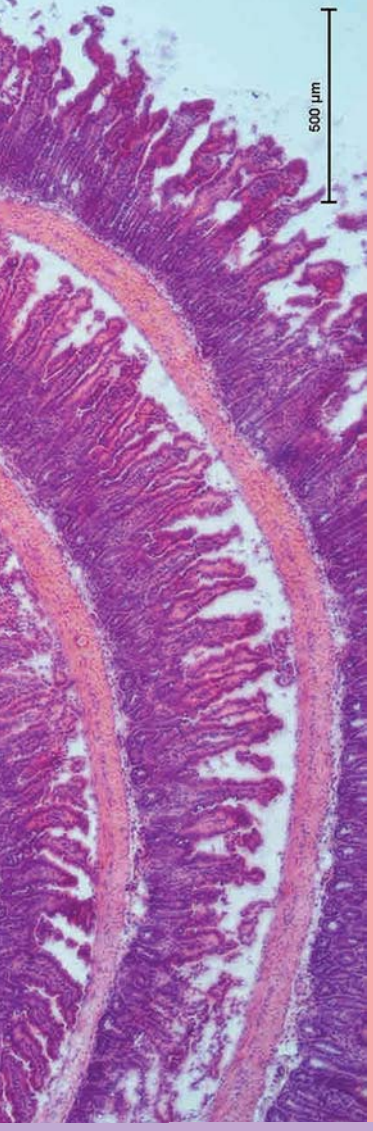
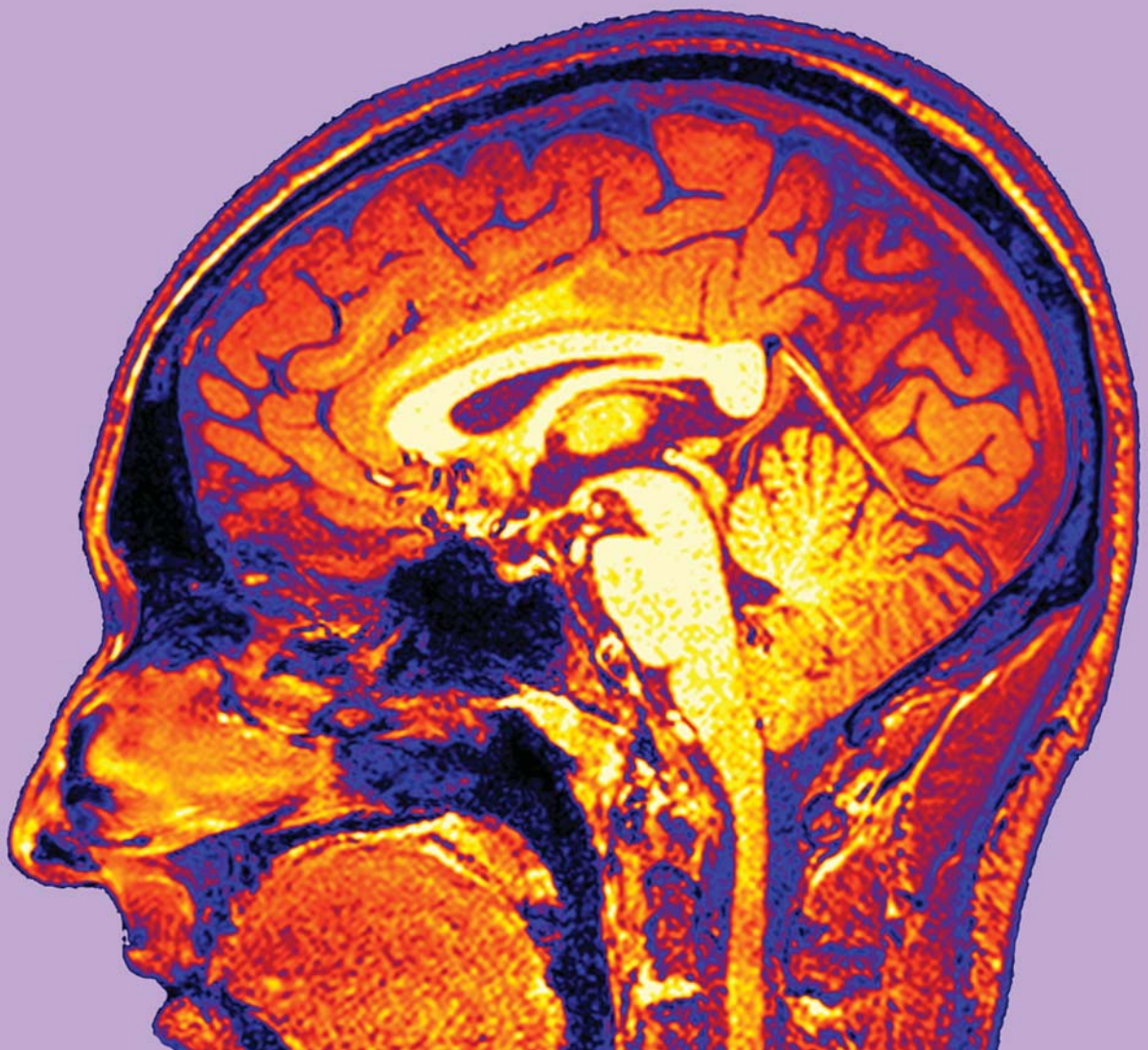


Scientific Report 2011/2012

DEPARTMENT OF MEDICINE

Faculty of Science
University of Fribourg
Switzerland



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The Department of Medicine of the Faculty of Sciences is devoted to teaching and research in the field of Medicine, Biomedical Sciences, Sport and Movement Sciences and Pharmacy. It is currently experiencing a very exciting momentum of transition and development with profound impact on research activities.

The Department of Medicine is one of the seven Departments of the Faculty of Sciences of our University. It hosts 13 full professors and 7 associate professors, 11 of whom were appointed in the last 5 years.

Several major innovations in the curricula have been implemented in recent years:

The introduction of the Bachelor and Master in Sport and Movement Sciences in 2009 led to the creation of two new professorships, one of which is currently endowed by the *Banque Cantonale de Fribourg*. The holders of these positions (Taube and Bresciani) have established innovative research activities in the field of motor control and in the perception and control of movements. The program in Sport and Movement Sciences is very successful and is attracting a growing number of students. This program will reinforce research on human subjects, which is one of the expertises of our Department.

The introduction of the Bachelor in Human Medicine has called for teaching in clinical disciplines. To this purpose, eight new chairs were created and nine professors appointed between 2009 and 2012 in Cardiology (Cook and Togni), Endocrinology (Lauber-Biason), Medicine, social sciences and the humanities (Wenger), Microbiology (Nordmann), Neurology (Annoni), Pathology (Rüegg), Pharmacology (Bourquin) and Psychiatry (Merlo). These appointments have brought new research competences to the Department (e.g. cancer, immunology, resistance to antibiotics and medicine in society).

The Bachelor in Biomedical Sciences, which was created in 2006, has strengthened teaching and research in neurosciences, metabolism and cardiovascular medicine. This is a unique program responding to a growing demand of students to be trained in clinically-relevant aspects of biomedical research. It is the only Bachelor program in Switzerland on this topic. Most students pursue their training by enrolling in Master programs at other Universities, most notably Bern, the partner institution for this program.

These new recruitments and new curricula lead to an important increase of the number of students (triplicated in the past 10 years) and fostered collaborations with the health care system of the Canton Fribourg, namely the *Hopital fribourgeois* (HFR) and the *Réseau fribourgeois de santé mentale* (RFSM) with direct impact on the quality of care of patients.

This evolution had profound impact also on the research conducted at the Department of Medicine. Current research activities are clustered in four topics:

- Cancer, Tissue Biology and Microbiology. This cluster consists of recently established groups. The Bourquin's group works on cancer immunology with emphasis on pharmacological regulation. The Rüegg's group works on tumor microenvironment, angiogenesis and metastasis with a strong translational component. Theilig's group is investigating kidney epithelial adaptations to kidney pathologies. The recently established Nordmann's group works on mechanisms of antibiotic resistance and their clinical relevance.

- Cardiovascular, Metabolism and Endocrinology is the second deep-rooted thematic cluster. The already established 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. 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).

- Neurosciences, one of the traditionally strong research themes of the Department, encompass 10 research groups (Annoni/Spierer, Bresciani, Celio, Kretz, Lavenex, Merlo, Rainer, Rouiller, Schwaller, Taube). The topics studied cover a broad spectrum of neurobiology and neurophysiology spanning from neuroanatomy to motoric regeneration after injury, visual signals processing, language processing and movement coordination. The new chairs of Neurology and Psychiatry have reinforced the clinical orientation of this research theme and have added excellent expertise in functional imaging.

- Medical Humanities. The Wenger group conducts research on the representations of the physician in time, different forms of medical communication in contemporary and historical contexts and aesthetics in medicine.

The unit of Biochemistry moved from the Department of Medicine to the Department of Biology in 2011 and is therefore not considered in this report. The reports of the professors appointed in late 2012 (Bresciani, Filgueira, Merlo and Nordmann) are largely based on work performed at their former host institutions.

The integration of the Department of Medicine within the Faculty of Sciences facilitates interactions and collaborations with other departments or institutes, most notably the Departments of Chemistry and Biology, and the Adolphe Merkle Institute. In addition the FriMat consortium supports projects in the field of material sciences spanning across different departments. In addition, several of the clinical professors have an appointment at HFR or at the RFSM to pursue clinical research and clinical duties.

All members of the Department have been highly successful in obtaining external research funding through national and international agencies and private foundations. Several members of the department are also members of national (e.g. NCCR) or international research (e.g. EU) consortia. In 2012 over 8.5 Mio CHF third parties funding were granted to members of the Department!

Over 340 papers and book chapters/books were published by Department's members in 2011-2012, several of which in top journals, including ACS nano, Cancer Research, Cancer Discovery, Cerebral Cortex, Circulation, Nature neurosciences, Neuron, Neurology, P.N.A.S., Stem Cells. Several publications have received media attention.

The Department is still evolving and developing to integrate the teaching and research activities of the recently recruited professors and several challenges lie ahead:

- Space. The Pérolles campus suffers from a deficit in office and laboratory space. The temporary building on the Charles-Aloyse Fontaine square will partially cover the needs for the Department from 2015 on. A definitive solution in which all research groups are hosted in one building will be reached with the construction of the planned Science Tower building.

- Life Sciences Center. The creation of a Life Sciences Center in which research clusters span across the Departments of Medicine and Biology, and possibly others will strengthen interactions among groups working on related topics, create common infrastructures and increase productivity and visibility.

- Equipment and technical platforms. In order to keep a competitive advantage, biomedical research requires the use of more and more sophisticated, expensive and complex equipments. It is necessary to create technical platforms, such as cellular and tissue imaging, non-invasive small animal imaging, fluorescence flow cytometry and cell sorting, DNA sequencing and bioinformatics, to optimize their use. Institutional support will be essential for running and maintaining these platforms.

- Young investigators. The recruitment of SNF professors, Ambizione and MHV fellows will be actively pursued within the thematic clusters in order to reinforce research, visibility and to identify new faculty recruitments.

In conclusion, the Department of Medicine is evolving through a very exciting time with a strong and positive impact on research. It is a time of challenges and opportunities with several ambitious projects ahead. We wish to keep this momentum alive and to join forces to make the Department an even more attractive and competitive place to perform cutting-edge biomedical research for the years to come. I wish to thank all members of the Department for their engagement toward this goal!

Professor Curzio Rüegg
Department President

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Cancer, Tissue Biology and Microbiology

The field of Cancer, Tissue Biology and Microbiology has recently emerged as a new research focus in the Departement of Medicine. With the arrival of five new professors since 2010, research groups studying some of the greatest health challenges of the twenty-first century have been established in Fribourg. The topics investigated include the interaction of cancer cells with their environment, in particular with the immune system, immunological responses in inflammation and infection, emerging resistances of pathogens against antibiotics and chronic kidney disease. Understanding the mechanisms that underlie the pathogenesis and progression of these diseases is a prerequisite for developing effective therapeutic strategies that will be of benefit to patients.

