stimulus. In two monkeys trained to perform such detection task, the simultaneous presentation was accompanied by shorter reaction times that when the same stimuli were presented in isolation. To test the hypothesis that the premotor cortex (PM; ***see Fig. 1***) is involved in such multisensory integration process (in addition to contributing to the control of the movement in response to the detection of the stimulus), single neuron recordings were derived from PM in monkeys performing this detection task (***Fig.2***).

The data show that a significant proportion of neurons in PM are influenced by acoustic, or visual stimuli, or both presented at the same time (***Table below Fig.2***). More neurons were influenced by simultaneous presentation of both stimuli than by single presentation (acoustic or visual).

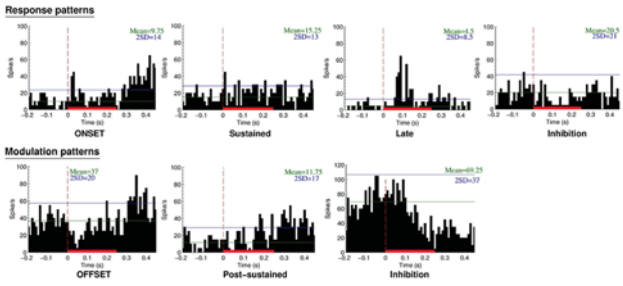

Table 2 | Proportion of neurons exhibiting a change in their activity as a function of the sensory modality and the epoch.

	Acoustic		Visual		Visuo-acoustic	
	Stimulus	Post-stimulus	Stimulus	Post-stimulus	Stimulus	Post-stimulus
Percent	25 ($n = 33$)	60.6 ($n = 80$)	21.2 ($n = 28$)	57.6 ($n = 76$)	34.1 ($n = 45$)	56.1 ($n = 74$)

Fig.2 - In two monkeys, the activity of individual neurons in the premotor cortex (PM) were recorded during the execution of the bimodal detection task (presentation of acoustic stimuli alone; presentation of visual stimuli alone; simultaneous presentation of acoustic and visual stimuli). *The peri-event histograms illustrate various patterns of neuronal responses in PM to the stimuli. The vertical dashed red bar is the onset of stimulus presentation. The duration of the stimulus is represented by the horizontal red bar.* **Response patterns** *are examples of responses time-locked to the stimulus whereas* **modulation patterns** *are cases when the activity was somewhat influenced (modulated) by the stimulus (weak relationship with the stimulus presentation). The table below provides the percent distribution of the PM neurons responding to acoustic stimuli alone, visual stimuli alone or to both stimuli presented simultaneously. Taken from Lanz et al. 2013a, Frontiers in Human Neuroscience (open access publication).*

Functional recovery from motor cortex lesion

After having demonstrated that a treatment (consisting in neutralizing a neurite growth inhibitor such as Nogo-A by administrating an anti-Nogo-A antibody) enhanced functional recovery from spinal cord lesion in adult macaque monkeys (see Freund P. et al., 2006, 2009), we have extended the benefit of this treatment (anti-Nogo-A antibody) to motor cortex lesion, also in macaque monkeys (Wyss et al., 2013). As shown in Fig. 3, anti-Nogo-A antibody treated monkeys generally exhibited a better functional recovery of the ability to grasp small objects from horizontal slots, requiring sophisticated manual dexterity (precision grip combined with wrist flexion). Electrophysiological data showed that recovery depended little on the re-appearance of functional sites in the lesioned M1 area, as assessed by intracortical microstimulation (ICMS; see Wyss et al., 2013). Based on pharmacological reversible inactivation, it was observed that functional recovery depended crucially on the intact premotor cortex (PM), located rostral to the lesion, which can take over part of the lost M1 function (Hoogewoud et al., 2013).

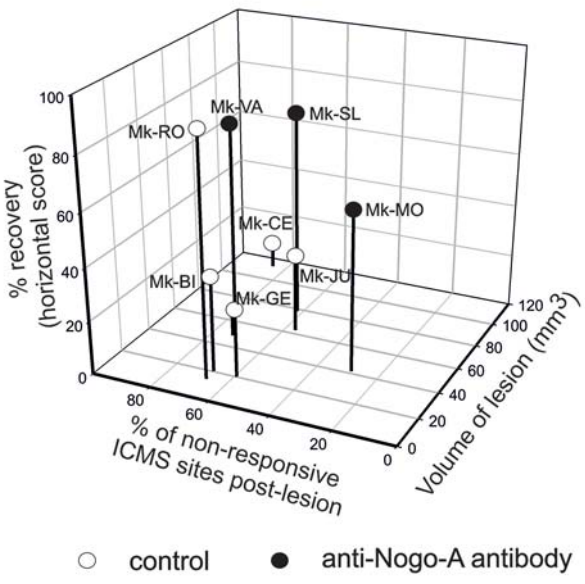

Fig.3 - Plot 3D of functional recovery (in %) of manual dexterity after motor cortex lesion (vertical axis), as a function of volume of cortical lesion and % of non-responsive ICMS sites, showing that anti-Nogo-A antibody treated monkeys (black circles) recover generally better their manual dexterity than untreated (control) monkeys (open circles). *The volume of lesion of Mk-GE is 48.7 mm3 and of Mk-VA is 20 mm3 (the lesion volume in the other monkeys is clearly visible in the above figure). ICMS=intracortical microstimulation (see text). The manual dexterity was assessed by the number of pellets retrieved in 30 sec from the horizontal slots in the modified Brinkman board task. Derived from Wyss et al. 2013 (Rest. Neurol. and Neurosci. 31; open access publication).*

Refinement of methods on the non-human primate model

In 2013, in collaboration with the University of Zürich, we have created an academic Swiss non-human primate centre, known as the SPCCR («Swiss Primate Competence Centre for Research»; see ***www.unifr.ch/spccr***). The goal is to offer to the Swiss academic institutions access to the non-human primate model and to guarantee high standards with focus on improving the welfare of non-human primates used in experiments (in line with the 3Rs initiative). In this context, two methodological refinements were developed recently in our laboratory. First, the anchoring of implants on the skull was optimized by eliminating the previously used dental cement, which was detrimental for the bone condition and risky in term of infection (Lanz et al., 2013b). Second, based on CT scans of the monkey's head, a 3D print (replicate) of the skull of the living animal was produced, from which it was possible to shape the implant as precisely as possible, for an optimal matching of the skull surface (Lanz et al., 2013b). This method is applicable to two types of implants, namely head fixation devices and chronic recording chambers (***Fig.4a***).

As a complement to standard intracranial recordings (using chronic recording chambers), we have developed a non-invasive approach to monitor brain activity by implementing EEG recordings in the macaque monkey, either under anaesthesia (Gindrat et al., 2014; ***Fig.4b***) or in the awake monkey (unpublished data). An EEG cap comprising 32 electrodes is placed on the monkey's head allowing recordings of Somato-Sensory Evoked Potentials (SSEPs) in response to peripheral electric stimulation (***Fig.4b***) or to tactile stimuli delivered on the skin surface. ■

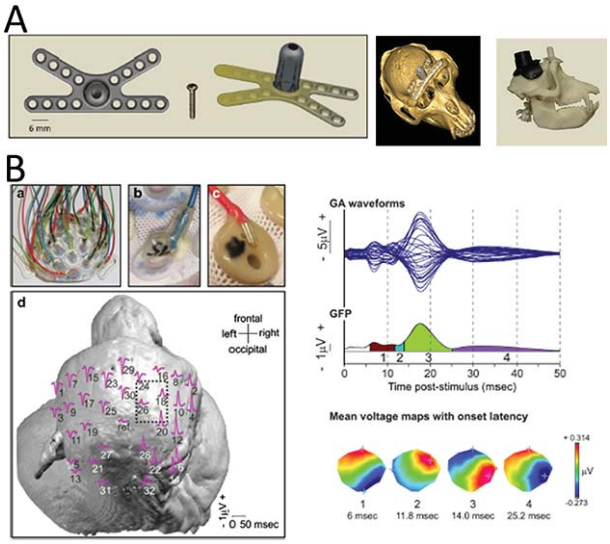

Fig4 - The panel A shows on the left the head fixating device (K shape), covered with hydroxyapatite (yellow) to favour bone growth over the implant and the positioning of the K shape head fixation device on the skull (middle). *On the right, 3D replicate of the monkey's skull with a typical chronic chamber made from tekapeek.*

The panel B illustrates EEG procedures and SSEP data in macaque monkeys. EEG cap used in macaque monkey (a) and detail of two types of electrodes attached to the EEG cap (b, c). Location on the monkey's head of the 32 electrodes and reference electrode, as well as their waveforms in response to electric stimulation of the left median nerve at the wrist (d). On the right, overlap of the SSEP waveforms at all electrodes after electric stimulation of the left median nerve (GA waveforms). GFP=global field potential and temporal extent of the distinct SSEP components identified by cluster analysis (4 components). On the bottom is the colour scaled mean voltage map obtained for each cluster defined in the GFP map.

Pictures taken from Lanz et al., 2013b and Gindrat et al. 2014 (open access publications; see references below).

Selected Publications

Lanz F, Moret V, ***Rouiller EM***[&]*, Loquet G*[&]
Multisensory integration in non-human primates during a sensory-motor task. Frontiers in Human Neurosciences Nov 20;7: 799, 2013a
[&]*Equal senior authorship*

Lanz F, Lanz X, Scherly A, Moret V, Gaillard A, Gruner P, Hoogewoud HM, Belhaj-Saif A, Loquet G, ***Rouiller EM***
Refined methodology for implantation of a head fixation device and chronic recording chambers in non-human primates. J. Neurosci. Meth. 219: 262-270, 2013b

Wyss AF, Hamadjida A*, Savidan J*, Liu Y, Bashir S, Mir A, Schwab ME,* ***Rouiller EM***[&]*, Belhaj-Saif A*[&]
Long-term motor cortical map changes following unilateral lesion of the hand representation in the motor cortex in macaque monkeys showing functional recovery of hand functions. Rest. Neurol. and Neurosci. 31: 733-760, 2013
**Equal first authorship*
[&]*Equal senior authorship*

Gindrat AD, Quairiaux C*, Britz J, Brunet D, Lanz F, Michel CM*[&] *and Rouiller EM*[&]
Whole-scalp EEG mapping of somatosensory evoked potentials in macaque monkeys. Brain Structure and Function May 2014 (Epub ahead of print)
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Beat Schwaller
Anatomy

Calcium signaling in health and disease

INTRODUCTION

Ca^{2+} signaling plays an essential role in almost all aspects of biological processes. For this, cells are equipped with sophisticated machinery named the Ca^{2+} signaling toolkit. Cytosolic Ca^{2+}-binding proteins of the EF-hand family including parvalbumin (PV), calbindin D-28k (CB) and calretinin (CR) are essential components of this toolkit, i.e. in those cells expressing these proteins. In my research we focus on the role of PV in the brain, mostly based on studies of transgenic mice carried out *in vitro* and *in vivo*.
In addition to its expression in specific neurons, CR is additionally expressed in a subfamily of tumors; most importantly CR serves as a specific marker for malignant mesothelioma (MM), a tumor strongly associated with asbestos exposure. In several projects, we investigate the putative role of CR in mesotheliomagenesis using *in vitro* (***Fig.1***) and recently also *in vivo* approaches using transgenic mouse models. Based on some similar characteristics of asbestos fibers and newly developed nanomaterials (NM), we also investigate mechanisms (uptake, intracellular distribution) of such materials in cells likely exposed to these materials after inhalation, i.e. in lung epithelial cells, macrophages, fibroblasts and finally mesothelial cells. Since CR has been identified as a *bona fide* Ca^{2+} sensor interacting with target proteins, we also investigate structural details of such interactions.