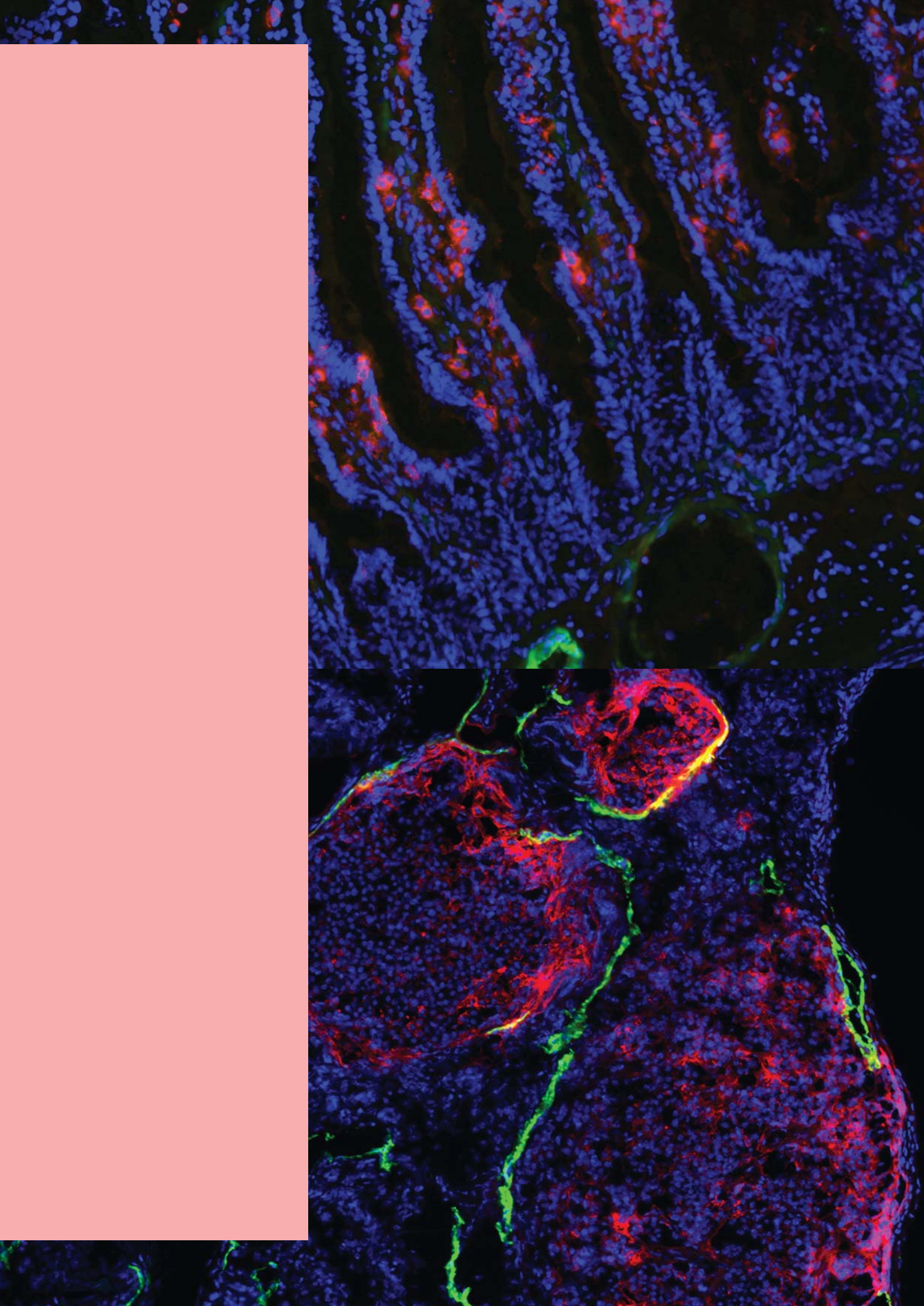
Carole Bourquin
Immunopharmacology of cancer

Luis Filgueira
Cell biology, immunology and clinical anatomy

Patrice Nordmann
Molecular and medical microbiology

Curzio Rüegg
Experimental and translational oncology

Franziska Theilig
Epithelial adaptations to renal pathologies



Carole Bourquin
Chair of Pharmacology

Immunopharmacology of cancer

INTRODUCTION

Immunological approaches for the treatment of cancer have strong therapeutic potential, in particular for the early elimination of metastases. Prof. Bourquin and her team focus on the stimulation of innate immunity, which represents the first step in the generation of an immune response, to foster the development of anticancer immunity. One promising strategy is the application of pharmacological substances that activate innate immunity through pattern-recognition receptors such as the Toll-like receptors 3, 7 and 9. These receptors, which are crucial for the initiation of immune responses, can be stimulated by specific molecular patterns present within nucleic acids. The use of synthetically produced oligonucleotides containing these molecular patterns allows for the pharmacological activation of these receptors as a therapeutic strategy.

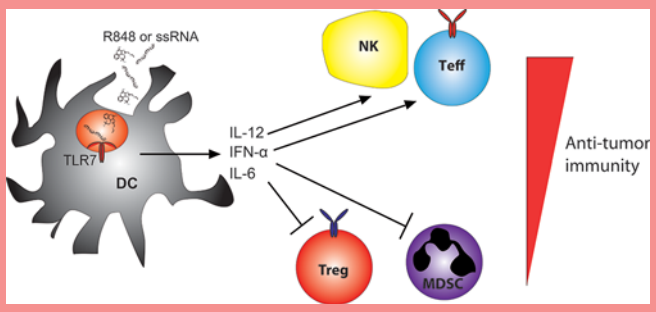


Fig.1 - Synthetic compunds or viral RNA activate Toll-like receptor 7 (TLR7) on dendritic cells (DC), followed by secretion of proinflammatory cytokines. *Those cytokines modulate adaptive immunity to favor tumor cell destruction by inhibiting regulatory cell types (Treg: regulatory T-cells and MDSC: myeloid dreived supressor cells) and promoting effector cells (NK: natural killer cells, Teff: T effector cells).*

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Systemic cancer immunotherapy with Toll-like receptor 7 agonists: Timing is everything

Compounds activating innate immunity through pattern-recognition receptors, such as the Toll-like receptor (TLR) 7 agonist imiquimod, have proven very effective in topical application against skin cancer. They have, however, to date met with limited success when applied systemically, despite the induction of immune responses. The disappointing clinical efficacy may be due to avoidable phenomena such as the development of receptor tolerance.

We have shown that a single injection of R848, a small molecule agonist of TLR7, leads to tolerance towards a second stimulation beginning 24h after injection and lasting for up to five days. In contrast, repeated stimulation within the first 24h results in an enhanced response. Of note, protocols used for clinical trials investigating systemic TLR7 stimulation in cancer have relied on single injections given every two to three days. According to our study, this schedule results in TLR7 tolerance and may explain the limited success of systemic treatment in these studies. Based on our findings, we designed a protocol of fractionated stimulation with R848 in cycles separated by 5-day intervals to circumvent tolerance. This protocol leads to efficient block of tumor growth in a cancer model and was more effective than the schedule used in clinical studies, although the cumulated dose was lower (Bourquin, Hotz et al., *Cancer Research,* 2011).

Our findings demonstrate that in-depth understanding of the molecular mechanisms of immune activation can foster the design of more effective treatment protocols that circumvent receptor tolerance. We plan to build on these results to include a new effector mechanism, receptor priming, in immunotherapy protocols. Based on a careful study of the signaling events leading to receptor priming, we aim to develop novel treatment protocols that effectively activate antitumor immunity. ▸▸

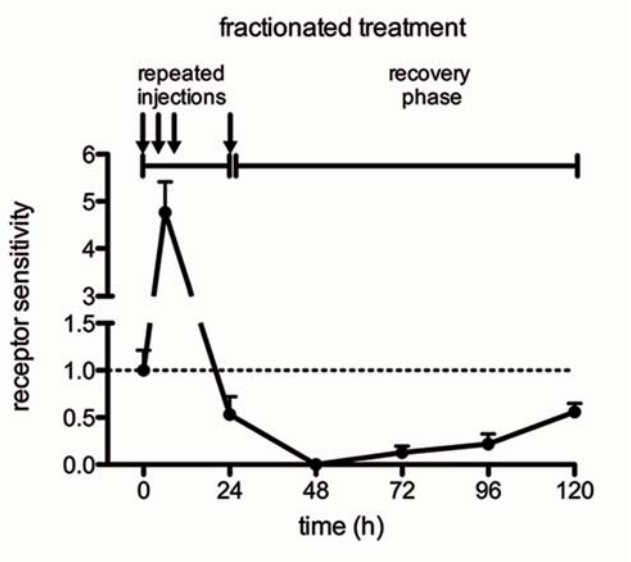

Fig.2 - The curve shows the kinetics of TLR7 sensitivity after a single injection of a synthetic agonist. *Our «fractionated» protocol takes advantage of initial increased sensitivity (see arrows indicating repeated injections) while avoiding stimulation in the tolerant state.* ▸▸

Toll-like receptor signaling blocks tumor-associated immunosuppression

An anticancer immune response can be suppressed by regulatory immune cells such as regulatory T cells or myeloid-derived suppressor cells (MDSC). The presence of these immunosuppressive cells is considered to be one of the main reasons for insufficient immunological tumor control. We have shown that the suppressive function of regulatory T cells and MDSC can be pharmacologically controlled by immunostimulatory oligonucleotides that activate Toll-like receptors (TLR) 7 and 9 (Anz et al., *J Immunol,* 2010; Anz et al., *Int J Cancer,* 2010; Zoglmeier et al., *Clin Canc* Res, 2011; Anz et al., *Histopath,* 2011). In particular, we have shown that TLR9 activation promotes maturation and differentiation of MDSC. These cells, which are normally poorly differentiated, lose their immunosuppressive activity through differentiation. We have defined the antitumoral cytokine IFNα, produced by plasmacytoid dendritic cells, as key effector for this phenotypical and functional change. We thus describe a novel mechanism by which TLR9 ligands promote antitumor responses.

We are currently investigating the impact of TLR stimulation on the migration of immune cells into tumors to determine whether, in addition to their regulatory function, the homing pattern of these cells is affected by immunopharmacological intervention. This ongoing project is performed within a research network focusing on cell migration that includes the group of Prof. Rüegg at the University of Fribourg, the Theodor-Kocher Institute in Berne, and the Institute for Biomedical Research in Bellinzona (www.cell-mig.ch).

Toll-like receptor immunostimulation by DNA origami nanostructures

We have shown that nanoparticles represent efficient drug delivery systems for immunoactive DNA and RNA oligonucleotides. Using gelatin-based nanoparticles, we have demonstrated that these carriers protect RNA oligonucleotides from degradation, facilitate their uptake by dendritic cells, and target these nucleic acids to the endosomal compartment where they are recognized by TLR7 (Bourquin, *J Immunother,* 2010). Further, we have shown that immunization with RNA oligonucleotide-loaded nanoparticles leads to the development of an efficient antitumoral response.

The 3D structure of DNA constructs can be controlled by a refolding technique termed DNA origami. We demonstrated that DNA origami nanostructures can function as programmable and nontoxic immunostimulants. In collaboration with Prof. Liedl from the Center of Nanoscience of the Ludwig-Maximilian University of Munich, we used DNA origami tubes decorated with TLR9-activating oligonucleotides to stimulate dendritic cells. The DNA constructs were taken up by dendritic cells and localized in the endosome, a necessary step for the triggering of TLR9. Activated dendritic cells produced cytokine mediators such as interleukin-6 and interleukin-12p70, a process that underlies the initiation of an immune response. In this work we have shown for the first time that DNA origami constructs represent an efficient vehicle for immunoactive oligonucleotides (Schueller et al., *ACS Nano*, 2011). Collaborations with Prof. Fromm (Dept. of Chemistry, University of Fribourg), and Profs. Fink and Rothen-Rutishauser (Adolphe-Merkle Institute, University of Fribourg) are ongoing to further explore the potential of nanomaterials for the immunopharmacology of cancer. ■

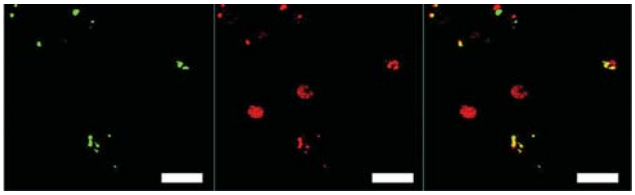

Fig.3 - Uptake of CpG-decorated DNA nanotubules into immune cells *(Schueller et al., ACS Nano, 2011).*

Selected Publications

Zoglmeier C, Bauer H, Nörenberg D, Wedekind G, Bittner P, Sandholzer N, Rapp M, Anz D, Endres S, ***Bourquin C***
CpG blocks immunosuppression by myeloid-derived suppressor cells in tumor-bearing mice. Clinical Cancer Research, 2011, 17:1765-75 (JIF 6,7). Comment in: Clinical Cancer Research, 2012, 17:1645-48

Bourquin C*, Hotz C, Noerenberg D, Voelkl A, Heidegger S, Roetzer LC, Storch B, Sandholzer N, Wurzenberger C, Anz D, Endres S*
Systemic cancer therapy with a small molecule agonist of Toll-like receptor 7 can be improved by circumventing TLR tolerance. Cancer Research, 2011, 71:5123-33 (JIF 7.5). Authors' View in: Oncoimmunology, 2012, 1: 227-228

Schüller VJ, Heidegger S, Sandholzer N, Nickels PC, Suhartha NA, Endres S, ***Bourquin C*****, Liedl T* (*contributed equally)*
Cellular Immunostimulation by CpG-Sequence-Coated DNA Origami Structures. ACS Nano, 2011, 5:9696-702 (JIF 9.9)

Luis Filgueira
Chair of Anatomy

Cell biology, immunology and clinical anatomy

INTRODUCTION

Luis Filgueira has joined the University of Fribourg in October 2012. Before, he was at the University of Western Australia (UWA).

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 with successful outcome and corresponding publications during the reporting time period.

The first topic of research covers the area of adult stem cells. In collaboration with the lactation research group (Peter Hartmann) at UWA and supervising the PhD student Foteini Hassiotou, a new population of breastmilk stem cells with pluripotent properties was discovered (Hassiotou et al. 2012).

The second topic of research covers the area of neuro-immunology, and more specifically microglia cells, the unique and only residential immune cells of the central nervous system. A new protocol was developed to generate human monocyte-derived microglia *in vitro* (Etemad et al., 2012).

The third topic covers the area of metals in biology. There, metal-based drugs and therapeutic devices have been investigated. Of special interest has been to visualize metal complexes and metal ions in cellular compartments (Wedlock et al. 2011). Additionally, the question was addressed, how metals may interfere with immune cells and functions, focusing on titanium (Chan et al., 2011).

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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 ***(Fig.1)***. 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.