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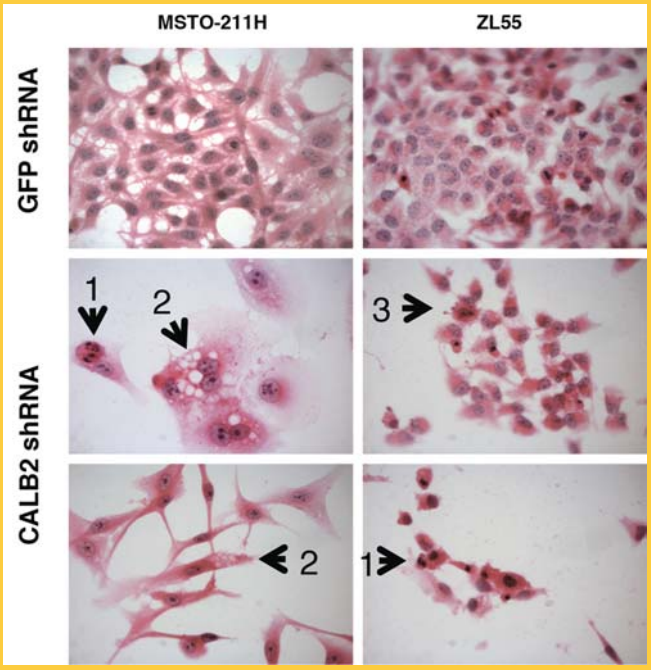

Fig.1 - Down-regulation of CR in malignant mesothelioma cells blocks proliferation and induces apoptosis. *HE staining of MSTO-211H and ZL55 cells after CALB2 #5 shRNA-mediated CR down-regulation showing morphological changes and apoptotic cells. MSTO-211H and ZL55 cells treated with GFP shRNA (first row) show no alterations in comparison to untreated control cells 96h post-infection. Cells depicted in the two lower rows were treated with CALB2 shRNA for 96 h. Remaining cells have pyknotic nuclei (1), are giant cells with vacuoles (2) and display plasma membrane blebbing (3) (from Blum W & Schwaller B, Intl. J. Cancer 133:2077-88, 2013)*

Further evidence of calretinin (CR) acting as a Ca^{2+} sensor in cerebellar granule cells and the important role of CR in proliferation and survival of mesothelioma cells *in vitro*

Besides the role of CR as a Ca^{2+} buffer affecting the shape and timing of intracellular Ca^{2+} signals, our lab has identified CR's Ca^{2+}-sensor function by demonstrating its ability to bind to the cytoplasmic linker between domains II and III of the pore-forming alpha subunit $\alpha_1$2.1 (P/Q type Ca^{2+} channel). In collaboration with the lab of J. Eilers & H. Schmidt, University of Leipzig, Germany, we investigated the diffusional mobility of CR in cerebellar granule cells (GC) by two-photon fluorescence recovery after photobleaching (FRAP). In comparison to dextrans of similar size, the mobility of CR inside the GC cytoplasm is rather slow and moreover, an increase in the cytoplasmic Ca^{2+} concentration in GC dendrites further reduces CR's mobility (***Fig.2***). CR's mobility is increased by the addition of a peptide embracing the EF-hand 5 domain of CR. This indicates long-lasting, Ca^{2+}-dependent interactions of CR with large and/or immobile binding partners in GC dendrites likely via the EF-hand 5 domain region and further supportive of a Ca^{2+} sensor function of CR.

Malignant mesothelioma (MM) are highly aggressive asbestos-related neoplasms, which show strong chemotherapy resistance, and there is no effective cure for MM so far. CR immunohistochemistry is widely used as a diagnostic marker for epithelioid and mixed (biphasic) mesothelioma. In a recent study we investigated CR's putative function(s) in tumorigenesis. We had shown before that CR protects against asbestos-induced acute cytotoxicity mediated by the AKT/PI3K pathway. Down-regulation of CR via lentiviral-mediated short-hairpin RNA significantly decreases the viability and proliferation of mesothelioma cells *in vitro*. The effect is particularly strong in epithelioid-dominated cell lines, but to a lesser extent is also seen in MM with prevalent sarcomatoid morphology. Depletion of CR leads these MM cell lines to enter apoptosis within 72 h post-infection via strong activation of the intrinsic caspase 9-dependent pathway. Down-regulation of CR in immortalized (non-malignant) mesothelial cells strongly blocks proliferation and causes a G1 block without decreasing viability or activating apoptosis pathways. These results demonstrate that down-regulation of CR has a strong effect on the viability of MM cells and that CR is essential for cells derived from MM. We anticipate these findings to reveal CR as a highly interesting new putative therapeutic target for MM treatment of especially the epithelioid, as well as of the mixed and possibly also the sarcomatoid MM type.

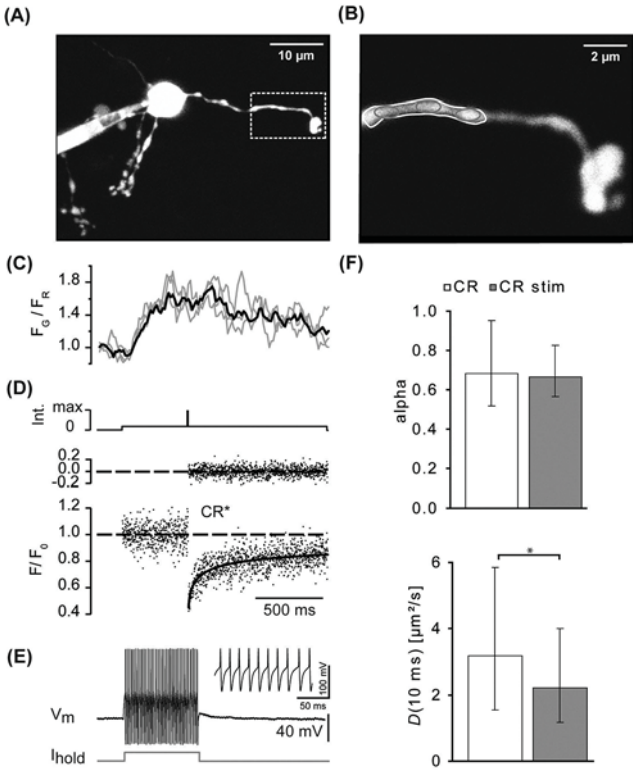

Fig.2 - Decreased mobility of fluorescently labeled calretinin (CR*) in granule cell dendrites during neuronal activity. **A)** *A cerebellar granule cell loaded with 50 µM OGB-1 and 50 µM Atto-637 via a somatic patch pipette. The box delineates the dendritic region (shown magnified in* **B)***) from which the fluorescence signals were recorded. The corresponding regions of interest are denoted by solid and dashed ellipses.* **C)** *OGB-1 ($\Delta F/F_0$) signals recorded from the dendritic regions indicated in* **B)** *after brief depolarization.* **D)***, FRAP time course of CR* during repetitive firing (average of six recordings). The continuous line represents a fit of the recovery to the subdiffusion equation.* **E)** *Voltage response (V_m) to a somatic current injection (I_{hold}) of the granule cell shown in* **A)** *leading to an increase in the intracellular Ca^{2+} concentration $[Ca^{2+}]_i$.* **F)** *The diffusional mobility of CR* is significantly decreased, when $[Ca^{2+}]_i$ in the dendrite is increased after depolarization (lower part) (image adapted from Arendt et al. (2013). Alpha values (anomalous subdiffusion coefficients) possibly reflecting cellular hindrances are not different in control and stimulated cells (upper part).*

The cytosolic Ca^{2+} buffer parvalbumin influences the temporal precision of neuron firing, modulates the firing properties of the reticular thalamic nucleus bursting neurons and affects visual thalamocortical circuits

Striatal fast spiking, PV-expressing interneurons (FSI) modulate striatal output by synchronizing medium-sized spiny neurons (MSN). In perforated patch recordings of brain slices of PV-/- mice, FSI were shown to fire more regularly and are more excitable than control (WT) FSI by a mechanism in which Ca^{2+} buffering is linked to spiking activity as a result of the activation of small conductance Ca^{2+}-dependent K^+ (SK) channels. In line with previous results at other synapses (e.g. cerebellar interneurons to Purkinje cells), paired-pulse facilitation at FSI to MSN synapses is also increased. This indicates that PV is essential for fine-tuning of the temporal responses of the FSI network and for the orchestration of MSN populations.
Most of mouse reticular thalamic nucleus (RTN) neurons are PVergic, receive afferences from both the thalamus and the cerebral cortex and send projections mainly onto thalamocortical neurons. Moreover, these neurons are characterized by low-threshold Ca^{2+} currents, I_T, mediated by Ca_V3-type channels. Extracellular *in vivo* recordings in anesthetized mice revealed the existence of 4 types of neurons characterized on the basis of their firing pattern. The 4 types are present in WT as well as in PV-/- mice; however one type, the medium bursting type is more prevalent in PV-/- mice and moreover these neurons show longer interspike intervals within the burst without the number of spikes being affected. Thus, we hypothesize that PV may affect the firing properties of RTN neurons via a mechanism associated with the kinetics of burst discharges. This is supported by the findings that I_T current-mediating $Ca_V3.2$ channels are more localized to the somatic plasma membrane of RTN neurons in PV-/- mice. Thus, the differential localization of $Ca_V3.2$ in the PV-/- neurons may affect bursting dynamics and cause subtle alterations in the regulation of the activity in the thalamocortical circuit. Finally the role of PV at the level of the thalamocortical circuit was investigated, as the involved regions, the dorsal lateral geniculate nucleus (dLGN), the visual cortex (VC) and the RTN contain a subpopulation of PV-expressing neurons. *In vivo* extracellular electrophysiological recordings simultaneously in dLGN, RTN and VC of anesthetized WT and PV-/- mice showed the firing rates of VC and RTN cells to be increased in PV-/- during spontaneous activity as well as in the presence of a photic stimulation; firing properties of dLGN cells was unaltered. Our analyses provide new evidence on the important role played by PV in regulating information processing in the central visual pathway suggesting that the ability to process information along parallel channels is decreased in the thalamocortical pathway of PV-deficient mice. ■

Selected Publications

Orduz D, Bischop DP, ***Schwaller B****, Schiffmann SN, Gall D*
Parvalbumin tunes spike-timing and efferent short-term plasticity in striatal fast spiking interneurons. J Physiol. 2013;591(Pt 13):3215-32. Epub 2013/04/05

Lintas A, ***Schwaller B****, Villa AE*
Visual thalamocortical circuits in parvalbumin-deficient mice. Brain Res. 2013. Epub 2013/05/07

Blum W, ***Schwaller B***
Calretinin is essential for mesothelioma cell growth/survival in vitro: A potential new target for malignant mesothelioma therapy? International journal of cancer Journal international du cancer. 2013;133(9):2077-88. Epub 2013/04/19

Arendt O, ***Schwaller B****, Brown EB, Eilers J, Schmidt H*
Restricted diffusion of calretinin in cerebellar granule cell dendrites implies Ca2+-dependent interactions via its EF-hand 5 domain. J Physiol. 2013;591(Pt 16):3887-99. Epub 2013/06/05

Alberi L, Lintas A, Kretz R, ***Schwaller B****, Villa AE*
The calcium-binding protein parvalbumin modulates the firing properties of the reticular thalamic nucleus bursting neurons. Journal of Neurophysiology. 2013;109(11):2827-41. Epub 2013/03/15

Wolfgang Taube
Chair of Movement and Sport Science
Motor control and motor learning

INTRODUCTION

Our research interest lies in the area of neural control of human movement and how interventions can induce neural plasticity to improve, restore or maintain neuromuscular function. In general, our research aims to clarify basic mechanisms of motor control, motor learning and training in order to transfer this knowledge into functional and applied settings, especially in the areas of sports sciences, prevention and rehabilitation. The work of our research can be categorized into three main domains:

1) Neural control of posture and neural plasticity in response to balance training;

2) Biomechanical analysis of motor tasks such as the comparison of overground and treadmill running;

3) Behavioural adaptations to non-physical training (mental training) and its underlying mechanisms.