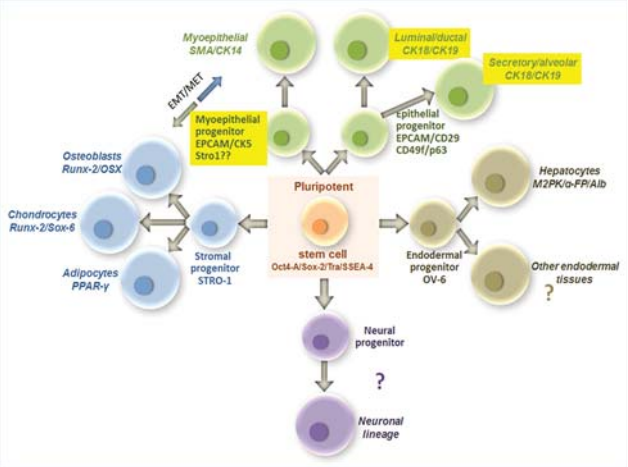

Fig.1 - Differentiation potential of human breastmilk stem cells with pluripotent properties.

Topic 2: Human microglia

Microglia are the only resident cells of the central nervous system, including the brain. They play a crucial role in health and disease, especially in infections, inflammatory responses and degenerative diseases. To date, the only way to investigate the role of microglia cells has been to use either animal models or to isolate microglia from brain tissue, which is very difficult in the context of human. In addition, many animal models do not really represent human diseases, including Alzheimer's disease. Furthermore, only few human microglia cell lines have yet been established from immortalized embryonic brain cells. Consequently, a new human microglia model was urgently required. We developed recently such a model by using freshly isolated human monocyte and culture them for 1 to 2 weeks in the presence of a cocktail of 4 cytokines, including M-CSF, GM-CSF, CCL2 and NGF, but in the absence of serum ***(Fig.2)***. The differentiated cells have all properties of human microglia, when compared with one established cell microglia cell line (HMC3). However, further comparison with brain derived human microglia will be done in the near future to validate the new model.

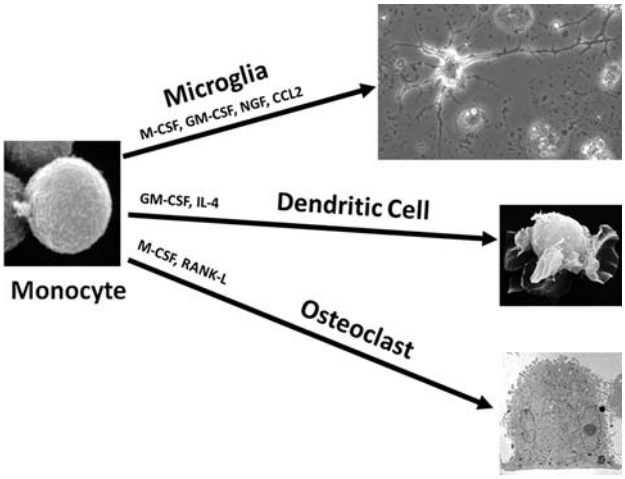

Fig.2 - Generation of various cell types in vitro, derived from freshly isolated human blood monocytes depends on specific cytokines.

Topic 3: Metals in biology

Extensive research has been done over the past 6 years to investigate how metals interact with bone and immune cells. The results of this research allowed us to propose new mechanisms for the better understanding of side effects of metal implants, focusing on orthopaedic devices ***(Fig.3)***. Those are usually implanted into bone, where osteoclastic activity acts on the metal surface with bio-corrosive release of metal ions. The ions are then interfering metabolically and structurally with many cells and tissues, including immune cells. Often, there is an immune response against metal-protein complexes which may result in anergy or allergy against those new antigens. In case of side effects of the metal implant, an allergic reaction takes place with activation and accumulation of metal specific T-lymphocytes at the side of the metal implant. The activated T-lymphocytes release a panel of cytokines that recruit and activate osteoclast-precursors, resulting in a vicious cycle with enhance biocorrosion and inflammatory reactions. ■

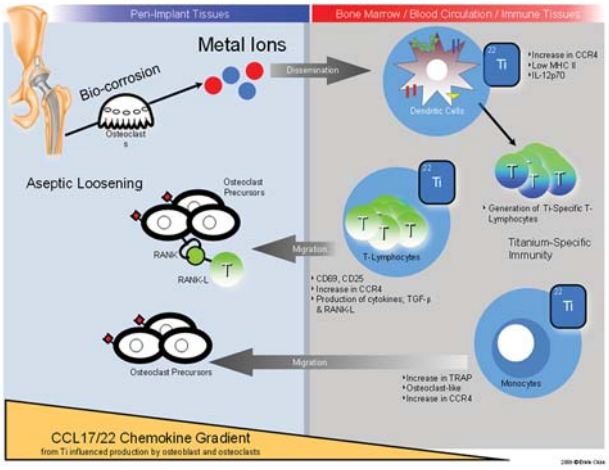

Fig.3 - Tissue-metal interaction. *Schematic explanation of the mechanisms that take place in the context of metal implants that are not well tolerated and where enhanced bio-corrosion results in specific allergic immune responses and in implant loosening due to activation of osteoclasts and bone resorption.*

◂◂

Selected Publications

Chan E, Cadosch D, Gautschi OP, Sprengel K, ***Filgueira L***
Influence of metal ions on human lymphocytes and the generation of titanium-specific T-lymphocytes. Journal of Applied Biomaterials & Biomechanics, 2011, 9, 137-143

Etemad S, Zamin RM, Ruitenberg MJ, ***Filgueira L***
A novel in vitro human microglia model: Characterization of human monocyte-derived microglia. Journal of Neuroscience Methods, 2012, 209, 79-89

Hassiotou F, Beltran A, Chetwynd E, Stuebe AM, Twigger AJ, Metzger P, Trengove N, Lai CT, ***Filgueira L****, Blancafort P, Hartmann PE*
Breastmilk is a novel source of stem cells with multi-lineage differentiation potential. Stem Cell, 2012, 30, 2164-2174

Patrice Nordmann
Chair of Microbiology

Molecular and medical microbiology

INTRODUCTION

Patrice Nordmann has joined the University of Fribourg in July 2013. Before he was at the University of Paris-Sud, INSERM and the hospital Bicêtre (Paris, France). The research interest of P. Nordmann is Emerging Antibiotic Resistances.

Antibiotic resistance is a multifaceted problem and truly a global challenge. Its worldwide spread may change significantly human medicine in the next years. As an example, more that 25,000 people die each year due to antibiotic-resistant bacteria in Europe. Emergence of pandrug-resistant bacteria and spread of even multidrug-resistant *E. coli* in the community (outside hospitals) are among the latest developments of this phenomenon. The emergence of such resistance traits is leading to impossible-to-treat infections and difficulties for prevention of infections (immunosuppressed patients, major surgery, transplantation medicine).

Research on antibiotic resistance aims at:

1) Increasing the knowledge on the origin, plasticity and diffusion of resistance genes.

2) Preventing their spread by implementing novel diagnostic tools.

3) Discovery of novel antibiotic molecules.

Our research is at the frontier between basic Sciences (Molecular Microbiology) and applied Sciences (Clinical Microbiology). It consist of two complementary approaches;

- Genetic and biochemical analysis of antibiotic resistance traits that are emerging worldwide.
- Development of novel diagnostic techniques for rapid identification of emerging antibiotic resistance traits and evaluation of novel antibiotic molecules.

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Genetic and biochemistry of emerging antibiotic resistances

Diffusion of antibiotic resistance of worldwide origin is reported currently in distantly-located areas. This is related to globalization of the world, increasing number of travels, and hospitalization of patients abroad. Therefore, we have established an informal network aimed to identify as rapidly as possible the emerging mechanisms of resistance. Biochemical and genetic analyses has been conducted with clinical isolates that have been first screened according to their multidrug resistance pattern results using phenotypic-based antibiotic susceptibility testing. Special focus has been made on Gram-negative bacterial species that are clinically relevant such as *Enterobacteriaceae (e.g. E. coli, K. pneumoniae…), Pseudomonas sp.* and *Acinetobacter sp.* We have identified several resistance determinants which are widespread now worldwide and clinically significant such as the extended-spectrum ß-lactamase CTX-M-15 which hydrolyses ß-lactams including cephalosporins and the carbapenemases of the OXA-48 type. Carbapenemases are proteins which are able to hydrolyze almost all ß-lactams including the carbapenems and which are also resistant to many other non ß-lactam antibiotics. By studying many multidrug resistant isolates from worldwide origin, we have identified that the recent spread of the the carbapenemases of the NDM type (New Dehli metallo-ß-lactamase), first identified from South-East Asia has spread at an alarming rate within the last two years ***(Fig.1)***. Genome analysis of one of those multidrug-resistant NDM-1 *E. coli* isolate lead us to identify the diversity of the antibiotic resistance traits which may be selected and gathered within a single bacterial genome.

Fig.1 - Worldwide distribution of carbapenemases NDM *(2010-2013).*

We have shown recently that the spread of the NDM-1 gene may have occurred from its reservoir organism first to *Acinetobacter baumannii* (a rare hospital-acquired pathogen), then to *Enterobacteriacae* ***(Fig.2)***. We are currently studying factors that may enhance expression (anticancer drug bleomycin since a bleomycin resistance gene is located next to the NDM-1 gene) ***(Fig.2)*** and gene plasticity of this resistance gene as well as novel antibiotic resistance genes and genetic elements we have discovered recently (insertion-sequence like elements).

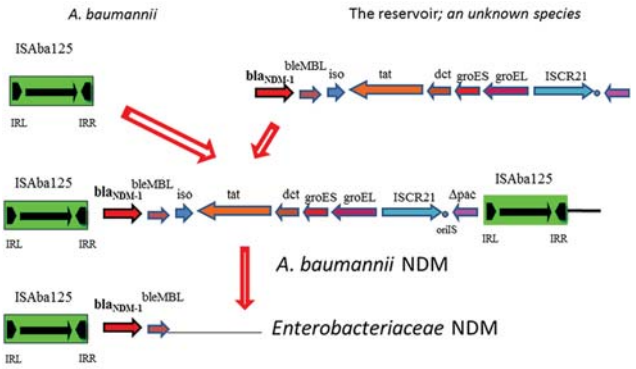

Fig.2 - A novel model of antibiotic gene transfer. A. baumannii *as an intermediate acceptor of antibiotic resistance gene.*

Rapid diagnostic techniques for the identification of antibiotic resistance and evaluation of novel antibiotic resistance molecules

Since very few novel antibiotic molecules will be marketed soon, control of antibiotic resistance is mostly based on the development of diagnostic techniques for the identification of emerging antibiotic resistance. Those techniques may help to design screening strategy for a better antibiotic stewardship of infected patients as well as a rapid isolation of colonized patients. We have developed rapid diagnostic tests for the identification of both the most important resistant determinants which are emerging in Gram negatives, the Carba NP test (carbapenemase detection) and ESBL NDP test (extended-spectrum ß-lactamase detection). The principle of those tests is based on the detection of acid production resulting from the ß-lactam hydrolysis. Carba NP test detects hydrolysis of a carbapenem ***(Fig.3)*** whereas the ESBL NDP test detects hydrolysis of an extended-spectrum cephalosporin. Those tests may be used with bacterial colonies but also directly with infected human samples ▸▸

such as blood and urines. Results are obtained in less than 2 hours with almost 100% sensitivity and specificity. They can be implemented in any clinical laboratory due to their simplicity and their low cost.

By collaborating with many labs and several biotech companies, we are participating also to the identification of novel antibiotic targets and the evaluation of the *in-vitro* and *in-vivo* antibiotic properties of novel molecules both using genetically well-defined bacterial isolates and clinical isolates. ■

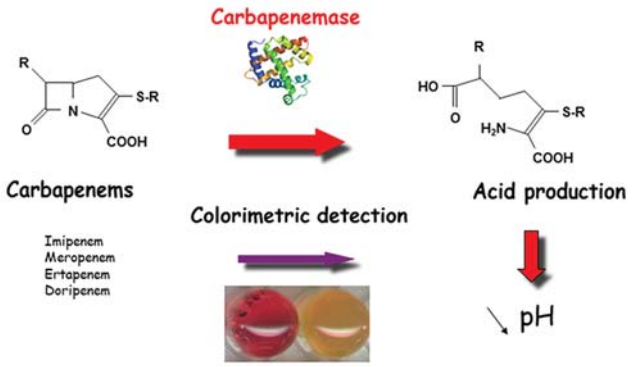

Fig.3 - The Carba NP test. *The principle of the test is based on the detection of acid production resulting from the hydrolysis of beta-lactam.*

Selected Publications

***Nordmann P**, Poirel L, Dortet L*
Rapid detection of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis, 2012, 18: 1503-1507

***Nordmann P**, Dortet L, Poirel L*
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Curzio Rüegg
Chair of Pathology

Experimental and translational oncology

INTRODUCTION

Cancer cells establish complex heterotypic multicellular interactions with the healthy neighboring tissue. This bidirectional communication between tumor cells and normal tissue, is called tumor host interaction. Research work in our laboratory focuses on the understanding how cancer cells modify their immediate surroundings or distant organs and exploit these modifications to their advantages. Unraveling this interaction is important for two reasons: firstly, it allows a better understanding of how cancer develop locally, progress, invade and form metastases. For examples, inflammation facilitates cancer progression, invasion and metastasis through the mobilization and recruitment of bone marrow-derived inflammatory cells that stimulate tumor cell proliferation, motility and angiogenesis. Inflammatory cells stimulated by the primary tumor modify the sites of future distant metastases to facilitate tumor cell seeding and growth. Secondly, it may open new therapeutic opportunities to prevent, detect or treat cancer. For example, tumor angiogenesis has emerged as a critical event in promoting tumor progression and metastasis, and its therapeutic inhibition provides survival advantages in selected cancers, in particular colorectal, renal and lung cancers. Non-steroidal anti-inflammatory drugs, such as Aspirin, have protective effect on some cancers, most notably of the gastrointestinal tract, and have some therapeutic anti-cancer effects.

We are interested in understanding how the growing tumor modify normal tissue to its advantage, how this modified tissue contributes to tumorigenesis, how therapeutic interventions modify this cross-talk, and what are the consequences. The questions we are addressing are:

1) How do cells of the microenvironment, in particular inflammatory cells, promote tumor growth and metastasis?

2) How does tumor angiogenesis modulate tumor dormancy?

3) How does the cross-talk between tumor cells and the microenvironment evolve during metastasis formation?

4) How do tumors and the microenvironment react to anticancer therapies and what are the consequences to tumor progression?

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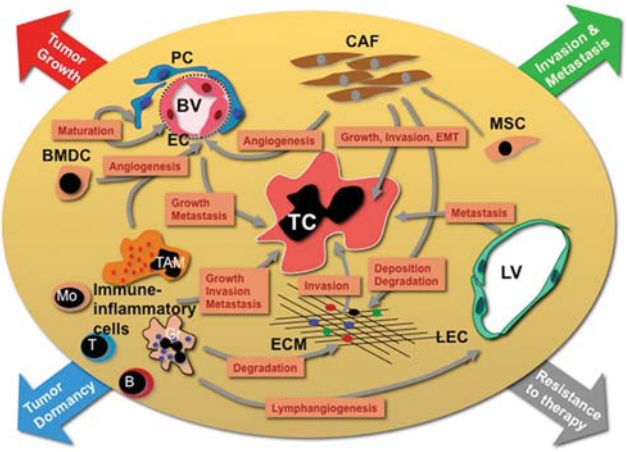

Fig.1 - The tumor microenvironment. *Tumor cells modify the normal tissue surrounding the tumor cells, by attracting or activating normal cells, including blood and lymphatic endothelial cells, stromal fibroblast, bone marrow-derived cells, immune and inflammatory cells. Tumor cells can also deposit or modify the extracellular matrix. In turn, the modified microenvironment promotes tumor progression by stimulating tumor growth and survival, and facilitating invasion and metastasis. Collectively these events will contribute to determine the outcome of tumor progression: growth, dormancy, invasion, and metastasis. They also contribute to determine therapy outcome. Abbreviations: B, B lymphocyte; BMDC, bone marrow-derived cells; BV, blood vessel; CAF, carcinoma associated fibroblast; EC, endothelial cell; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; Gr, granulocyte; LEC, lymphatic endothelial cell; LV, lymphatic vessel; Mo, monocyte; MSC, mesenchymal stem cell; PC, pericyte; T, T lymphocyte; TAM, tumor associated monocyte/macrophage; TC, tumor cells.*

Inhibition of the Kit ligand/c-Kit axis attenuates metastasis in a mouse model mimicking local breast cancer relapse after radiotherapy

Local breast cancer relapse after breast-saving surgery and radiotherapy is associated with increased risk of distant metastasis formation. The mechanisms involved remain largely elusive. We used the 4T1 syngeneic, orthotopic breast cancer model to identify mechanisms of postradiation metastasis. Tumors growing in preirradiated mammary tissue had reduced angiogenesis and were more hypoxic, invasive, and metastatic compared with control tumors. Increased metastasis involved the mobilization of $CD11b^{+}c\ Kit^{+}Ly6G^{high}Ly6C^{low}$ myeloid cells through the HIF1-dependent expression of Kit ligand (KitL) by hypoxic tumor cells. Pharmacologic inhibition of HIF1, silencing of KitL and inhibition of c-Kit with a blocking antibody or a tyrosine kinase inhibitor prevented the mobilization of $CD11b^{+}c\ Kit^{+}$ cells and attenuated metastasis. Our work defines KitL/c-Kit as a previously unidentified axis critically involved in promoting metastasis of 4T1 tumors growing in preirradiated mammary tissue. Pharmacologic inhibition of this axis represents a potential therapeutic strategy to prevent metastasis in breast cancer patients with local relapses after radiotherapy.

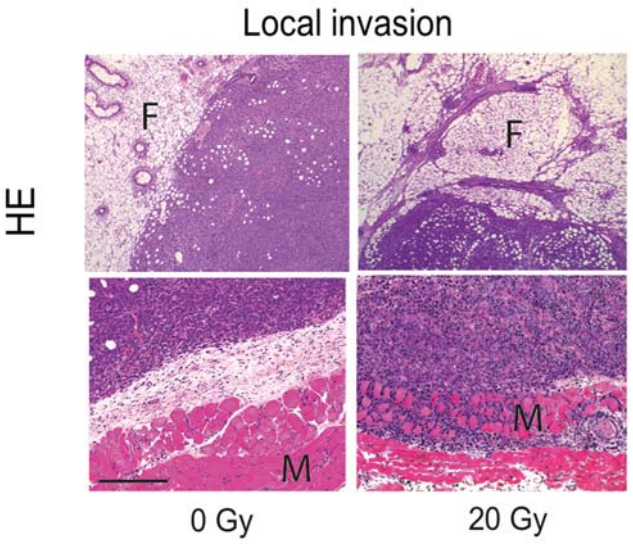

Fig.2 - Stroma irradiation promotes invasion. *Tumors growing in non-irradiated tissues (left images) are well-delimited and poorly invasive to fat (upper panels) and muscle (lower panels) tissues, while tumors growing in pre-irradiated tissues (right images) are invasive to fat and muscle tissues.*

Akt/PKB-mediated phosphorylation of Twist1 promotes tumor metastasis through a cross-talk between PI3K/Akt and TGF-β signaling axes

Metastatic breast tumor cells display an epithelial-mesenchymal transition (EMT) that increases cell motility, invasion, and dissemination. The transcription factor Twist1 has been shown to promote EMT and metastasis, but the signaling pathways regulating Twist1 activity remain elusive. In collaboration with the group of Dr. B. Hemmings, FMI, Basel, we have shown that Twist1 is ubiquitously phosphorylated in 90% of invasive human breast tumors. Akt/protein kinase B (PKB)-mediated Twist1 phosphorylation promotes EMT and breast cancer metastasis by modulating its transcriptional target TGF-β2, leading to enhanced TGF-β receptor signaling, which in turn maintains hyperactive phosphoinositide 3-kinase (PI3K)/Akt signaling. Preventing phosphorylation of Twist1, as well as depletion of TGF-β2, significantly impaired the metastatic potential of cancer cells in vivo, indicating a key role of phosphorylated Twist1 (phospho-Twist1) in mediating cross-talk between the PI3K/Akt and TGF-β/Smad signaling axes that supports metastatic tumor development. Our results describe a novel signaling event linking PI3K/Akt hyperactivation in tumor cells to direct regulation of Twist1 activation and tumor metastasis.

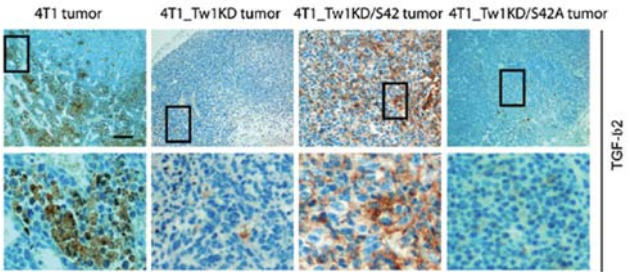

Fig.3 - Immunohistochemistry staining of TGFβ2 in 4T1 primary tumors. *TGFβ2 expression is present in wild type tumors (4T1) or in tumors with silenced Twist1 (Tw1KD) and reconstituted with wild type Twist1(Tw1KD/S42) but absent in tumors with silenced Twist1 (Tw1KD) and reconstituted with phosphorylation-deficient Twist1 (Tw1KD/S42A). S42 is a direct AKT prosphorylation site on Twist1.*

Identification of MAGI1 as a tumor-suppressor protein induced by cyclooxygenase-2 inhibitors in colorectal cancer cells

Cyclooxyganase-2 (COX-2), an enzyme in the prostaglandin synthesis pathway, is overexpressed in many cancers and contributes to cancer progression through tumor cell-autonomous and paracrine effects. Regular use of non-steroidal anti-inflammatory drugs or selective COX-2 inhibitors (COXIBs) reduces the risk of colon cancer (CRC) development and progression. In an effort to better understand the tumor-suppressive mechanisms of COXIBs, we identified MAGUK with Inverted domain structure-1 (MAGI1), a scaffolding protein implicated in the stabilization of adherens junctions, as a gene upregulated by COXIB in CRC cells and acting as tumor suppressor. Overexpression of MAGI1 in CRC cell lines SW480 and HCT116 induced an epithelial-like morphology; stabilized E-cadherin and β-catenin localization at cell-cell junctions; enhanced actin stress fiber and focal adhesion formation; increased cell adhesion to matrix proteins and suppressed Wnt signaling, anchorage-independent growth, migration and invasion in vitro. Conversely, MAGI1 silencing decreased E-cadherin and β-catenin localization at cell-cell junctions; disrupted actin stress fiber and focal adhesion formation; and enhanced Wnt signaling, anchorage-independent growth, migration and invasion in vitro. MAGI1 overexpression suppressed SW480 and HCT116 subcutaneous primary tumor growth, attenuated primary tumor growth and spontaneous lung CRC metastasis, and decreased the number and size of metastatic nodules in an experimental model of lung metastasis. These results identify MAG1 as a COXIB-induced inhibitor of the Wnt/β-catenin signaling pathway, with tumor-suppressive and anti-metastatic activity in CRC. ■

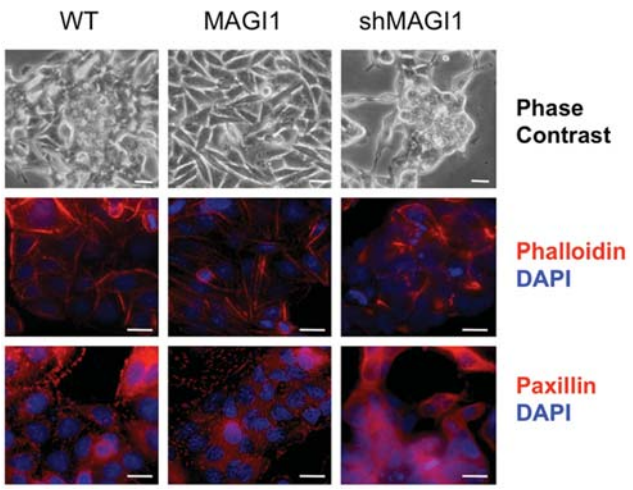

Fig.4 - MAGI1 modulates colorectal cancer cell morphology. *Phase-contrast microscopic images and immunostaining of F-actin (phalloidin) and paxillin (paxillin) of wilde type (WT), MAGI1-overexpressing (MAGI1) and MAGI1-silenced (shMAGI1) SW480 cells. Nuclei were counterstained with DAPI. MAGI1 overexpression induced a flattened epithelial morphology, actin stress fiber and paxillin-positive focal adhesion formation, whereasMAGI1 silencing caused cell rounding and aggregation, and loss of actin stress fibers and focal adhesions.*

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Franziska Theilig
Anatomy

Epithelial adaptations to renal pathologies

INTRODUCTION

Chronic kidney disease is characterized by the decline in renal excretory, homeostatic and endocrine functions. Most of the time, the primary event is a glomerular injury. With ongoing progression and glomerular extracapillary proliferation, tubulointerstitial damage occurs with the development of nephron loss and fibrotic lesions, which finally result in terminal renal failure. Renal tubulointerstitial damage is the final common pathway of all forms of renal disease leading to chronic kidney disease (CKD). The recent research has focused on ideas on how glomerular injury expands onto the tubulointerstitium. The chronic hypoxia hypothesis states that chronic oxygen deprivation to the tubulointerstitial compartment is the underlying reason for the scarring process which is based on a compromise of postglomerular capillary circulation. Furthermore, renal hypoxia is also thought to result from a combination of structural and functional changes which include: 1) capillary rarefaction, 2) compromise of peritubular blood flow resulting from glomerular injury which may involve the efferent arterioles and affect the blood supply for the tubule, 3) vasoconstriction from altered levels of vasoactive factors and signalling molecules, 4) increased oxygen demand from hyperfiltration and tubular hypertrophy, 5) limited oxygen diffusion as a consequence of extracellular matrix expansion and 6) renal anemia. Hypoxia and stabilization of hypoxia-inducible factor (HIF) has been documented in chronic renal diseases of different etiologies with the presentation of desired and undesired effects. Experimental evidence indicated that hypoxia may accelerate the progression of chronic renal disease through its effects on renal cell survival, inflammatory recruitment, collagen gene expression, extracellular matrix turnover and may promote epithelial-mesenchymal transition. However, results on the impact of hypoxia on the progression of CKD remained controversial and are therefore addressed in our studies.