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SECRETARY
Béat Golliard-Kaech
Jasmine Vallelian

MAITRE ASSISTANT
Didier Staudenmann

LAB MANAGER
Martin Keller

POSTDOCTORAL FELLOWS
Christian Leukel (part-time)
Jacques Robadey (part-time)
Xavier Chenevière (works mainly as Conseiller aux études)

PHD STUDENTS
Martin Keller
Audrey Mouthon
Johanna Hänggi
Konstantin Beinert
Jan Ruffieux
Michael Wälchli
Karin Sonderegger
Lilian Roos
Rahel Ammann

UNDERGRADUATES
Christoph Mayer
Erik Reichelt
Yves-Alain Kuhn
Maria Ruffieux

Brain activity during observation and motor imagery of different balance tasks: an fMRI study

After immobilization, patients show impaired postural control and increased risk of falling. Therefore, loss of balance control should already be counteracted during immobilization. Previously, studies have demonstrated that both motor imagery (MI) and action observation (AO) can improve motor performance. The current study elaborated how the brain is activated during imagination and observation of different postural tasks to provide recommendations about the conception of non-physical balance training. For this purpose, participants were tested in a within-subject design in an fMRI-scanner in three different conditions: (a) AO+MI, (b) AO, and (c) MI. In (a) participants were instructed to imagine themselves as the person pictured in the video whereas in (b) they were instructed simply to watch the video. In (c) subjects closed their eyes and kinesthetically imagined the task displayed in the video. Two tasks were evaluated in each condition: (i) static standing balance and (ii) dynamic standing balance (medio-lateral perturbation). In all conditions the start of a new trial was indicated every 2 seconds by a sound.

During AO+MI of the dynamic task, participants activated motor centers including the putamen, cerebellum, supplementary motor area, premotor cortices (PMv/d) and primary motor cortex (M1). MI showed a similar pattern but no activity in M1 and PMv/d. In the SMA and cerebellum, activity was generally higher in the dynamic than in the static condition. AO did not significantly activate any of these brain areas.

Our results showed that (I) mainly AO+MI, but also MI, activate brain regions important for balance control; (II) participants display higher levels of brain activation in the more demanding balance task; (III) there is a significant difference between AO+MI and AO. Consequently, best training effects should be expected when participants apply MI during AO (AO+MI) of challenging postural tasks.

Difference in mechanical work expenditure between overground and treadmill locomotion

Despite the finding of some biomechanical differences (e.g. stance phase) between overgound (OG) and treadmill (TM) locomotion, most studies assume no relevant peculiarity of TM locomotion. The aim of this study was to investigate whether the mechanical energy costs differ between TM and OG and how this is related to changes in kinematics and muscular activity. Ten healthy subjects walked and ran with the same velocities OG and on the TM. Full body kinematics allowed to estimate contact time, heel-toe delay, landing angle, and center of mass (COM) to determine force variation (ΔF), leg stiffness, as well as potential, kinetic vertical/forward, elastic and total mechanical energy (Ep, Ekv, Ekf, Ee, Em) from which we determined the respective means and variations (ΔE's). Moreover the activity of eight lower limb muscles was assessed.

Although mean Em showed no difference between conditions, we found a significant reduction in ΔEkf for TM walking and running (-5%, -8%) that was accompanied by a more vertical landing angle and a higher leg stiffness resulting in a lower mean Ee. Moreover running, but not walking, showed a reduction in ΔEm (-8%) for each step and a reduction of the activity of leg muscles that was accompanied by a reduction in heel-toe delay (-31%) on the TM. The current study showed for the first time a difference in movement execution between OG and TM locomotion that has consequences on the mechanical energetic costs. The reduced ΔEm and the decrease in muscle activity indicate that running, but not walking, requires less mechanical work expenditure on the TM compared with OG.

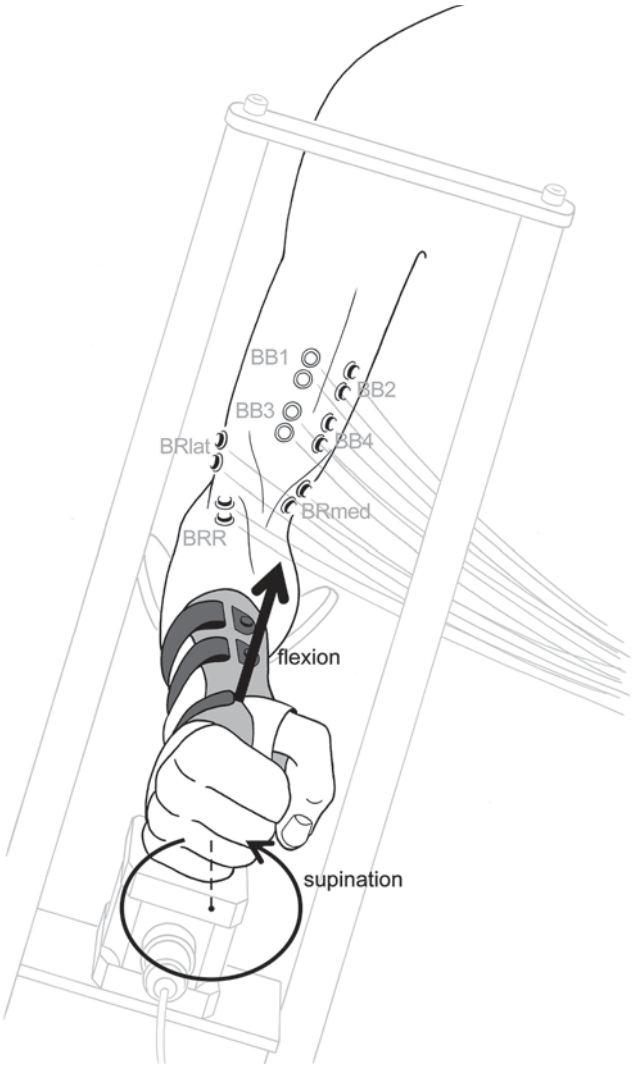
Changes in corticospinal transmission following 8 weeks of ankle joint immobilization

Joint immobilization has previously been shown to modulate corticospinal excitability. The present study investigated changes in the excitability of distinct fractions of the corticospinal pathway by means of conditioning the H-reflex with transcranial magnetic stimulation (TMS) of the primary motor cortex (Hcond). This method allows assessment of transmission in fast (monosynaptic) and slow(er) (polysynaptic) corticospinal pathways. 9 participants underwent 8weeks of unilateral ankle joint immobilization during daytime, 7 participants served as controls. The measures obtained before and after immobilization included stretch- and H-reflexes assessing excitability of the spinal reflex circuitries, TMS recruitment curves estimating overall changes in corticospinal excitability, and Hcond. TMS recruitment curves showed an overall increase in corticospinal excitability following immobilization. Importantly, Hcond revealed significant facilitation of conditioned reflexes, but only for longer conditioning intervals, suggesting that immobilization increased excitability only of slower, indirect corticospinal pathways. No changes were observed in the control group. Immobilization had no significant effects on spinal reflex measures. 8 weeks of ankle joint immobilization was accompanied by pathway-specific modulation of corticospinal transmission. It is particularly interesting that fast corticospinal projections were unaffected as these are involved in controlling many, if not most, movements in humans.

Brachialis muscle activity can be assessed with surface electromyography

The brachialis muscle (BR) represents an important elbow flexor and its activity has so far mainly been measured with intramuscular electromyography (EMG). The aim of this study was to examine whether the activity of the BR can be assessed with surface EMG without interference from the biceps brachii (BB). With eight subjects we measured surface EMG of the arm flexor synergists, BR, BB, and brachioradialis (BRR) during two isometric voluntary ▸▸

contraction types: 1) pure elbow flexion and 2) elbow flexion with a superimposed forearm supination. Since the BR and BB have a distinct biomechanical function, an individual activity of the BR can be expected for the second contraction type, if the BR can be assessed independently from the BB. The correlation coefficients between EMG amplitudes and flexion force (supination torque) were determined. During pure flexion the activities of all synergists were similarly correlated with the flexion force (r=0.96±0.02). During flexion+supination the activity of the BR was distinct from the activity of the BB, with a 14% higher correlation for the BR with the flexion force and a 40–64% lower correlation with the supination torque. The BB predicted supination torque substantially better than the BR and BRR (r=0.93±0.02). The current results demonstrate that the activity of the BR can be assessed with surface EMG as it was distinct from the BB during flexion+supination but predicted flexion force equally well as BB during the pure flexion contraction. ■



Selected Publications

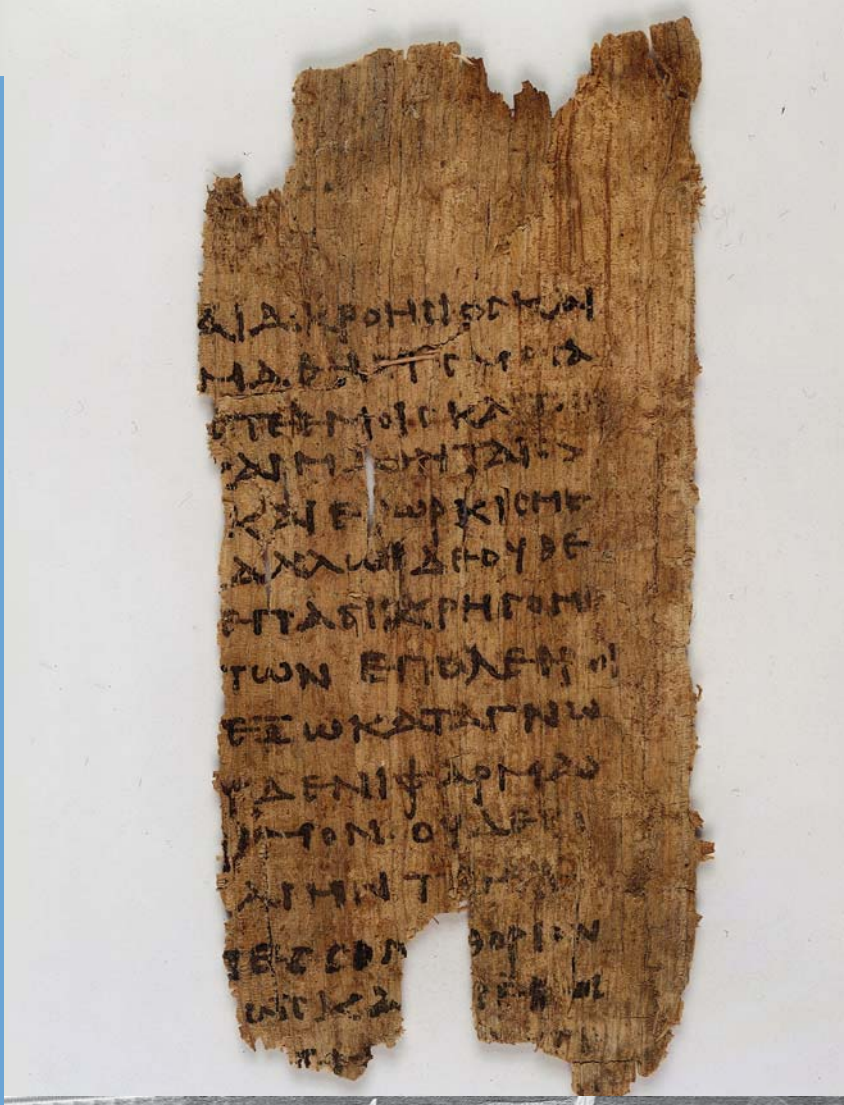
Beinert K, ***Taube W***
The effect of balance training on cervical sensorimotor function and neck pain. Journal of motor behavior 45:271-278, 2013

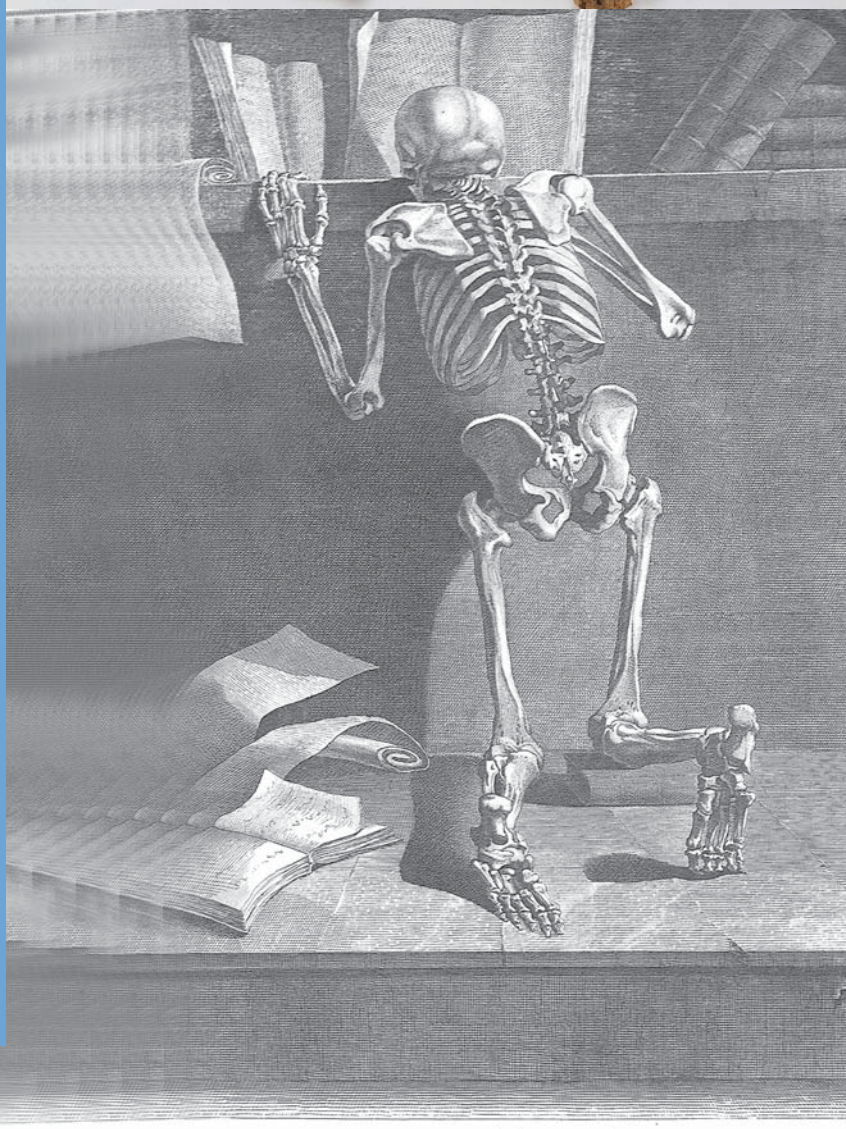
Taube W*, Leukel C, Nielsen JB, Lundbye-Jensen*
Repetitive Activation of the Corticospinal Pathway by Means of rTMS may Reduce the Efficiency of Corticomotoneuronal Synapses. J. Cereb Cortex, 2014

Keller M, Lauber B, Gehring D, Leukel C, ***Taube W***
Jump performance and augmented feedback: immediate benefits and long-term training effects. Human movement science 36:177-189, 2014b

Medical Humanities Medicine and society forms a cluster whose vocation is to confront biomedical science and medical practice with their social, ethical and cultural stakes.

The research projects are based on team searching between the representatives of the different disciplines and institutions. The research domains concern notably the representations of the medical doctor and medicine in the arts, the rhetoric of scientific discourse, and the history of the relationship between doctors and patients. One part of the research also concerns the interactions between medical humanities and digital humanities: it explores, inter alia, the influence of IT on medical practice.





Orate ne intretis in tentationem

Alexandre Wenger

Medicine, social sciences and the humanities

Alexandre Wenger
Chair of Medicine and Society
Medicine, social sciences and the humanities

INTRODUCTION

The Medicine and Society chair focuses its research and teaching activities on the relationship between **medical practice** and its **social implications**. Social sciences and the humanities will be drawn upon to:

1) reflect on the contemporary developments in healthcare

2) foster interdisciplinary dialogue

3) highlight the ethical, social, cultural, legal, economic or intellectual aspects of medical practice

4) help students position themselves as future practitioners within a rather complex health system

GROUP LEADER
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SECRETARY
Margrit Walthert

ASSISTANT LECTURER
Julien Knebush, PhD

POSTDOCTORAL FELLOW
Radu Suciu, PhD

DOCTORAL CANDIDATE
Bénédicte Prot

Recruitement is underway for new collaborators who will join the team. Namely a web developer, engaged to lead an online experiment in cultural data curation, and two scientific collaborators as part of an SNF Project on the figure of the physician-poet in the 20th century.

Main Research Activities

Our research deals mainly with the interactions between the biomedical sciences and the arts, namely:

- past and present representations of the physician (novels, paintings, contemporary mass media) and their impact on doctor/patient relationships.
- forms of medical communication in contemporary and historical contexts (ie medical case histories and scientific evidence, scientific poetry, narrative based medicine, etc.).
- aesthetics and medicine (medical metaphors in literature, artistic representations of diseases, etc. from the 16th to the 20th century)

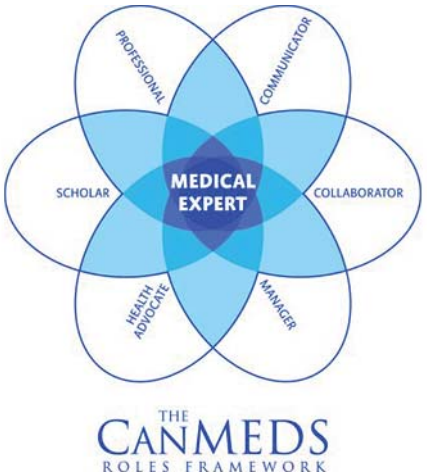
Medicine and Society Teaching Program

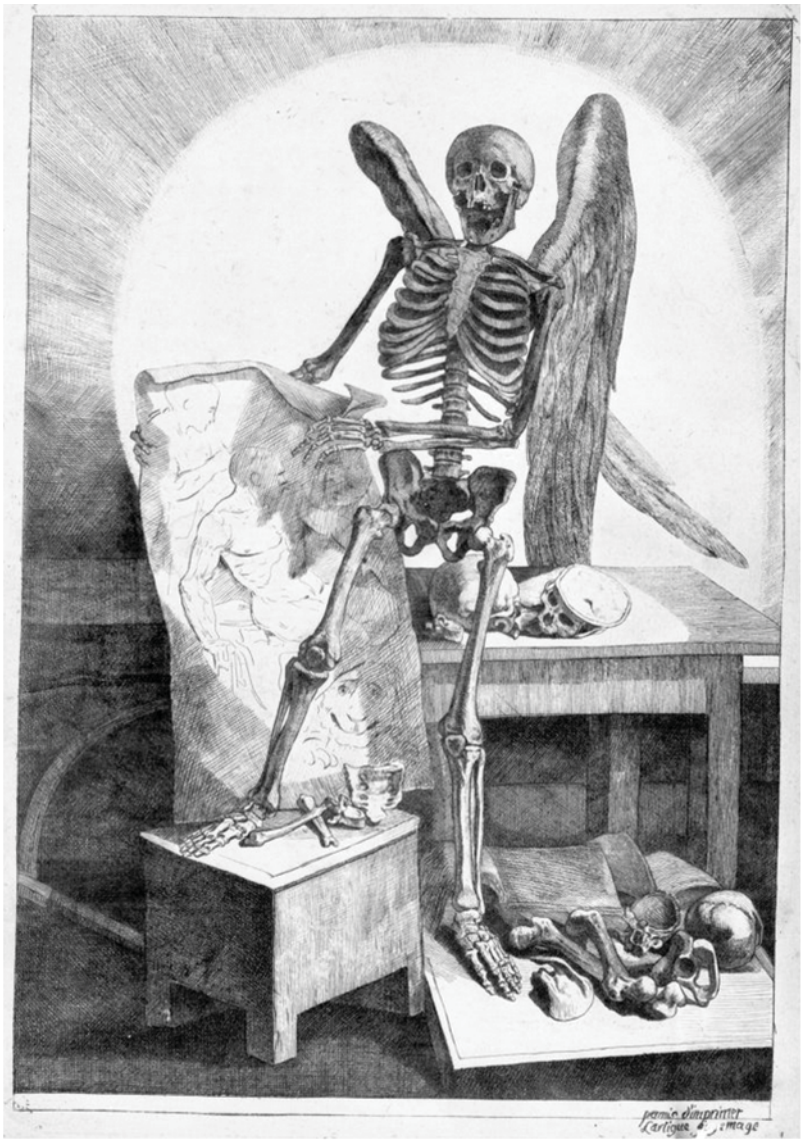
Since its official launch in October 2012, custom courses have been offered to students as part of their bachelor degree. In the first year, the program focuses on a number of ex cathedra lectures. During the second and mostly the third year, a more interactive and interdisciplinary approach is projected: previously selected case-studies will be presented and discussed with students.

The Medicine and Society lectures are given by renowned specialists, helping students to get accustomed to a vast array of bio-ethics, medical humanities or public health related issues:

- ***Ethics*** (Christina Aus der Au Heymann, UniBas; Eve Rubli Truchard, CHUV; Markus Zimmermann-Acklin, UniFr)
- ***Public health*** (Philippe Chastonay, UniFr)
- ***History of Medicine*** (Hubert Steinke, UniBe)
- ***Literature, cinema and medicine*** (Alexander Wenger, UniFr; Julien Knebusch, UniFr)
- ***Medical Law*** (Jean-François Dumoulin, UniFr; Christiana Fountoulakis, UniFr; Alexis Overney UniFr; Franz Werro, UniFr)
- ***Medical Anthropology*** (Corina Salis-Gross, UniBe)
- ***Health Economics*** (Stéphane Guérard, UZh)
- ***Health geography*** (Pascal Handschumacher, Univ. Strasbourg)
- ***Neuroscience and philosophy*** (Bernard Baertschi, UniGe)
- ***Medicine and the media*** (Pierre-Alain Raeber, UniFr; Patrick Nussbaum, RTS)
- ***Creative writing*** (Julien Knebusch, UniFr, Alexander Wenger, UniFr)

Every year, a seminar is organised as part of the program around a current or controversial subject related to medicine and society (e.g. DRGs, e-health, etc). The lectures and seminars prepare students to better understand their future roles within the medical community. In this respect, the Medicine and Society program follows closely the *Swiss Catalogue of Learning Objectives for Undergraduate Medical Training* as well as the *CanMEDS Roles Framework*. ■





Gamelin, Jacques, *Nouveau recueil d'ostéologie et de myologie*, 1779 (BIUS open access).