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Tubular deficiency of von Hippel-Lindau attenuates renal disease progression in anti-GBM glomerulonephritis

In many kidney diseases, the original insult primarily involves the glomerulus and may then pass onto the tubulointerstitium. Several hypotheses link glomerular disease to tubular injury; perhaps the foremost hypothesis involves chronic tubular hypoxia. The reported effects of hypoxia and consecutive stabilization of hypoxia-inducible factors (HIFs), however, are controversial. Hypoxia induces interstitial fibrosis but also has beneficial effects on renal disease progression when HIF is activated pharmacologically. To analyze the impact of HIF on tubulointerstitial disease development in primary glomerular disease, transgenic von Hippel Lindau (VHL)-knockout mice were generated and null expression was induced before the onset of autoimmune IgG-mediated anti-glomerular basement membrane glomerulonephritis (GN). Tubular VHL knockout and, thus, local HIF-α stabilization increased renal production of vascular endothelial growth factor, tumor growth factor-β(1), and platelet-derived growth factor-B, resulting in augmented formation of capillaries and interstitial matrix, and conversion of fibroblasts to myofibroblasts. Within the glomerular disease, VHL knockout reduced the glomerular damage and attenuated tubulointerstitial injury. Likewise, proteinuria, plasma urea concentration, and tubulointerstitial matrix were decreased in VHL knockout with GN. These findings shown that tubular HIF-α stabilization in glomerular disease is beneficial for disease outcome. In comparison with VHL knockout alone, GN is a much stronger activator of fibrosis such that stimuli other than hypoxia may be considered important for renal disease progression. ■

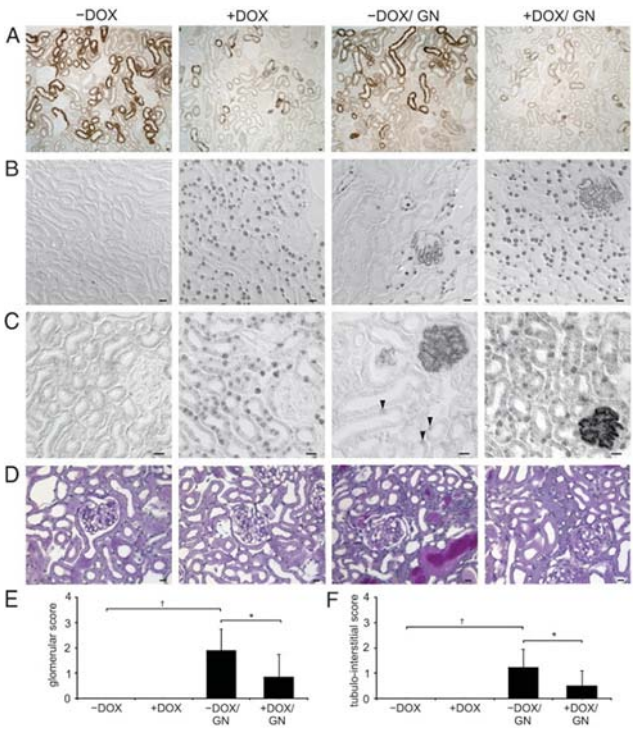

Fig.1 - Induction of VHL knockout and anti-GBM GN. ***A:*** *Immunohistochemical staining of VHL. The proximal tubule shows strong signals with predominance in the convoluted portion. Induction of the VHL knockout is depicted in +DOX and +DOX/GN showing a strong reduction in VHL abundance appearing with a mosaic pattern.* ***B*** *and* ***C:*** *Immunohistochemical staining of HIF-1α (**B**) and HIF-2α (**C**). Administration of doxycycline induced strong nuclear HIF-1α/HIF-2α accumulation in the tubular epithelial cells of +DOX and +DOX/GN. No signal was detectable in −DOX. On induction of GN (−DOX/GN), connecting tubule cells revealed HIF-1α (**asterisks**) and single proximal tubule cell HIF-2α (**arrowheads**) expression.* ***D:*** *PAS staining. In +DOX increased glomerular and peritubular formation of capillaries without structural alteration of the tubulointerstitium are shown. GN presents the typical features, however, less glomerular and tubulointerstitial injury were encountered in +DOX/GN compared with −DOX/GN.* ***E*** *and* ***F:*** *Glomerular damage score (**E**) and tubulointerstitial damage score (**F**). *P < 0.05 for −DOX versus +DOX; †P < 0.05 for control versus GN. Scale bars: 20 µm.*

Selected Publications

Theilig F*, Enke AK, Scolari B, Polzin D, Bachmann S, Koesters R*
Tubular deficiency of von Hippel-Lindau attenuates renal disease progression in anti-GBM glomerulonephritis. Am J Pathol, 2011, 179(5):2177-88

Cardiovascular, Metabolism and Endocrinology

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 and metabolic 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 and endocrine dysfunctions.

Stéphane Cook & Mario Togni
Translational and clinical cardiology

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Anna Lauber-Biason
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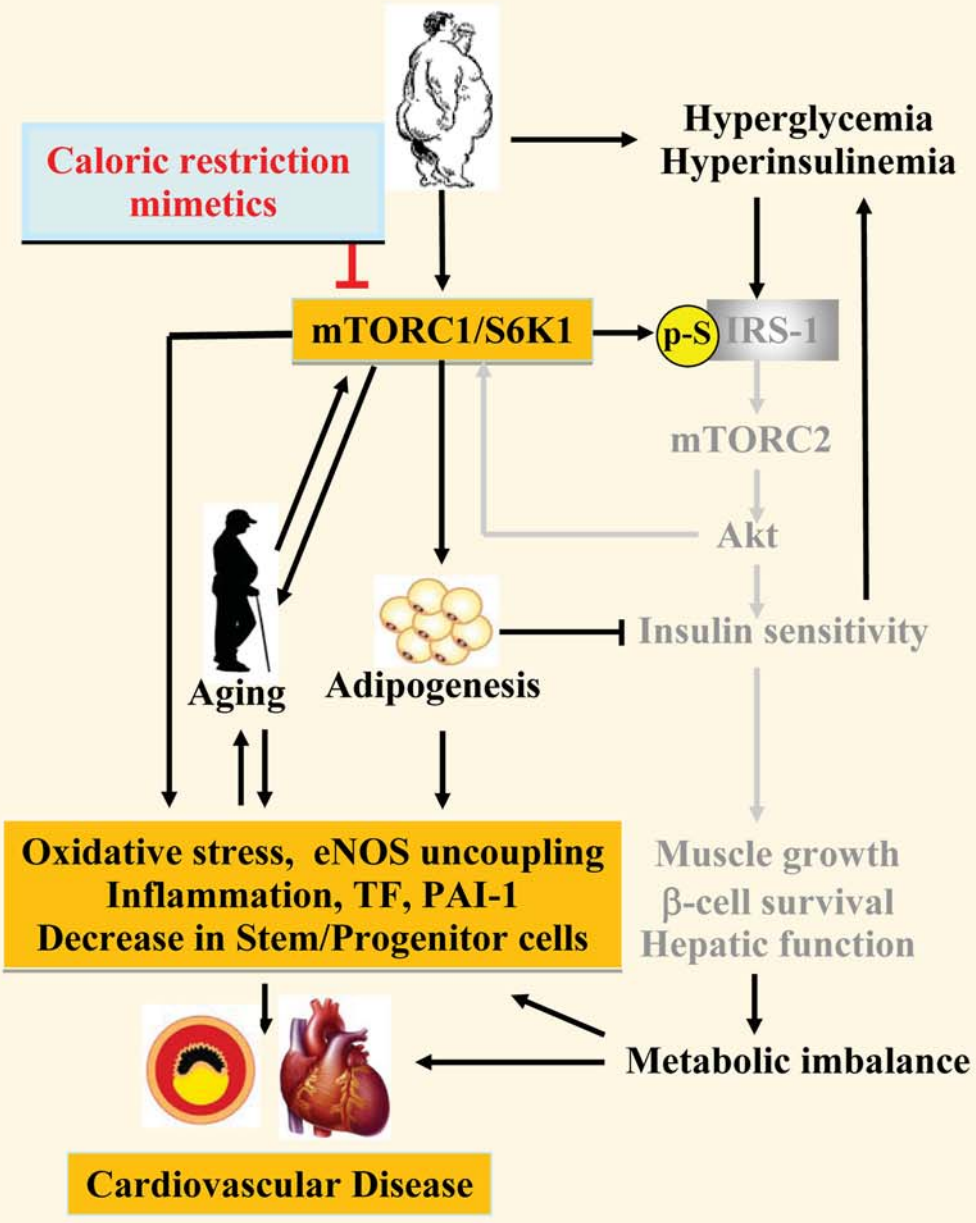
Caloric restriction mimetics
Hyperglycemia
Hyperinsulinemia
mTORC1/S6K1
p-S
IRS-1
mTORC2
Akt
Insulin sensitivity
Aging
Adipogenesis
Oxidative stress, eNOS uncoupling
Inflammation, TF, PAI-1
Decrease in Stem/Progenitor cells
Muscle growth
β-cell survival
Hepatic function
Metabolic imbalance
Cardiovascular Disease

Stéphane Cook
Mario Togni
Chair of Cardiology
Translational and clinical cardiology

INTRODUCTION

Myocardial infarction remains the first cause of morbidity and mortality in Switzerland as well as in most industrialized countries worldwide. In the vast majority of the cases, myocardial infarction is caused by the rupture (or erosion) of a so-called «vulnerable» atherosclerotic plaque, with secondary thrombosis formation and partial or complete occlusion of one coronary artery.

The research carried out in our laboratory aims at reducing the morbidity associated with myocardial infarction. This research is multifaceted, includes clinical and preclinical research and is structured in two different areas: vulnerability of atherosclerotic plaque, and improvement in clinical outcome after myocardial infarction.

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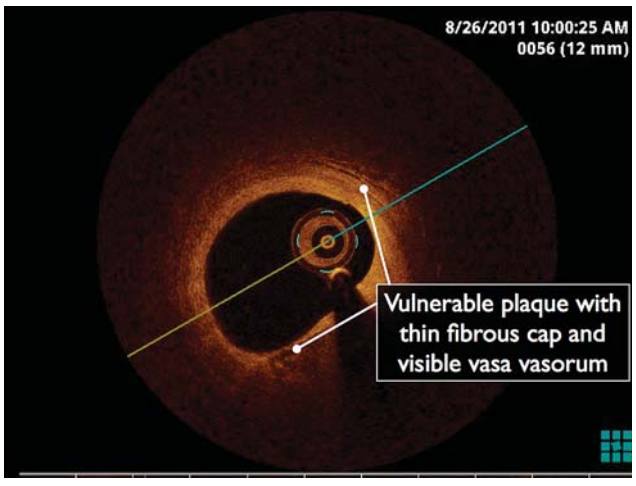

Fig.1

Vulnerability of atherosclerotic plaque

An atherosclerotic plaque is at an increased risk of rupture depending on the presence (or absence) of dedicated «intrinsic» and «extrinsic» factors. Intrinsic risk factors are multiple and only scarcely known. These intrinsic factors are mainly associated with hypoxic, inflammatory and thrombogenic stimuli. On the plaque-level, these factors trigger an increased activity of special enzymes excreted by macrophages (matrix metalloproteinases-MMPs), surge neovascularisation with the presence of leaky microvessels that provoke intraplaque haemorrhage and allow subsequent deposition of free cholesterol, macrophage infiltration and enlargement of the necrotic core. Using intravascular imaging, our group is able to discriminating key morphological pattern *in vivo* in humans, and *ex vivo* in various animal models ***(Fig.1)***.
On a patient-level, these factors are more often found in patients with diabetes mellitus, smoking habit, hypercoagulable/hypofibrinolytic states and high circulating tissue factor. Based on the most up-to-date researches, some biomarkers of vulnerability have been identified. Such examples are F2-isoprostanes, hs-CRP, urinary microalbumin, myeloperoxidase, or lipoprotein-associated phospholipase A2. These biomarkers are however difficult to measure at the bedside since gradient up to 1000-fold are found between blood harvested at plaque vicinity and peripheral blood. Since the footprint of this intrinsic inflammatory activity is partly trapped during the formation of coronary thrombus, our team investigates in parallel the structure and the presence of various biomarkers in the thrombus harvested from the occluded coronary arteries at time of percutaneous revascularisation ***(Fig.2)***.

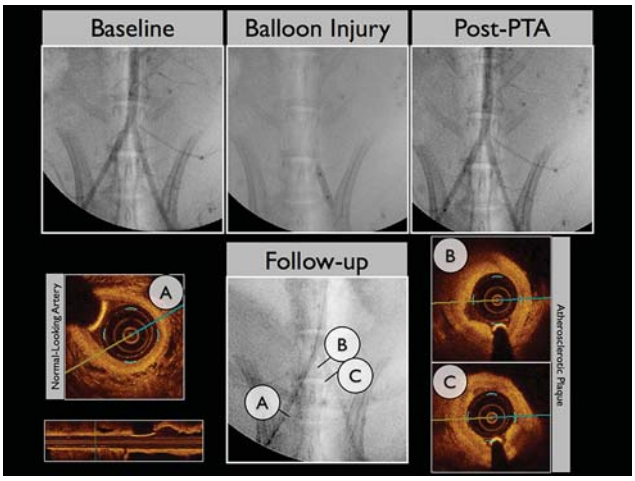

Fig.2

Finally, we are trying stabilizing the vulnerable plaques using new means and work in close collaboration with two laboratories at the EPFL in Lausanne. The second observation is that symptomatic plaque rupture often happens in particular situations, such as intense sentiments (positive or negative) or forced sports activities. These triggers are usually named extrinsic risk ▸▸

factors. In most cases, these factors significantly influence the vessel shear stress and the local procoagulable state via multiple biological parameters, such as adrenergic activity, blood pressure, heart rate, blood viscosity, or platelet activity. Due to the kind and the ephemeral nature of these latter factors, research in the field is intensely related to psychology. We therefore built up an emotional follow-up of patients who suffered from acute myocardial infarction, and actively collaborate with the cardiovascular rehabilitation center at HFR Billens.

Improvement in clinical outcome after myocardial infarction

The occurrence of myocardial infarction is correlated with an increased morbidity and mortality in the affected population. These rates of complications decreased significantly during the last two decades. For example, the current mortality is about 18% at 5-year after a myocardial infarction (STEMI or NSTEMI). The currently most common complications are related to either the coronary revascularization (percutaneous coronary intervention – PCI or coronary artery bypass graft surgery-CABG), or to the decrease in contractile cardiac mass (heart failure). Accordingly, the most active part of clinical research performed in our «clinical trial unit» focuses on the improvement of revascularization's techniques, as for instance, the study of partly or fully bioabsorbable coronary stents. In parallel, our preclinical research team led by PD Dr. Marie-Noëlle Giraud aims to rescue the loss of contractile cardiac mass *in vitro*, *ex vivo* and in preclinical models, a so-called «reparative cell therapy».