Selected Publications

Wenger A
«La place de l'histoire naturelle dans *La Nouvelle Justine*, ou Sade lecteur de J. B. Robinet», in *Romance studies* vol. 32/3, 183-193, 2014. Special Issue *Sade, l'inconnu?*

Wenger A
«Médecine, littérature, histoire», DHS 46, 323-336, 2014

Online publication
Medicine and food. A digital exhibition. Accessible on the Internet at the address manger.unifr.ch (for French) and essen.unifr.ch (for German)

Third party funding to group leaders

Group Carole Bourquin

Swiss National Science Foundation - Project: «Immunotherapy of gastric cancer: Enhancing T-Cell recruitment into tumors»

Swiss National l Science Foundation - ProDoc Program - ProDoc, Cell Migration Research Module 2 - Project: «Tumorgenesis and metastasis»

Swiss National l Science Foundation - ProDoc Program - ProDoc, Cell Migration Research Module 3 - Project: «Soluble factors in Cell Migration»

Swiss National Science Foundation - Project: «NCCR - Bio-inspired Material»

Swiss National Science Foundation - Project: «Understanding of interaction of nanoparticles with B lymphocytes in vitro and in vivo»

Swiss National Science Foundation - Equipment Grant 'R'Equip' - Project: «Microchip-based flow cell sorting in biomedicine and material sciences»

Swiss Cancer League - Project: «Enhancing anticancer immunity through sequental stimulation of innate immune pathways»

Group Abdul G. Dulloo

Swiss National Science Foundation
(Individual Research Grants 2010-2013; 2014-2017)

Group Anna Lauber-Biason

Swiss Society for Endocrinology and Diabetology Cohort Study (2014-2015)

Group Pierre Lavenex

SNF 2012-2015

Group Jean-Pierre Montani

SNF-122554 Mechanisms of cardio-vascular and autonomic dysregulation induced by caffeinated soft drinks in humans.
01.03.2009 - 30.09.2013

SNF-NCCR-Kidney.CH Regulation of energy metabolism by the kidney.
01.08.2010 - 31.07.2014

SNF-NCCR-Kidney.CH Dietary amino acids: impact on progression of renal diseases.
01.08.2014 - 31.07.2018

SNF-135684 (G. Solinas) Investigating the role of PI3Kgamma in obesity-related diseases.
01.05.2011 - 30.04.2014

SNF-152998 (G. Solinas) Investigating the Role of PI3Kgamma in Obesity and Insulin Resistance.
1.5.2014 - 30.4.2016

Group Patrice Nordmann

TEMPOTEST 2010 - 2013: An Integrated Tool-Kit for the Clinical Evaluation of Microbial Detection and Antibiotic Susceptibility Point-of-Care Testing Technologies. (Coordinator: JP Hays, Netherlands)

ITRIBiS 2013 - 2015: Improving Translational Research Potential at the Institute of Biomedicine of Seville. (Coordinator : Prof. José Lopez-Barneo, Spain)

R-GNOSIS 2011 - 2016: Resistance in Gram-Negative Organisms : Studying Intervention Strategies. (Coordinator : M. Bonten, Utrecht, Netherlands)

MAGIC-BULLET 2011 - 2014: Optimization of treatment with off-patent antimicrobial agents of aeruginosa and other multidrug-resistant Gram negative bacilii. (Coordinator: José Miguel Cisneros Herreros, Sevilla, Spain)

Group Gregor Rainer

ESF EURYI Program, 2008-2016

SNF Prodoc Program, 2012-2015

SNF Research grant, 2012-2015

EPFL-HU joint initiative, 2013-2014

SNF Requip, 2014

Group Eric M. Rouiller

NCCR Neuro, external partner, 2001 - 2013

Swiss National Science Foundation, grant No 132465, 2010 - 2013

Swiss National Science Foundation, Grant «Semester of Research for outcoming member of the research council», No 144990, August 2012 - January 2013

Swiss National Science Foundation, partner in Sinergia grant «Prometheus» No 125408, 2010 - 2013, prolongation till March 2014

Swiss National Science Foundation, grant No 149643, 2013 - 2016

CUS (Swiss University Conference) and SERI (State Secretariat for Education, Research and Innovation) grant to support the SPCCR (Swiss Primate Competence Center for Research) at UniFr and UniZh, program PCI 8, 2013 - 2016

Group Curzio Rüegg

SNSF Sinergia 2015 - 2018 (Co-applicant: V. Djonov and G. Solinas)
CRSII3_154499 Investigating the Role of Class-1 PI3K signaling in Obesity-Mediated Tumor Promotion: the interplay between fat metabolism, inflammatory cells and angiogenesis

SNSF R'Equip, 2014 316030_157752 Microchip-based flow cell sorting in biomedicine and material sciences

SNSF R'Equip, 2014 (Co-applicant: PI MN Girard) High frequency, high resolution Ultrasound imaging platform (Vevo2100) for preclinical imaging

SNSF NCCR Bioinspired Materials 2014 - 2018 Targeting Single Cancer Cells with a Self-Amplifying Nanoparticle System

SNSF ProDoc, DFMP3_137079_1_RM2, extension 2015 - 2016
«Cell migration in tumorigenesis and metastasis» as part of the ProDoc «Cell migration»

Fondazione Sassella, 2103 - 2014 Unraveling systemic effects of local radiotherapy contributing to prevent or promote distant breast cancer metastasis

Medic Foundation 2015 - 2018, Unravelling mechanisms of breast cancer dormancy

Swiss Cancer League 2015 - 2018, KSF-3513-08-14- Unraveling cellular and molecular mechanisms of breast cancer metastasis to the brain

Group Beat Schwaller

SNF 2010 - 2013

San Salvatore 2012 - 2014

Sinergia 2014 - 2017

SNF 2015 - 2018

Group Wolfgang Taube

SNF 2012 - 2015
Wolfgang Taube (main applicant) and Jean-Marie Annoni (co-applicant): «Observational and imaginary balance training - Evaluation of behavioural changes and their underlying neural adaptations»

BASPO 2013 - 2014
Xavier Chenevière (main applicant) and Wolfgang Taube (co-applicant): «Unmittelbare Effekte und Langzeiteffekte verstärkenden Feedbacks auf die Laufökonomie»

BASPO 2013 - 2014
Wolfgang Taube (main applicant) and Martin Keller (co-applicant): «Does the age of children affect the adaptations in response to balance training?»

BASPO 2012 - 2013
Didier Staudenmann (main applicant) and Wolfgang Taube (co-applicant): «Biomechanisch-energetische Differenzen bei der Fortbewegung auf dem Laufband und auf dem Boden»

Group Alexandre Wenger

Swiss National Science Foundation - Research project grant

Group Zhihong Yang

SNF, April 1, 2012 - March 31, 2015

CSC Project, October 1, 2012 - September 30, 2016

Swiss Heart Foundation, 2013 - 2014

Swiss Heart Foundation, 2014 -2015

NCCR-Kidney.CH, 2014 - 2018

External experts for grant evaluation:

Swiss National Science Foundation, 2013

DFG-Sonderforschungsbereiche, Forschungszentren, und Exzellenzcluster of the Julius-Maximilians-University Würzburg, Germany, 2013

Max-Kade-Foundation, 2013

Publications

Group Carole Bourquin

Heidegger S, Anz D, Stephan N, Bohn, B, Herbst T, Fendler WP, Suhartha N, Sandholzer N, Kobold S, Hotz C, Eisenächer K, Radtke-Schuller S, Endres S, Bourquin C
Virus-associated activation of innate immunity induces rapid disruption on of Peyer's patches in mice. Blood, 2013, 122:2591-9

Yan Y, Jiang W, Spinetti T, Tardivel A, Castillo R, Bourquin C, Guarda G, Tian Z, Tschopp J, Zhou R
Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. Immunity, 2013,38(6):1154-63

Heidegger S, Kirchner S, Stephan N, Bohn B, Suhartha N, Hotz C, Anz D, Sandholzer N, Stecher B, Rüssmann H, Endres S, Bourquin C
TLR activation excludes circulation naive CD8+ T cells from gut-associated lymphoid organs in mice. J. Immunol., 2013, 190:5313-20

Kobold S, Steffen J, Chaloupka M, Grassmann S, Henkel J, Castoldi R, Zeng Y, Chmielewski M, Schmollinger JC, Schnurr M, Rothenfußer S, Schendel DJ, Abken H, Sustmann C, Niederfellner G, Klein C, Bourquin C, Endres S
Selective bispecific T cell recruiting antibody and antitumor activity of adoptive T cell transfer. J Natl Cancer Inst. 2014, 107(1):364

Anz D, Kruger S, Haubner S, Rapp M, Bourquin C, Endres S
The dipeptidylpeptidase-IV inhibitors sitagliptin, vildagliptin and saxagliptin do not impair innate and adaptive immune responses. Diabetes Obes Metab., 2014, 16 :569-72

Roehnisch T, Then C, Nagel W, Blumenthal C, Braciak T, Donzeau M, Böhm T, Flaig M, Bourquin C, Oduncu F** **shared senior authorship*
Phage idiotype vaccination: first phase I/II clinical trial in patients with multiple myeloma. Journal of Translational Medicine, 2014, 12:119

Group Stéphane Cook & Mario Togni

Smits PC, et al.
Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet., 2013, 381(9867):651-60

Fournier S, Puricel S, Morawiec B, Eeckhout E, Mangiacapra F, Trana C, Tapponnier M, Iglesias JF, Michiels V, Stauffer JC, Beggah A, Monney P, Gobet S, Vogt P, Cook S, Muller O
Relationship between time of day and periprocedural myocardial infarction after elective angioplasty. Chronobiology International., 2014, 31(2):206-13

Frobert A, Valentin J, Cook S, Giraud MN
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Group Gregor Rainer

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Group Eric M. Rouiller

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*Equal first authorship

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[&]Equal senior authorship

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[&]Equal senior authorship

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*Equal first authorship
[&]Equal senior authorship

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*Equal first authorship
[&]Equal senior authorship

Group Curzio Rüegg

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Group Beat Schwaller

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Group Wolfgang Taube

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Group Alexandre Wenger

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Marchal H (dir.), Chométy P, De Mulder C, Élie B, Guellec L, Laniel-Musitelli S, Louâpre M, Seth C, Wanlin N, Wenger A
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Dünne J, Mahler A, Knebusch J (éds.)
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On-line events

Knebusch J, Prot B, Suciu R, Wenger A
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Suciu R. Contributions au catalogue en ligne de l'exposition Le Lecteur à l'œuvre, Fondation Martin Bodmer, Avril 2013

Articles

Prot B
Le Médecin de l'amour (1787) de F.-A. Doppet : la fiction au service d'une nouvelle théorie médicale. TrOpics. Revue électronique des Lettres et Sciences humaines de l'Université de La Réunion. Fictions et sciences, 2013, 1, 67-78

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Group Zhihong Yang

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This study was highlighted by an Editorial in JAHA written by *Drs. Deepesh Pandey, Lewis Romer and Dan E. Berkowitz* (http://jaha.ahajournals.org/content/2/4/e000392.full.html?etoc)