The recently discovered regenerative potential of the heart has fostered researchers' focus and reparative cell-based therapy has emerged and became a clinical reality ***(Fig.3)***. Initial goal was to transplant cells within the injured myocardium to induce neo-myocardium formation and neovasclarisation. However, the enthusiastic breakthrough reported in the early 21st century was followed by cautious warnings and numerous drawbacks that fostered a bed to bench return. Nowadays, the prevailing mechanism to explain cell therapy beneficial outcome relies on the secretion of paracrine cytoprotective factors from implanted cells that stimulate stem cell recruitment and in situ regenerative mechanism. Accordingly, the actual trend for cardiac cell therapy focuses on strategies that enhance cell engraftment and survival and boost paracrine effect.

Our goal is to improve reparative cell therapy. We investigated different matrices that may favour cell implantation, retention and survival.

We showed that epicardial implantation of solid and hydrogel matrices seeded with stem cells induced as stabilisation of heart function and decreased dilatation. We recently developed an innovative process to deliver stem cell to injured myocardium that resulted in improved contractile capacity of the myocardium and reduced fibrosis. We will further refine this therapeutic approach and identify mechanism for the observed adaptive remodeling. ■

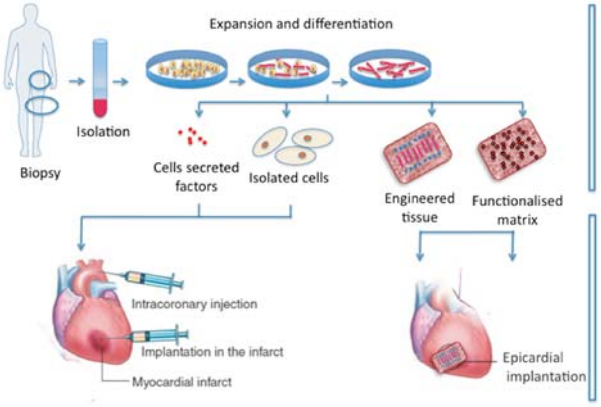

Fig.3

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Cook S
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Abdul Dulloo
Physiology

Nutritional energetics and body composition regulation

INTRODUCTION

That obesity predisposes to chronic metabolic diseases has long been known. Independently of excess weight, however, large fluctuations in body weight at some point earlier in life also predisposes to abdominal obesity, type 2 diabetes and cardiovascular diseases. These cardiometabolic risks have been demonstrated in men and women who in young adulthood experienced weight fluctuations involving the recovery of body weight after weight loss due to disease, famine or voluntary slimming by **dieting**, or when weight fluctuations occurred much earlier in life and involved ***catch-up growth*** after earlier growth retardation. In addressing the pathways by which such weight fluctuations predispose to fatness and chronic cardiometabolic diseases, our research focuses on the mechanisms that regulate body composition (fat mass and lean mass) during weight recovery, and how they confer increased susceptibility for development of insulin resistance and impaired glucose homeostasis.

Over the period 2011-2012, our investigations were focused on two main topics:

1) The mechanisms underlying adipose tissue plasticity in the regulation of fat storage during weight recovery, and how these mechanisms are influenced by a high fat foods.

2) A mechanistic explanation centered upon human body composition autoregulation as to how dieting may predispose to increased fatness.

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Glucose flux into adipose tissue during catch-up fat: Antagonism by dietary fat via *Randle cycle* competition

Catch-up growth, a risk factor for type-2 diabetes and cardiovascular diseases, is characterized by hyperinsulinemia and accelerated body fat recovery (catch-up fat). Using a rat model of semistarvation-refeeding that exhibits catch-up fat, we previously reported that during refeeding on a low-fat diet, glucose tolerance is normal but insulin-dependent glucose utilization is decreased in skeletal muscle and increased in adipose tissue, where adipogenesis and *de-novo* lipogenic capacity are concomitantly enhanced. Our work over 2011-2012 demonstrated that isocaloric refeeding on a high-fat diet blunts the enhanced *in-vivo* insulin-dependent glucose utilization for *de-novo* lipogenesis (DNL) in adipose tissue. These are shown to be early events of catch-up growth that are independent of hyperphagia and precede the development of overt adipocyte hypertrophy, adipose tissue inflammation or defective insulin signaling. These results suggest a role for enhanced adipose tissue DNL as a glucose sink in regulating glycemia during catch-up growth, which is blunted by exposure to a high fat diet, thereby contributing, together with skeletal muscle insulin resistance, to the development of glucose intolerance. Our findings are presented as an extension of the «Randle cycle hypothesis» whereby suppression of DNL constitutes a mechanism by which dietary lipids antagonize glucose utilization for storage as triglycerides in adipose tissue, thereby impairing glucose homeostasis during catch-up growth; this is depicted in ***Fig.1*** below.

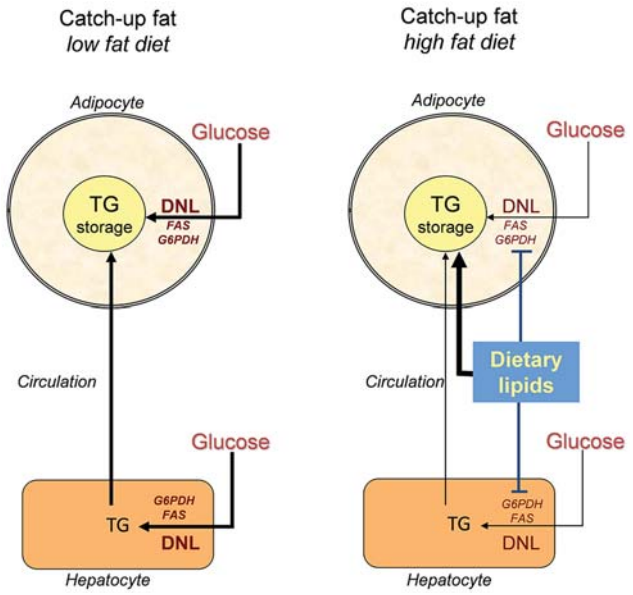

Fig.1 - Direct competition between glucose and lipids for fat storage as triglycerides in adipocytes*. During catch-up fat on low-fat (high-carbohydrate) diet, the increased de-novo lipogenesis (DNL) pathway leads to enhanced insulin-dependent glucose utilization in adipose tissue and liver, which hence contribute in maintaining normal blood glucose homeostasis. By contrast, during catch-up fat on high-fat diet, the increased availability of dietary lipids markedly inhibit the activity of key lipogenic enzymes (G6PDH and FAS) and provides substrates for TG synthesis and storage in adipose tissue. Thus, substrate competition between dietary fat and carbohydrates for TG storage in adipose tissue, via the inhibition of DNL, will lead to diminish glucose utilization in adipocytes and hepatocytes thereby promoting glucose intolerance during catch-up growth.*

How dieting makes some fatter?

«Dieting makes you fat» embodies the notion that dieting to control body weight, with consequential weight cycling, predisposes the individual to acquire even more body fat. While this notion is controversial, its debate underscores the large gap which exists in our understanding of basic physiological laws which govern the regulation of human body composition. In addressing the plausibility and mechanistic basis by which dieting may predispose to increased fatness, our research on this topic integrates our previous and more recent results derived from the re-analysis of classic longitudinal studies of human starvation and refeeding. These suggest that feedback signals from both fat and lean tissues contribute to recovering body weight through effects on energy intake and thermogenesis, and that a faster rate of fat recovery relative to lean tissue recovery (i.e. preferential catch-up fat) is a central outcome of body composition autoregulation that drives fat overshooting. A main implication of these findings is that the risk of becoming fatter in response to dieting is greater in lean than in obese individuals. This contention, which draws support from our recent findings ***(Fig.2** below)*, is in line with prospective studies indicating more consistent association with increased risks for major weight gain in initially normal-weight subjects than in initially overweight and obese subjects attempting to lose weight by dieting.

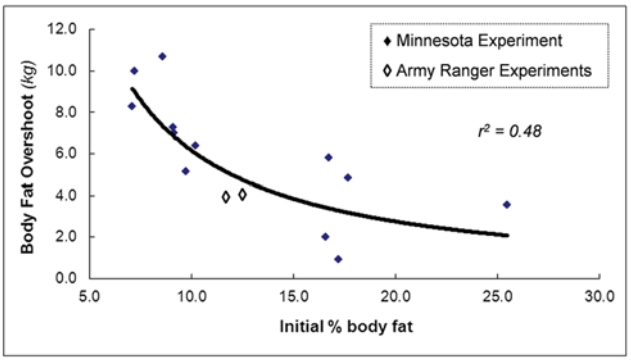

***Fig.2 - Relationship between the extent of fat overshooting and the initial (pre-starvation) percentage body fat**. The exponential curve is drawn from data (♦) on the 12 men who participated in all phases of the Minnesota experiment. The symbol (◊) represent the mean value for men (n=10) participating in each of two US Army Ranger training experiments.*

With the prevalence of dieting increasing among individuals in the normal-weight range (due to pressure for a slim image, body dissatisfaction or athletic performance) and accumulating evidence suggesting increased cardiometabolic risks associated with weight fluctuations in the non-obese population groups, the notion that dieting makes some fatter warrants greater experimental scrutiny and deserves greater public health concern than so far acknowledged. ■

Selected Publications

Marcelino H, Veyrat-Durebex C, Summermatter S, Sarafian D, Miles-Chan J, Arsenijevic D, Zani F, Montani JP, Seydoux J, Solinas G, Rohner-Jeanrenaud F, ***Dulloo AG***
A Role for adipose tissue de-novo lipogenesis in glucose homeostasis during catch-up growth: A Randle cycle favoring fat storage. Diabetes, 2013, 62: 362-72

Dulloo AG*, Jacquet J, Montani JP*
How dieting makes some fatter: from a perspective of human body composition autoregulation. Proc Nutr Soc, 2012, 71:379-89

Dulloo AG
The search for compounds that stimulate thermogenesis in obesity management: From pharmaceuticals to functional food ingredients. Obesity Reviews, 2011, 12: 866-83

Anna Lauber-Biason
Chair of Endocrinology

Experimental and translational 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*** that is the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual and ***sex differentiation*** that takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. At the beginning of gestation (1st and 2nd week) human embryos of the two sexes differ only for their karyotypes, 46, XY in the male and 46, XX in the female. Starting at week 3 specific genes lead to the differentiation of the gonads, which in turn produce hormones inducing anatomical and psychological differences, leading to behavioral differences that are ultimately influenced by the social environment. Generally speaking, factors influencing sex determination are transcriptional regulators, whereas factors important for sex differentiation are secreted hormones and their receptors.

It is important to notice that most of the knowledge on the factors involved in sexual development came from studies of cases in whom the genetic or the gonadal sex does not match the phenotypical sex, i.e. patients affected by defects of sex development (DSD) and from animal models.

Although factors involved in male sexual development have been well studied, the pathways that regulate female sexual determination remain incompletely defined. To date, no genes have been shown to play a role in ovarian development equivalent to that played by the SRY gene in testicular development.

These factors are the focus of our research.

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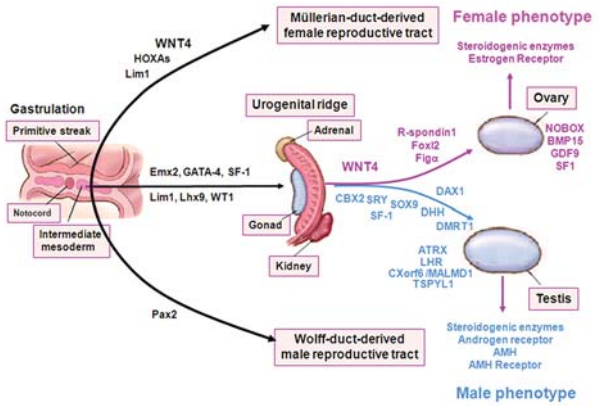
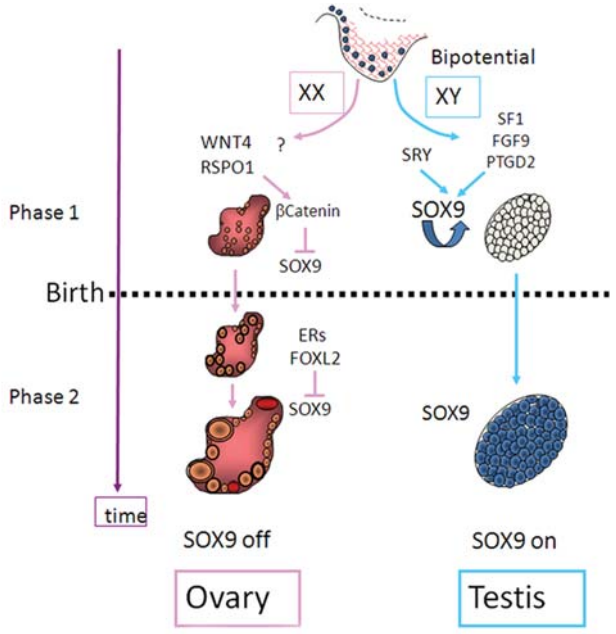


Modified from McLaughlin, NEJM 2004, 350:367

b.)



Biason-Lauber, Semin Reprod Med 2012; 30: 387-395

***Fig.1 - Sex developmental pathways**. a.) General, b.) WNT4 and other players.*

We identified new factors involved in sex development in humans by studying patients with defects of this process (disorders or variants of sex development, DSD). Two examples follow.