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Dissertations

Group Carole Bourquin

PHD THESES
Nina Suhartha
LMU Munich
Friederieke Saathoff
LMU Munich
Moritz Rapp
LMU Munich

MD THESES
Helen Bauer
LMU Munich
Bernadette Bohn
LMU Munich
Alex Jarosch
LMU Munich
Sophie Kirchner
LMU Munich
Nicolas Stephan
LMU Munich

MASTER OF BIOMED THESES
Isabelle Wey
BMS UniFR
Inès Mottas
BMS UniFR
Eva Schrom
BMS UniFR
Matthieu Piccand
BMS UniFR

BACHELOR OF BIOMED THESES
Sevil Necetin
BMS UniFR
Ludiwine Aeby
BMS UniFR
Lukas Studer
BMS UniFR

MENTORING
Julia Esser
Réseau romand de mentoring pour femmes
Francesca Siclari
Réseau romand de mentoring pour femmes

Group Abdul G. Dulloo

PHD THESES
Delphine Sarafian, 2013
University of Fribourg

Group Anna Lauber-Biason

PHD THESES
Mariangela Franco

MASTER OF MEDICINE THESES
Anna Baumann
University of Zurich
Raphael Persi
University of Zurich

Group Pierre Lavenex

PHD THESES
Grégoire Favre, 2013

Group Jean-Pierre Montani

PHD THESES
Fabio Zani (February 2013)

MASTER MED THESES
Luis Miguel Girona (April 2014)

Group Patrice Nordmann

PHARMACY THESES
Caroline Errera, 2013
Université de Paris Sud

PhD THESES
Anais Potron, 2013
Université Paris Sud
Aurélie Jayol, 2014
Université Paris Sud
Frédéric Amado, 2014
Université Paris Sud

MASTER DEGREE THESES
Sébastien Ducroz, 2013
Université Paris Sud
Samira Abbas, 2013
Université Paris Sud
Aurélie Jayol, 2013
Université Paris Sud
Nicolas Kieffer, 2014
Université Claude Bernard Lyon 1
University of Fribourg

BACHELOR OF BIOMED THESES
Bettina Zimmermann, 2014
University of Fribourg

Group Gregor Rainer

PhD THESES
Anwesha Bhattacharrya, 2013
Julia Veit, 2013
Filomena Petruzziello, 2014

Group Eric M. Rouiller

PHD THESES
Florian Lanz

MASTER THESES
Michela Fregosi
Ekaterina Fortis
Camille Roux

Group Curzio Rüegg

DOCTORATE IN SCEINCES, PhD THESES
Qiang Lan
University of Lausanne
Yu-Ting Huang
University of Lausanne

MASTER OF MEDICINE THESES
Arnaud Prin
University of Bern
Ronan Gabriel
University of Bern

Group Beat Schwaller

PHD THESES
Lenke Horvath, PhD thesis, co-director, together with Prof. L. Forro, EPFL.
Walter Blum, PhD thesis

Group Wolfgang Taube

PHD THESIS
Martin Keller

MASTER THESES
Grégoire Andrey
Luc Mory
Bastien Delacombaz
Anita Marti
Mattia Werner
Baptiste Jaquet
Benjamin Corpataux
Sarah Kershaw
Melanie Messerli
Flavie Bruelhart
Yves Crettenand
Camille Muller
Marie Bussard
Erik Reichelt
François Kolly

Group Zhihong Yang

PHD THESES
Yuyan Xiong, 2014
Zongsong Wu, 2014

MASTER OF SCIENCE
Michael Forbiteh Fru, 2014

MASTER OF BIOMEDICAL SCIENCE
Olivier Blanchard, 2014

Meetings organised by Department members

Group Carole Bourquin

Career Day in Life Sciences, University of Fribourg, Faculty of sciences, Fribourg, Switzerland, January 15, 2014

Public Outreach
Workshops pour enfants: 125 year jubilee UniFR, «Un médicament, comment ça se découvre?», Fribourg, Düdingen, Romont, Châtel-St.Denis, 2014

Group Abdul G. Dulloo

7th Fribourg Obesity Research Conference (FORC-2013), Sept. 2013, DepMed, UNIFR
Theme: Pathways from dieting to obesity, to weight regain, and to the metabolic syndrome

Group Anna Lauber-Biason

Symposium «Die Transition der pädiatrischen Patienten zur Erwachsenen-Endokrinologie» Au Parc Hotel, Fribourg, Switzerland, November 7th, 2013; 3 CME Credits SGP, SGED, SGAM, SGIM

Group Jean-Pierre Montani

Organization of the Fribourg Obesity Research Conference (FORC-2013), Fribourg (September 12, 2013)

Organization of the Annual meeting of the Swiss Physiological Society, Fribourg (September 9, 2014)

Group Patrice Nordmann

Practical Workshop – Emerging Antibiotic Resistance, University of Fribourg, Switzerland, December 19, 2013

Genomes Training, University of Fribourg, Switzerland, November 3 - 6, 2014

Group Curzio Rüegg

2nd Research day in medicine, DepMed and HFR
(with J.M. Annoni UNIFR, L. Alberi and D. Hayoz, HFR, Fribourg), May 22, 2013

3rd Research day in medicine, DepMed and HFR
(with J.M. Annoni UNIFR, L. Alberi and D. Hayoz HFR, Fribourg), May 21, 2014

Group Alexandre Wenger

Wenger A, Vasset S. Raconter la maladie au 18e siècle. International Workshop. Paris, November 28-29, Paris

Group Zhihong Yang

2nd Joined AGLA & Cardiovascular and Metabolic Research Meeting, the 10th and 11th January 2013. Bern: Arnold von Eckardstein (Zurich), Jürg H. Beer (Baden), David Carballo (Geneva), Georg Noll (Zurich), Walter F. Riesen (Diessenhofen), Brenda Kwak (Geneva), Ernst Niggli (Bern), Christian Matter (Zurich), Zhihong Yang (Fribourg), Christian Zuppinger (Bern)

3rd Joined AGLA & Cardiovascular and Metabolic Research Meeting, the 16th and 17th January 2014. Fribourg: Arnold von Eckardstein (Zurich), Jürg H. Beer (Baden), David Carballo (Geneva), Georg Noll (Zurich), Walter F. Riesen (Diessenhofen), Brenda Kwak (Geneva), Ernst Niggli (Bern), Christian Matter (Zurich), Zhihong Yang (Fribourg), Christian Zuppinger (Bern)

Lectures and seminars given by Department members

Group Carole Bourquin

«Timing is everything: Improving the outcome of cancer immunotherapy», Berne Immunology Club, Berne, Switzerland, 2013

Immunostimulatory oligonucleotides for the treatment of cancer: Optimization of delivery technology; Bayimmunet, Regensburg, Germany, 2013

«Cancer immunotherapy: Breakthrough of the year 2013», St Gallen, Switzerland, 2014

«The battle against cancer: what can nanoparticles do for us?», Adolphe-Merkle Institute, Fribourg, Switzerland, 2014

«Cancer Immunotherapy: Taking lessons from nature», Geneva Immunology Club, Geneva, Switzerland, 2014

«Adjuvants for cancer vaccines: timing is everything», Cancer: Antibodies Vaccines/Adjuvants & Delivery 2014, Lausanne, Switzerland, 2014

«Cancer immunotherapy: Timing is everything!», Immunofest 2014, Munich, Germany, 2014

«Pouvons-nous activer nos défenses immunitaires contre le cancer?», 125e Jubilé de l'Université de Fribourg, Romont & Fribourg, Suisse, 2014

Group Abdul G. Dulloo

Invited Speaker (AG Dulloo)

The New York Academy of Sciences Conference, New York, USA, March 2013
Theme: The Good Fat: Understanding Adipogenesis and Function of Brown Fat
Lecture: The search for compounds that stimulate brown fat mediated thermogenesis

European Association for the Study of Obesity (EASO) Scientific Advisory Board, Brussels, March 2013
Workshop theme: Beyond Body Mass Index
Lecture: Beyond BMI: from a perspective of body composition autoregulation

12th International Association for the Study of Obesity (IASO) Stock Conference, Hamburg, Sept 2013
Theme: Functional body composition and related aspects in research on obesity and cachexia
Lecture: Regulation of body composition: Body components – brain feedbacks in weight control

7th Fribourg Obesity Research Conference, Fribourg, September 2013
Theme: Pathways from dieting to obesity, to weight regain, and to the metabolic syndrome
Lecture: Autoregulation of fat storage during weight regain: Adipostats & proteinstats awaiting discovery.

Symposium de la Division d'Endocrinologie, Diabétologie et Obésité pédiatrique, DMCP CHUV, Lausanne, Oct. 2013
Theme: «Traitement de l'enfant obèse; multiples facettes»
Lecture: Est-ce que les régimes amaigrissants font grossir?

Deuxième Journée VD-GE de nutrition pour le praticien, Morges, Oct. 2013
Theme: Le jeûne dans tous ses états
Lecture: Physiologie du jeûne.

The Obesity Society Annual Scientific Meeting: The Obesity Week, Atlanta, USA, Nov.2013
Symposium: How poverty might contribute to obesity: from a physiological perspective
Lecture: Thrifty metabolism in catch-up growth trajectories to later obesity and the metabolic syndrome

12th International Congress on Obesity, Kuala Lumpur, Malaysia, March 2014
Symposium: Perspectives on Energy balance
Lecture: Perspectives on energy balance and body composition regulation: Adipostats and proteinstats awaiting discovery.
3rd International Conference on Recent Advances and Controversies in Measuring Energy Metabolism (RACMEM 2014), Tokyo, Japan, October 2014
Symposium: Exercise and energy metabolism

Lecture: Energy expenditure of low-level and isometric exercise: Exploring new approaches to study thermogenesis

Group Anna Lauber-Biason

Invited talks

The battle of the sexes: insights in human sex development. Institute of Anatomy, University of Zurich, February 25, 2013

Steroid and hypertension. Schweizerische Gesellschaft für Endokrinologie und Diabetologie (SGED) SGED Frühjahr Meeting Bregenz, March, 2013

«Ich bin dick weil schon meine Eltern dick waren und deshalb sind auch unsere Kinder dick, Punkt!» Was tun als Pädiater? Schweizerische Akademie für Psychosomatische und Psychosoziale Medizin (SAPPM) Meeting, Berne, April 25, 2013

DSD: medizinische Aspekte. Intersexualität. Medizinische, ethische und rechtliche Fragestellungen. University of Zurich, May 30, 2013

Pro and cons in the molecular genetic diagnosis of CAH. 7th European Society for Pediatric Endocrinology (ESPE) Advanced Seminar in Developmental Endocrinology: adrenal disorders. Berne, May 31, 2013

Congenital Adrenal Hyperplasia: from biology to clinic. Aerztliche Weiterbildung HFR , June 6, 2013

AGS: Pränatale Diagnose, pränatale Therapie, Neugeborenen Screening, Molekulare Diagnostik. AGS-Initiative Meeting, Zurich, Nov 2, 2013

46, XY Variation/Disorder of Sex Development. SGED Herbsttagung, Berne, Nov 15, 2013

Abstracts

Franco Mariangela, Costa EMF, Mendonca BB, Lauber-Biason A
Role of CBX2 in human sex development. Abst MON-587. 95th Endocrine Society Annual Meeting, San Francisco (USA), June 15-17, 2013

Invited talks

Why boys will be boys and girls will be girls: human sex development and its disorders. Klinisch- biochemisches Kolloquium, University Children's Hospital Zurich, May 12, 2014

Why boys will be boys and girls will be girls: Geschlechtsentwicklung beim Mensch. Swiss Medical Student Convention (SMSC) Meeting «Sex - Gender - Identity», Basel, November 9, 2014

Der Kampf der Geschlechter: die Geschlechtsentwicklung und ihre Defekte. UniFR Alumni Jahrestagung, November 14, 2014

Abstracts

Eid Wassim, Opitz L, Biason-Lauber A
CBX2 in sex development: Identifying CBX2 binding targets in the human genome. Abst 14483 OR44-1 (oral presentation). International Congress of Endocrinology/The Endocrine Society Annual Meeting (ICE/ENDO) 2014, Chicago (USA), June 21-24, 2014

Eid Wassim, Opitz L, Biason-Lauber A
Genome-wide identification of CBX2 targets: insights in the human sex development network. Abst 55 (oral presentation). SGED Herbsttagung Berne, Nov. 27-28, 2014

Group Pierre Lavenex

Memory development. Lavenex, P. Spring Hippocampal Research Conference, Taormina, June 2013

How does one (re)build a brain to learn and remember? Lavenex P; Annual Meeting of the Swiss Federation of Clinical Neuroscience Societies, Montreux, June 2013.

Faut-il encore apprendre et mémoriser? Cohen PF, Courant M, Lavenex P, Zimmerman B; Café scientifique, Université de Fribourg, March 2013.

Emission CQFD. Prix Nobel de Médecine 2014. Radio Télévision Suisse. Lavenex P; October 2014

How does one (re)build a brain to learn and remember? Lavenex P; Temple University, Philadelphia, March 2014.

Postnatal development of memory circuits. Lavenex P; Annual Meeting of the Eastern Psychological Association, Boston, March 2014.

Group Jean-Pierre Montani

«Acute cerebrovascular effects of energy drink consumption», National Institutes of Physiological Sciences (NIPS), Okazaki, Japan (host, Professor Ryusuke Kakigi, April 3, 2013)

«Cardiovascular effects of energy drinks», Department of physiology, Hyogo College of Medicine at Kobe, Japan (host, Professor Yoshitaka Oku, April 9, 2013)

«Role of Sugary Drinks in the Pathogenesis of Cardiovascular Diseases» Department of physiology, Shinshu University at Matsumoto, Japan (host, Professor Hiroshi Nose, April 11, 2013)

«A Guytonian approach of sodium homeostasis and blood pressure control», Department of integrative physiology, Nara Women's University at Nara, Japan (host, Professor Kenju Miki, April 14, 2013)

«Acute cardiovascular responses to the ingestion of sugary drinks» Department of physiology, Kawasaki Medical Center at Kurashiki, Japan (host, Professor Satoshi Mohri, April 24, 2013)

«Cardiovascular effects of fructose» Department of physiology, Okayama Medical Center, Japan (hosts, Professors Keiji Naruse and Ken Takahashi, April 26, 2013)

«Impact of energy drinks on the cardiovascular system», Department of physiology and cardiothoracic surgery, University of Porto, Portugal (host, Professor Adelino Leite Moreira, June 4, 2013)

«Pathways from dieting to weight regain, to obesity and to the metabolic syndrome», Fribourg Obesity Research Conference, FORC-2013 (Symposium

Introduction, September 12, 2013)

«Dieting and weight cycling as risk factors for cardiometabolic diseases: Who are at risks?», Fribourg Obesity Research Conference, FORC-2013, (symposium talk, September 12, 2013)

«Role of whole body blood flow autoregulation in salt-loading hypertension: insights from computer simulations with Guyton's large circulatory model», 36th annual meeting of the Japanese Society of Hypertension, Osaka, Japan (October 25, 2013)

«Impact of nutrition on health», Josei Community Center, Tsuyama, Japan (sponsored by the Swiss-Japan 150th anniversary of diplomatic relations, May 10, 2014)

«Increased cardiac workload by a high-salt meal in healthy subjects», 37th annual meeting of the Japanese Society of Hypertension, Yokohama, Japan (October 19, 2014)

Group Patrice Nordmann

Worldwide spread of carbapenemase in *Enterobacteriaeceae* and their control, 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Berlin, Germany, April 2013

ESBL detection in *Enterobacteria-ceae* and the state of the art of carbapenemases in *Enterobacteriaceae*, 16th Pan American Meeting in Infectious Diseases, Santiago, Chile, May 2013

The irreversible invasion by Carba-penemase-producing *Enterobacteria-ceae*, 71st Congress of the Swiss Microbiology Meeting, Interlaken, Switzerland, June 2013

Emerging Antibiotic Resistance, Science in 2013, Göteberg, Sweden, June 2013

From Multidrug to pandrug resistance to antibiotics, Symposium bioMérieux, Geneva, Switzerland, September 2013

Carbapenemases in Gram negative, Pathobiology and Veterinary Public Health, Vetsuisse Faculty, University of Zurich, Switzerland, October 2013

Les entérobactéries : pandémies des BLSE et désormais des carbapénèmases, Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse, Paris, France, November 2013

Detection of broad-spectrum β-lactamases, Symposium in Microbiology, European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Verona, Italy, November 2013

Clinical significant broad spectrum β-lactamases, Symposium Roche; novel strategy for antibiotic development, Basel, Switzerland, December 2013

Emerging Resistance to Antibiotics, University of Lausanne, Switzerland, January 2014

Emerging Antibiotic Resistances in Gram negative, University of Geneva, Switzerland, January 2014
Carbapenemases in *Enterobacteriaceae* : the phantom menace, University of Bern; Club Pathologie Infectieuse, Switzerland, January 2014

Carriage and Laboratory Detection of Multi-drug Resistant Bacteria in Low and Middle Income Countries, in collaboration with the Japanese Association of Infectious Diseases, 16th International Congress on Infectious Diseases (ICID), Cape Town, South Africa, April 2014

Carbapenemase-producing *Enterobacteriaceae* in 2014: spread and detection, Symposium in Microbiology, European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Verona, Italy, May 2014
Update on OXA carbapenemase, 24th European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Barcelona, Spain, May 2014

Spread and Identification of Carbapenemase Producers in *Enterobacteriacae* in 2014, 114th General Meeting of the American Society for Microbiology (ASM), Boston, USA, May 2014

Emerging antibiotic resistance; here is the storm, University of Zurich, Switzerland, May 2014

Carbapenemases in *Enterobacteriaceae* in France and Switzerland, 72nd Annual Assembly of the Swiss Microbiology Meeting (SMM), Fribourg, Switzerland, June 2014

ESBL and carbapenemase-producing *Enterobacteriaceae* in 2014: spread and detection, 13th European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Summer School, Sigtuna, Sweden, July 2014

Rapid Identification of Key Resistance Mechanisms: Molecular and Biochemical Tools, and Screening Methods for Colonized Patients, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2014, Washington DC, USA, September 2014

The growing issue of antibiotic resistance with a focus on multi-resistant Gram negatives, the 3rd Union of European Medical Specialists and European Federation of Clinical Chemistry & Laboratory Medicine Congress, EuroLabfocus, Liverpool, UK, October 2014

Threat in ICU: Gram negative bacteria resistance, the 5th Congress of the European Academy of Pediatric Societies, Barcelona, Spain, October 2014

Emerging antibiotic resistance in Gram negatives, Symposium bioMérieux, Geneva, Switzerland, October 2014

1. Emerging Resistance: general concept
2. Extended-spectrum β-lactamases in *Enterobacteriaceae*
3. Carbapenemases in *Enterobacteriaceae*
4. Emerging Resistance in *Pseudomonas aeruginosa* in *Acinebacter baumannii*
5. Emerging Resistances to aminoglycosides and to colistin
6. Antibiotherapy: the future

Escherichia coli produisant des carbapénèmases: pathogènes émer-gents de diffusion mondiale, Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse, Paris, France, November

2014

Emerging Antibiotic Resistance : a state of emergency, Biozentrum, University of Basel, Switzerland, November 2014

Carbapenemases and ESBL, International Sepsis Forum, Paris, France, December 2014

Group Eric M. Rouiller

Eric M. Rouiller, 10.03.2013, «Re-arrangement of connectivity and functional motor recovery after lesion of the spinal cord or motor cortex», 33rd European Winter Conference on Brain Research, Brides-les-Bains, France.

Eric M. Rouiller, 11.09.2014, «Behavioral variability of manual dexterity in macaques», Hand, Brain and Technology, CSF Conference, Monte-Verita (Ascona), Tessin, Switzerland.

Group Curzio Rüegg

IRA-CHUV-UNIL, Lausanne, Switzerland, January 1, 2013

SCOPES workshop, University of Kragujevac, Serbia, January 25, 2013

Institute of Biochemistry and Genetics, Department of Biomedicine, University of Basel, Switzerland, February 5, 2013

Gray Institute for Radiation Oncology & Biology, Department of Oncology, University of Oxford Oxford, UK, March 4, 2013

Summer symposium on Breast Cancer, DKF, University of Bern, July 5, 2013

University of Kragujevac, Serbia, August 23, 2013

Annual Meeting, Canceropole Grand Sudouest, Limoges, France, October 15 Radio-Oncology Department, University Hospital Zürich, November 25, 2013

Actelion, Basel, January 20, 2014

Annual Meeting, Swiss Society of Pharmacology and Toxicology, January 30, 2014

Kick-Off meeting SmArteR Consortium, Berlin, Germany June 26-27, 2014

International Biennial Congress of the Metastasis Research Society, Heildelberg, June 28-July 1, 2014

Post-TUMIC Meeting, University of Heidelberg Mannheim, Mannheim, Germany, July 2, 2014

University of Kragujevac, Serbia, July 7-8, 2014

Group Franziska Theilig

«Corin in proteinuric kidney diseases» invited lecture at the international congress meeting of the Amercian Society of Nephrology Nov, 2012

«Wie kommt es beim nephrotischem Syndrom zu Ödemen? Eine neue Antwort auf diese Frage» invited lecture at a nephrological symposium Munich, 2013

«mTORC1/ and -2 induced signalling pathways regulate renal proximal tubular endocytosis» invited talk at the international congress meeting of the Amercian Society of Nephrology Nov, 2013
«Possible mechanisms for the edem development in proteinuric kidney diseases», University of Lausanne, May 22, 2014

Group Alexandre Wenger

Knebusch J, Dünne J. Kann man «scapes» ohne «land» denken ? Überlegungen zu Arjun Appadurais

Wenger A. Les Medical Humanities à Fribourg. Worshop Medical Humanities, Académies suisses (ASSH et ASSM), Bern 26 mars 2013

Wenger A. Prophylaxie de la syphilis, d'hier à aujourd'hui. Colloque de l'Unité VIH, Genève, HUG, 9 avril 2013

Suciu R. Le Lecteur à l'œuvre, Conférence Uni3, Université de Genève, 4 mai 2013

Wenger A. Le Personnage sadien : de l'histoire naturelle à la fiction romanesque. Univ. of Oxford, colloque international Sade, l'inconnu ? Nouvelles approches critiques, 24-25 mai 2013

Prot B. Les symptômes de la réclusion. La critique de la prison dans la correspondance du marquis de Sade. XIIIe colloque Jeunes Chercheurs du CIERL (Univ. Laval). Montréal 30-31 mai 2013

Theorie der deterritorialisierenden Flüsse. Journée d'étude «Welt und/ oder Erde», Vergleichende Literatur- und Kulturwissenschaft, Universität Bonn, 31 mai et 1er juin 2013