WNT4 and sex development

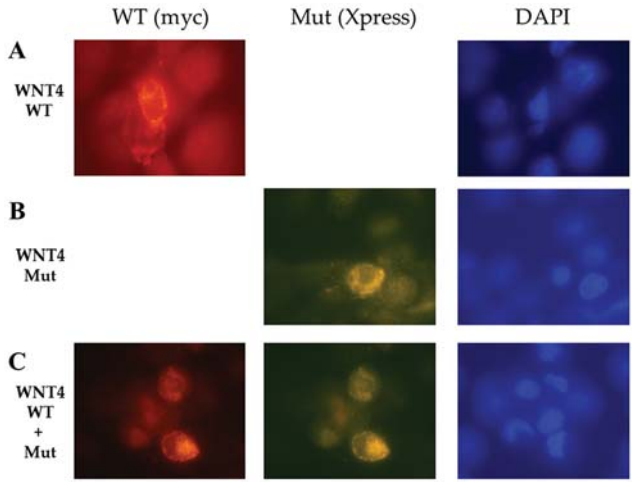
WNT4 (Wingless-type MMTV iNTegration site family, member 4), is a member of the WNT family of secreted molecules that function in a paracrine manner to affect a number of developmental changes, mainly by preventing the degradation of beta catenin. In the ovary, Wnt4 is produced in somatic cells (pre-granulosa cells). Wnt4 up-regulates *Dax1*, a gene known to antagonize the nuclear-receptor steroid factor 1, and thereby inhibits steroidogenic enzymes. Vainio and collaborators studied a mouse model in which Wnt4 is ablated and observed that, whereas both male and female *Wnt4*-knockout mice have similar defects in kidney development and adrenal function, gonadal development and steroidogenic function are affected exclusively in female *Wnt4*-knockout mice. *Wnt4*-knockout female mice are masculinized, as demonstrated by the absence of Müllerian ducts and the presence of Wolffian ducts, and express the steroidogenic enzymes 3β-hydroxysteroid dehydrogenase and 17α-hydroxylase, which are required for the production of testosterone and are normally suppressed in the developing female ovary. The ovaries of these mice also have less oocytes, suggesting a role of Wnt4 in the life of female germ cells.

WNT4 deficiency: implications for human sex development

In humans, more copies of WNT4, due to duplication of chromosome 1p31-p35, were found in a patient with ambiguous genitalia, severe hypospadia, fibrous gonads and remnants of both Müllerian and Wolffian ducts, *i.e.* male-to-female sex reversal. On the other end of the spectrum, when both copies of the gene are inactive, as in the case of homozygote mutations, a severe clinical entity, called the SERKAL syndrome, results. The syndrome was described in three 46,XX fetuses and is characterized by female-to-male sex reversal with ambiguous genitalia, gonadal morphology ranging from ovotestis to normal testis, renal agenesis, adrenal hypoplasia, pulmonar and cardiac abnormalities.

In the middle of such spectrum one might expect to find patients with intermediate defects of sex development. Searches for clinically relevant *WNT4* mutations sometimes in large cohorts of these patients were unsuccessful until we described the first case, a woman without structures derived from Müllerian ducts (uterine and fallopian tubes) who had unilateral renal agenesis and clinical signs of androgen excess. Her phenotype is strikingly similar to that of *Wnt4*-knockout female mice. This constellation of findings prompted us to search for mutations in the *WNT4* gene in this patient. Direct sequencing of PCR-amplified exonic fragments revealed a heterozygous mutation leading to a E226G/WT missense exchange in the WNT4 protein. In search for causes of the defective signaling, we found that the E226G mutant protein appears to be trapped inside the cell, likely because of defective post-translational lipid modification, necessary for WNT proper function. The recent identification of three additional patients with a similar phenotype and mutations in WNT4 confirmed its role in ovarian and female reproductive tract development in women. These data also helped to refine the phenotype of WNT4 deficiency in humans. In fact, it appears that the absence of uterus (and not other Müllerian abnormalities) and the androgen excess are the pathognomic signs of WNT4 defects, suggesting that this might be a clinical entity distinct from the classical Mayer-Rokitansky-Kuster-Hauser syndrome. WNT4 deficiency is also known as «Biason-Laubersyndrome» (http://ghr.nlm.nih.gov/condition=wnt4mullerianaplasiaandovarian ▸▸

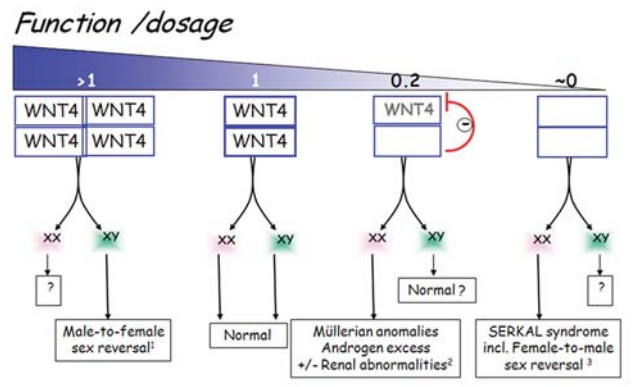
dysfunction). The functional studies performed in these cases suggested that the mechanisms of deficiency range from lack of lipid modification (and probable misfolding), to misfolding and formation of intractable aggregates, to defects in receptor binding.



Biason-Lauber et al, Hum Rep 2007, 22: 224-229

Fig.2 - Functional consequences of WNT4 mutation.

As often seen in sex development, WNT4 is certainly involved in a dosage-sensitive sex-determining process. In fact, while too much WNT4 activity (duplication) induces feminization of the male, too little WNT4 activity (homozygous loss-of-function mutation) induces exactly the opposite, i.e. masculinization of the female. Since WNT4 inhibits the male development in the female and males do not need WNT4 for their sex development, situations between these two extremes are characterized by different degrees of masculinization of the female. Although the presence of negative dominance renders the case arithmetically more complex, the relationship between activity levels and phenotype of WNT4 abnormalities is rather striking and corroborates the idea that sex differentiation is a matter of dosage. We plan to investigate the role of WNT4 and its partner in the onset of ovarian abnormalities in 46,XX patients.



1. Jordan et al, Am J Hum Genet 68:1102-9 (2001)
2. Biason-Lauber et al, N Engl J Med 351:792-8 (2004), Biason-Lauber et al, Hum Reprod 22:224-229 (2007),
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Biason-Lauber, Sex Dev 2008, 2:210-218

CBX2 and disorders of sex development

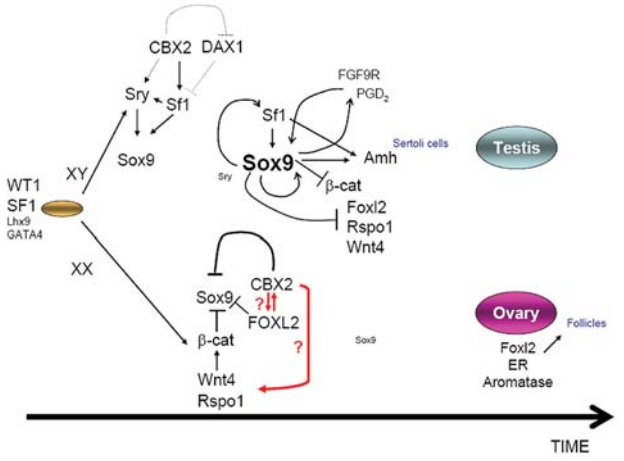
CBX2/M33 is a member of the Polycomb group (PcG) proteins, highly conserved regulatory factors initially discovered in *Drosophila*. PcG genes are best known for their role in maintaining silent expression states of Hox genes during development. They act by regulating chromatin structure and chromosome architecture at their target loci. Targeted ablation of M33, the homolog of *Drosophila* Polycomb, causes male-to-female sex reversal in mice. Apart from their sterility, 50% of M33 knock-out genetically male mice were phenotypically perfect females (ovaries with follicles, uterus and normal external genitalia), placing M33 upstream of Sry in the murine sex development cascade. Similarly, we made the intriguing discovery of a loss-of-function double heterozygote mutation state in a 46,XY girl with normal ovaries at histology, normal uterus and external female genitalia, accidentally diagnosed because of a discrepancy between prenatal karyotype and phenotype at birth. Functional studies demonstrated that the mutated CBX2 does not properly bind to and does not adequately regulate the expression of target genes essential for sex development such as SF1/NR5A1. Our data identify CBX2 as essential for normal human male gonadal development, suggest that it lies upstream of SRY in the human sex development cascade and identify a novel autosomal recessive cause of defect of sex development. From a mechanistic point of view, we demonstrated that CBX2 might has a role as transactivator distinct from its known function as chromatin-modifier. The exact position of CBX2 in sex development cascade is still unknown and the role of CBX2 in ovarian development and maintenance is yet to be explored. The existence of a «master regulator» of ovarian development influencing FOXL2, WNT4 and RSPO1 has been hypothesized. By determining the role of CBX2 we plan to gain insights in such master regulator network and to identify its potential targets. Our recent identification of a second patient with CBX2 mutation and 46, XY DSD will help to gain new informations in the physiological role of CBX2 in humans.

Relevance:

Defects of sexual development are not rare, having a prevalence of 1:3000-5000, and an increasing interest by the media and the public. Elucidation and clarification of defects of sexual differentiation is essential for the improvement of care and management of patients affected by these anomalies. A precise diagnosis would render decisions regarding surgical and medical treatment prompter and easier, and would prevent unnecessary physical and psychological stress for patients, families and health providers A deeper understanding of these conditions will have impact on the quality of life of the

◂◂ *Fig.3 - WNT4 dosage and manifestation of disease.*

patients and their families, with clear benefit for the community. In particular, studies on WNT4 and CBX2 will shed more light on ovarian development, a terrain still relatively unexplored. Clinically, if the similarity between mouse and human phenotype remains throughout life, unexplained sterility or premature ovarian insufficiency in women might be a unique sign of CBX2 abnormalities in the human population. For women's health, the clarifications of mechanisms underlying the life and maintenance of ovarian function will open the way for a swift evaluation of potential ovarian reserve and help prevent infertility and early menopause in women at risk by timely measures, such as oocytes preservation or even identifications of biomarkers for stem cells recovery. Furthermore, knowledge acquired by studying rare diseases might help clarify the still unknown pathophysiology of more common and complex diseases such as polycystic ovary syndrome, a condition affecting 5-8% of the reproductive aged women and it is the leading cause of androgen excess (hirsutism and acne), anovulation, infertility and eventually metabolic syndrome. ■



Modified from Biason-Lauber, Best Practice & Research Endocrinol Metab, 2010, 24:163-186

Fig.4 - Mammalian sex development: factors and their time-line.

Selected Publications

Philibert P, ***Biason-Lauber A****, Gueorguieva I , Stuckens C, Pienkowski C, Lebon-Labich B, Paris F, Sultan C*
Molecular analysis of WNT4 gene in 4 adolescent girls with Mullerian duct abnormality and hyperandrogenism (atypical MRKH syndrome). Fertil Steril, 2011, 95:2683-2686

Flück CE, Meyer-Böni M, Pandey AV, Kempná P, Miller WL, Schoenle EJ, ***Biason-Lauber A***
Why Boys will be Boys: Two Pathways of Fetal Testicular Androgen Biosynthesis Are Needed for Male Sexual Differentiation. Am J Hum Genet, 2011, 89. 201-218

Jean-Pierre Montani
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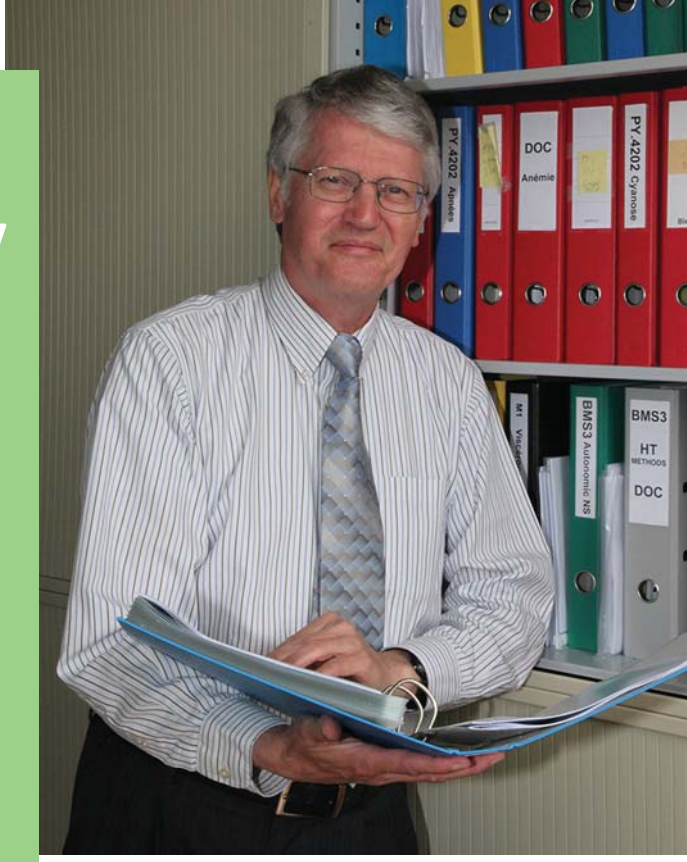
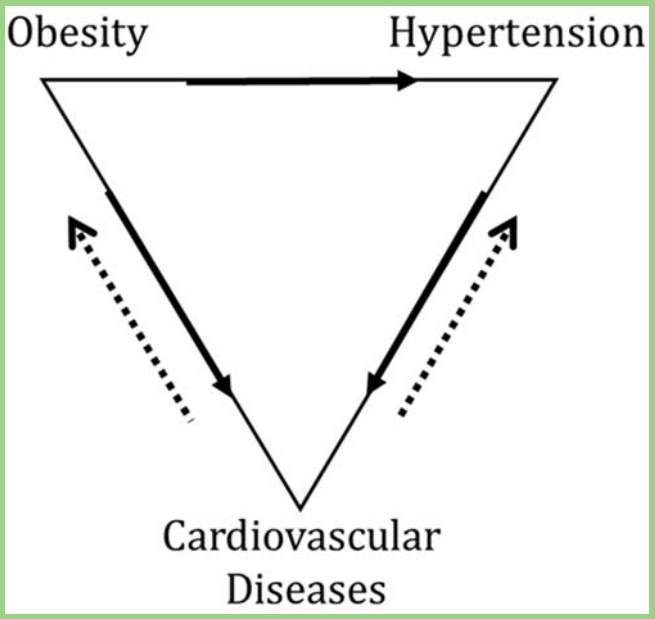
Cardiovascular and metabolic physiology



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, leading to a vicious triangle.