Suciu R, Wenger A. Musée virtuel de Médecine et société : un projet expérimental de pédagogie et de recherche à l'Université de Fribourg, ITD Bern, 6 juin 2013

Wenger A. De la pratique de la littérature à la pratique de la médecine. Conférence inaugurale du Congrès international des sciences humaines en médecine et santé ; Discours, récits en santé, Univ. de Picardie, Amiens 20-22 juin 2013

Knebusch J. The figure of the poet-doctor after the decline of scientific poetry. Withney Humanities Center, Yale University, 3 juillet 2013

Knebusch J, Dünne J. Le milieu du monde : comment penser la mise en situation littéraire à l'époque de la globalisation ? Congrès de l'Association Internationale de Littérature Comparée, Université Paris-Sorbonne, 19 juillet 2013

Wenger A. Physiologie, histoire naturelle et fiction romanesque : le corps dans La Nouvelle Justine de Sade et dans Le Rêve de d'Alembert de Diderot. Lyon, ENS, 18 septembre 2013

Suciu R. Activités de recherche en Digital Humanities, Workshop « Fabula numerica », Labex Obvil, Université Paris-Sorbonne, 24 octobre 2013

Suciu R. Robert Burton et son Anatomie de la mélancolie, Séminaire « La mélancolie au carrefour de la peinture, de la musique, de l'histoire et de la psychiatrie », 25 octobre 2013, Univ.

de Genève

Suciu R, Wenger A, Médecine et alimentation (Poster presentation). Digital Humanities Internat. Symposium, Lausanne, 2014

Wenger A. Littérature et oncogénétique : un cas pratique. Worshop Medical Humanities, Académies suisses (ASSH et ASSM), Bern 25 mars 2014

Wenger A., Marchal H. Sciences et sexualité. Sémin. de recherche (org. Jean-Louis Jeannelle, Martine Lavaud) Paris, Univ. Paris IV Sorbonne, 11 avril 2014

Suciu R. Idea Factory: The Future of Internet, Forum de l'OCDE, Paris, mai 2014

Prot B. Le nu dans l'imagerie médicale du 18e siècle (Poster presentation). Journée d'Etude Jeunes Chercheurs. Recherches Emergentes en Sciences Humaines et Sociales, 10 juin 2014, E.D. Stanislas, Université de Lorraine, Nancy

Knebusch J. La résidence d'écrivain : enjeux de géographie littéraire. Séminaire Vers une géographie littéraire, EA 4400, Univ. Paris 3, 13 juin 2014

Louis-Courvoisier M, Wenger A. Les Medical Humanities en Suisse. Groupe de travail « Médecine, pédagogie, SHS », Univ. Lyon 1, 12 sept. 2014

Wenger A. Pour une histoire culturelle du médecin, labmeeting iEH2, UniGe, 21 septembre 2014

Trellu L, Wenger A. Regards croisés sur la prophylaxie de la syphilis : hier et aujourd'hui. Colloque iEH2, 1er déc. 2014

Wenger A. La syphilis : entre art et médecine. Colloque d'infectiologie. Hôpitaux Univ. de Genève, 18 déc. 2014

Group Zhihong Yang

Arginase-II: The molecular interface connecting atherosclerosis, diabetes, and aging. University of Zürich. March 19, 2013

Further achievements

Group Carole Bourquin

Vice-presidency Department of Medicine, 01.08.2012-31.07.2014

Journal Cover, Blood, Volume 122, Number 15, October 10, 2013

Poster prize at the 2nd Research Day 2013, UNIFR/HFR Medicine, «Virus-associated activation of innate immunity» (Tina Herbst-Aeschbacher)

Poster prize at the 2nd Research Day 2013, UNIFR/HFR Medicine, «Omega-3 fatty acids prevent inflammation» (Thibaud Spinetti)

Best Master thesis 2014, Alumni students, «Characterization of the efficacy of CD8+ T cell activation by dendritic cells treted with a combination of patterm recognition receptor ligands» (Mottas Inès)

Group Abdul G. Dulloo

Outstanding Poster Award at European Society for Clinical Nutrition and Metabolism Meeting (ESPEN 2014, Geneva)
Presented by Nathalie Charrière (PhD student)
Postprandial thermogenesis and substrate oxidation in response to galactose – the forgotten sugar: Comparison with glucose and fructose in healthy young adults
Charrière N, Miles-Chan J, Montani JP, Dulloo AG

Press Highlights at 20th European Congress on Obesity (ECO-2013 – Liverpool, UK)
Presented by Nathalie Charrière (PhD student)
Water-Induced Thermogenesis: Beyond H2O
Charrière N, Miles-Chan JL, Montani JP, Dulloo AG

Selected paper for oral communications at 20th European Congress on Obesity (ECO-2013, Liverpool, UK).
Presented by Jennifer Miles-Chan (postdoctoral fellow)
Heterogeneity in metabolic rate and substrate oxidation during standing vs sitting in young adults: Phenotyping according to magnitude and time-course
Miles-Chan JL, Delphine Sarafian D, Montani JP, Schutz Y, Dulloo AG

Expert committees
- Member of Scientific Advisory Board for the European Association for the Study of Obesity (EASO), Workshop theme: Beyond Body Mass Index, Brussels, March 2013
- Member of Evaluation Panel for the German Federal Ministry of Education and Research (BMBF). Evaluation of «Competence Cluster in Nutrition Research»; Berlin, July 3-4, 2014

Editorial Board Member/Consultancy
International Journal of Obesity
Frontiers in Integrative Physiology
Molecular Metabolism

Group Anna Lauber-Biason

Member of the managing Committee and Swiss Representative of COST Action BMI1303 («European Cooperation in the Field of Scientific and Technical Research») DSDnet: «A systematic elucidation of differences of sex development» SBFI Nr. C13.0273

Group Pierre Lavenex

Associate Professor, Institute of Psychology, UNIL

Secretary of the Swiss Society for Neuroscience, 2011 - present

Council Member of the Foundation «Recherche pour la Vie», 2010 - present

Editorial Board Member:

Neuroscience Bulletin, 2011 - present
Frontiers in Neuroscience, 2007 - present
Neuroscience, 2005 - present

Group Jean-Pierre Montani

Accreditation expert for the Biomedical sciences curriculum of the Faculty of Medicine of the University of Liège (March 2013)

Nomination to the Editorial Board «Current Hypertension Report» (November 2013)

Nomination as Review Editor for «Frontiers in Hypertension» (April 2014)

Group Patrice Nordmann

Direction Unité INSERM U914, Kremlin Bicêtre, Résistances émergentes aux antibiotiques, Université Paris Sud, France (2013-2014)

Direction Centre National de Références, associé à la résistance aux antibiotiques, Hôpital de Bicêtre, Kremlin Bicêtre, France (2013-2014)

Editorial boards; Emerging Infectious Diseases, Future Microbiology, Plos One

Prize: the Excellence Award in Clinical Microbiology and Infectious Diseases 2013 (cum laude), P. Nordmann. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID), ECCMID meeting, Berlin, Germany, April 2013

Meeting board; RICAI: Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse, Paris, France (2013-2014)

European patent (n=2): Inhibitors of β-lactamases (Nordmann P, Poirel L, Girlich D) taken on behalf of University of Fribourg)

Group Curzio Rüegg

Deputy-director of the NCCR Bioinspired Materials

Election to the review panel of the advanced mobility Fellowships scheme (SNF APM) of the Swiss National Science Foundation

Marketing of COLOX, a blood-based test for the early detection of colon polyps and colon cancer, in collaboration with Diagnplex a previously co-funded company

Co-funder of a news start up-company (Novigenix) in the field of molecular cancer diagnostic

Attraction of a Ambizione fellow (Alberto Santamaria) from the EPFL

Group Wolfgang Taube

Martin Keller won two prices:
• «Young Investigator Award 2014» of the European College of Sport Science
• «DVS Nachwuchspreis 2013» of the Deutsche Vereinigung für Sportwissenschaft

Audrey Mouthon attended as a finalist in the young investigator competition of the «Société suisse des sciences du sport»

Group Zhihong Yang

Mr. Yuyan XIONG received the poster award at the meeting «3rd Research Day in Medicine», May 21, 2014 at the DepMed

Mr. Yuyan XIONG received the Faculty Prize in Medicine and Biology 2014 for his doctoral thesis.

The work by Xiong Y et al. «Arginase-II Induces Vascular Smooth Muscle Cell Senescence and Apoptosis Through p66Shc and p53 Independently of Its L-Arginine Ureahydrolase Activity: Implications for Atherosclerotic Plaque Vulnerability. J Am Heart Assoc. 2013 Jul 5;2(4):e000096. doi: 10.1161/JAHA.113.000096» was highlighted by an Editorial in JAHA written by Drs. Deepesh Pandey, Lewis Romer and Dan E. Berkowitz (http://jaha.ahajournals.org/content/2/4/e000392.full.html?etoc)

Acknowledgments

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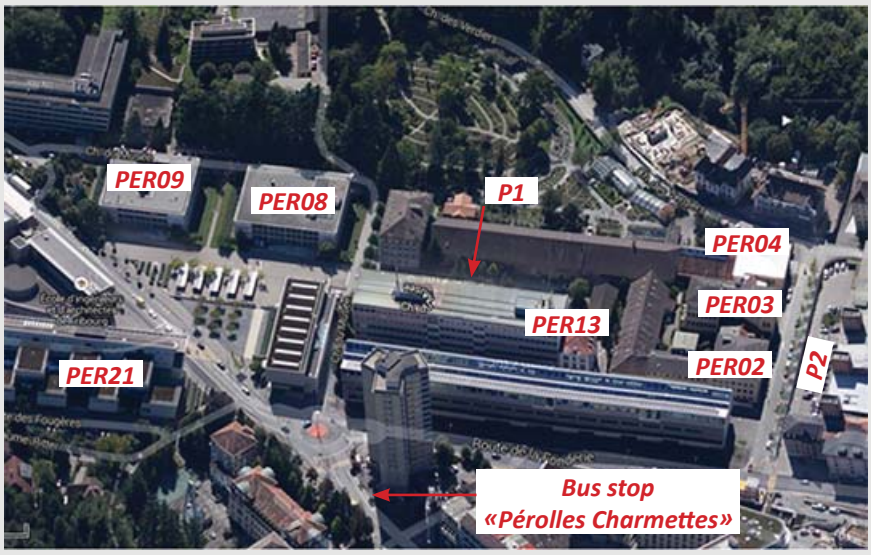
Visiting the Department of Medicine at UNIFR

The Department of Medicine is located on the «Boulevard de Pérolles» close to both the center of Fribourg and the river «Sarine» (in German «Saane»).

Our campus is easily accessible from the railway station:
On foot (Boulevard de Pérolles) in 15 - 20 minutes or with public transportation in five minutes. Take bus line 1 «Marly», line 3 «Pérolles» or line 7 «Clinique». Exit at bus stop «Pérolles Charmettes».

By car: Highway exit «Fribourg Sud», direction «Marly». Metered parking exists next to the «Natural History Museum» (P1), along «Rue Albert Gockel» (P2) or behind the «College of Engineering and Architecture of Fribourg» (P3) - limited to 3 - 8 hours in most cases and operates from 8 a.m. until 6 p.m., Monday through Friday/Saturday.
There are no parking vignettes available.



PER13
- Department of Medicine

PER02
- Anatomy
- Pathology

PER03
- Anatomy
- Medical Humanities

PER04
- Microbiology

PER09
- Cardiology
- Endocrinology
- Neurology
- Pharmacology
- Physiology
- Psychiatry

PER21
- Movement and Sport Science (PER08 - Laboratories)

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