In particular, our interests focus on the importance of the diet (fats and sugars), ranging from animal studies (chronic high fat or high fructose diets) to human studies (with acute cardiovascular monitoring after the ingestion of soft drinks or high salt meals).

Additional interest touches space medicine for a better understanding of orthostatic intolerance and the mechanisms to prevent it after reentry from long-term space flights. Finally, although it is well known that metabolic diseases, obesity and diabetes lead to a progressive reduction in kidney function, it is not known whether a primary reduction in renal function may alter glucose and lipid homeostasis.

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Cardiovascular and cerebrovascular effects of soft drink consumption

Consumption of refined sugars in the form of soft drinks is increasingly recognized as a public health concern with major implications for cardiovascular diseases. These adverse consequences might be exacerbated by caffeine, which is often added to soft drinks, particularly in popular «energy» drinks. In young healthy subjects, we tested whether the acute consumption of an energy drink would impact on hemodynamic variables, particularly affecting blood pressure and cerebral blood flow velocity. We also tested whether consuming a popular energy drink would potentiate the cardiovascular responses to a mental stress test.

Our results show that consumption of an energy drink increases blood pressure and heart rate, and thus the workload to the heart, and decreases cerebral blood flow velocity, the later due to stimulation of breathing resulting in decreased end-tidal CO_2 and cerebral vasoconstriction. Performing a mental arithmetic task imposes an additional cardiovascular load with higher absolute values of blood pressure and heart rate. Interestingly, prior ingestion of an energy drink did not decrease the number of mistakes during the arithmetic test. 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 and cerebrovascular diseases.

Weight cycling, a metabolic and cardiovascular risk factor

The repetition of periods of diet-induced weight loss and periods of weight gain, a phenomenon known as weight cycling, is common in obese adults and adolescents. Using young growing rats with cycled food intake on a normal chow (cycles of 3 days of food restriction followed by 3 days of food excess) followed by 2 weeks of high fat controlled refeeding, we analyzed body weight and body composition changes, as well as hormonal profile, key enzymes of the lipid metabolism and controllers of the oxidative balance. The results show that the lipogenic machinery is maximally activated before refeeding. In addition, stress hormones are activated and key regulators of the oxidative balance show that weight cycling may promote oxidative stress. Altogether, our studies show that weight cycling show a detrimental metabolic profile, with fat accumulation and activation of stress and oxidative pathways.

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 was to test the converse, whereas a primary decrease in kidney function (as induced by uninephrectomy, UniNX) can alter whole body metabolism, leading thus potentially to a vicious cycle in metabolic diseases. To that purpose, we studied young Sprague Dawley male rats before and after uninephrectomy or sham surgery performed at ~6 weeks of age, analyzing body weight, organ and fat pad weights, whole body composition (by carcass analysis), plasma and tissue levels of various metabolic and inflammatory markers, at different time points after surgery.

Uninephrectomy led to a sustained decrease in whole body fat mass and individual fat pads. There is evidence for increased lipolysis with sustained increases in plasma glycerol, in hormone sensitive lipase and adipocyte triglyceride lipase in all fat pads studied. The mechanisms of increased lipolysis are not related to circulating hormones (as leptin, insulin, ghrelin, thyroid hormones, ..., are similar in UniNX or sham animals), but could be related to the lipolytic effects of elevated circulating cytokines (IFNγ, GM-CSF), to other intracellular factors capable of regulating lipolysis such as the farnesoid X receptor (FXR), which is also elevated after UniNX, or to simple sympathetic activation.

UniNX results in low grade of chronic inflammation as determined by increases in cytokine levels in serum. Some of these cytokines are increased only transiently whilst other such as IFNγ and GM-CSF remain steadily elevated after UniNX. The sources for the elevated circulating cytokines are not the fat pads themselves, nor the liver, nor the kidney since IFNγ, GM-CSF levels are normal or decreased in those tissues. However, a splenic source is hypothesized as IFNγ, GM-CSF contents of the spleen are increased. The mechanisms for splenic activation are, however, not known.

The liver, as a key organ of lipid metabolism, may also be involved in the overall phenotype as liver size and liver glycogen content were decreased. The liver free fatty acid transporter CD36 and lipoprotein lipase remained increased after UniNX, suggesting lipid consumption with possible intrahepatic futile cycles. Finally, the brain may be an important player, as immune cytokines IFNγ, GM-CSF, may also alter metabolism via a direct action of the brain. We show an elevation of IFNγ-Receptor, GM-CSF-Receptor, and melanocortin 4 receptor (MC4R) mRNA levels in brain stem and hypothalamus. We hypothesize that IFNγ and GM-CSF act on brain areas to stimulate the MC4-R, which in turn may activate the sympathetic nervous system to promote lipolysis.

Counter-measures to prevent orthostatic syncope

At orthostatic vasovagal syncope, there appears to be a sudden decline of sympathetic activity. As mental challenge activates the sympathetic system, we hypothesized that doing mental arithmetic in volunteers driven to the end point of their cardiovascular stability may delay the onset of orthostatic syncope. We first studied the impact of mental arithmetic stress test on the cardiovascular responses during head-up tilt, to show that mental arithmetic test attenuates the drop in blood pressure and cardiac output during orthostasis.

We then investigated in healthy male subjects whether ▸▸

orthostatic tolerance time (driven by the combination of head-up tilt and graded lower body negative pressure) could be prolonged with added mental challenge (2 min before the expected presyncope time). Our studies indicate that mental challenge improves orthostatic tolerance significantly. Additional mental loading could be a useful countermeasure to alleviate the orthostatic responses of persons, particularly in those with histories of dizziness on standing up, or to alleviate hypotension that frequently occurs on return to earth from the spaceflight environment of microgravity. ■

Selected Publications

Dulloo AG, Jacquet J, ***Montani JP***
How dieting makes some fatter: from a perspective of human body composition autoregulation. Proc Nutr Soc, 2012, 71(3):379-389

Sharp MK, Batzel JJ, ***Montani JP***
Space physiology IV: mathematical modeling of the cardiovascular system in space exploration. Eur J Appl Physiol, 2012, (in Press)

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INTRODUCTION

Atherosclerotic coronary heart disease remains the leading cause of death in our society. The increasing burden of obesity and associated type-II diabetes and the global accelerating aging population are the major risk factors for coronary artery disease. Oxidative stress, endothelial dysfunction, and inflammation have been evidently shown to be the important mechanisms involved in the pathogenesis of atherosclerosis, diabetes, and age-associated vascular dysfunction which is referred to as «vascular aging». Recent research shows that endothelial nitric oxide synthase (eNOS)-uncoupling appears to be an important mechanism of oxidative stress, whereby eNOS generates large amount of $O_2^{\cdot-}$ instead of the vasoprotective NO from L-arginine. Arginase-I and II have been shown to metabolize and deplete intracellular L-arginine for NO production, leading to decreased eNOS function and endothelial dysfunction. On the other hand, increased arginase-I activity in macrophages has been shown to associate with anti-inflammatory functions of the cells. The role of arginase-II in macrophage inflammatory responses is rarely investigated. Our research in 2011 and 2012 has focused on the signaling transduction pathways that regulate arginase-II expression/activity in endothelial cells and macrophages in atherosclerosis, type-II diabetes, and age-associated vascular dysfunctions.

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Loic Borcard

Crosstalk between arginase-II and S6K1 promotes eNOS-uncoupling, leading to endothelial inflammation and aging

eNOS-uncoupling and enhanced endothelial expression of adhesion molecules, i.e. vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are characteristics of vascular aging. Our studies show that S6K1 is hyperactive in senescent human endothelial cells and also in the aortas of old rats and mice. Using pharmacological and genetic approaches, we demonstrate that persistent activation of a vicious cycle between S6K1 and arginase-II causes eNOS-uncoupling, resulting in enhanced $O_2^{\cdot-}$ and decreased NO production, which accelerates endothelial premature senescence and inflammatory adhesion molecule expression in cultured human cells. Moreover, inhibition of S6K1 or arginase-II either pharmacologically or genetically re-couples eNOS function, i.e., restores NO production, leading to decrease in VCAM-1 and ICAM-1 expression in the senescent human endothelial cells as well as in the aortas of the old mice.
Our work explored a previously unidentified crosstalk between S6K1 and arginase-II in oxidative stress and vascular inflammation mediated by eNOS-uncoupling in age-associated vascular disease. The results suggest that targeting S6K1 and/or arginase-II could decelerate vascular aging and age-associated cardiovascular disease development.

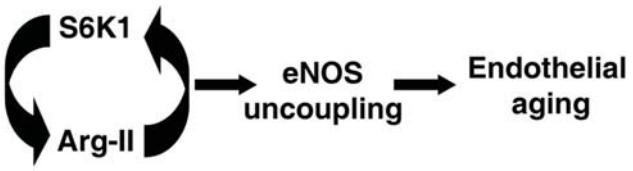

Fig.1 - Scheme illustrating mutual positive crosstalk between S6K1 and Arg-II in endothelial aging.

Arginase-II promotes macrophage inflammatory responses and mitochondrial reactive oxygen species formation, contributing to type-II diabetes and atherogenesis

Macrophage infiltration into the vascular wall, adipose tissues, and other organs/tissues triggers tissue inflammations and accelerates atherosclerosis and obesity-associated insulin resistance and type-II diabetes. The role of arginase-I in macrophages has been shown to associate with anti-inflammatory functions, whereas the role of arginase-II in macrophage inflammatory responses remains unidentified. We demonstrate that in human monocytes, silencing arginase-II gene decreases the monocyte adhesion to endothelial cells and their production of proinflammatory cytokines. Macrophages differentiated from bone marrow cells of arginase-II deficient (Arg-II$^{-/-}$) mice express decreased levels of lipopolysaccharid-induced proinflammatory mediators, whereas reintroducing Arg-II cDNA into the Arg-II$^{-/-}$

macrophages restores the inflammatory responses, with concomitant enhancement of mitochondrial reactive oxygen species. Scavenging of the reactive oxygen species prevents the Arg-II gene-mediated inflammatory responses. Moreover, high-fat-diet-induced infiltration of macrophages in various organs and expression of proinflammatory cytokines in adipose tissue are blunted in Arg-II$^{-/-}$ mice which reveal lower fasting blood glucose and improved glucose tolerance and insulin sensitivity. Furthermore, ablation of Arg-II gene in the atherosclerosis-prone ApoE–deficient mice (ApoE$^{-/-}$Ar-II$^{-/-}$) display reduced lesion size with characteristics of stable plaques. In vivo adoptive transfer experiments reveal a lower monocyte tissue infiltration activity as well as a less chemotactic tissue microenvironment of the ApoE$^{-/-}$Arg-II$^{-/-}$ mice as compared to the ApoE$^{-/-}$Arg-II$^{+/+}$ control animals.

The results for the first time demonstrate that arginase-II promotes macrophage proinflammatory responses through mitochondrial reactive oxygen species, contributing to insulin resistance and atherogenesis. Targeting arginase-II represents a potential therapeutic strategy in type II diabetes mellitus and atherosclerosis. ■

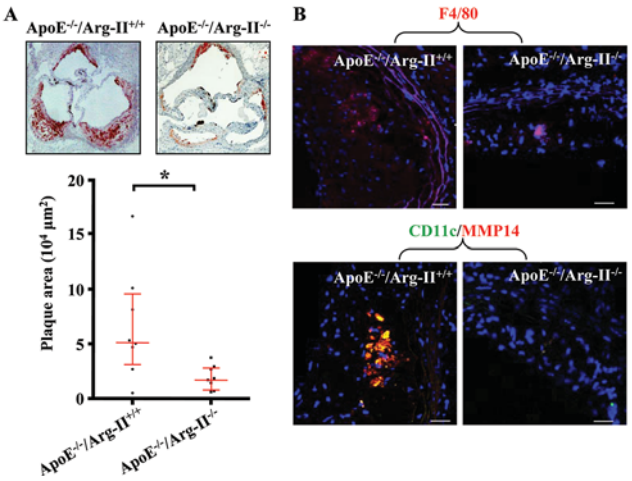

Fig.2 - Targeted disruption of Arg-II reduced atherosclerosis in ApoE$^{-/-}$ mice fed high fat diet for 10 weeks. *A, Representative images showing Oil Red O staining of plaques in aortic roots of ApoE$^{-/-}$Arg-II$^{+/+}$ and ApoE$^{-/-}$Arg-II$^{-/-}$ mice. Quantifications of the lesions are presented in the graph below the stains. Data shown are medians with 25th and 75th percentiles from 8 animals of each group. At least 7 equally spaced cryosections of aortic roots per mouse were evaluated. B, Representative confocal microscopic images showing macrophage accumulation in the lesions stained with antibodies against F4/80 (red), or CD11c (green) and MMP14 (red). All sections were counterstained with DAPI (blue). The merged images are shown. Scale bars=10 μm.*

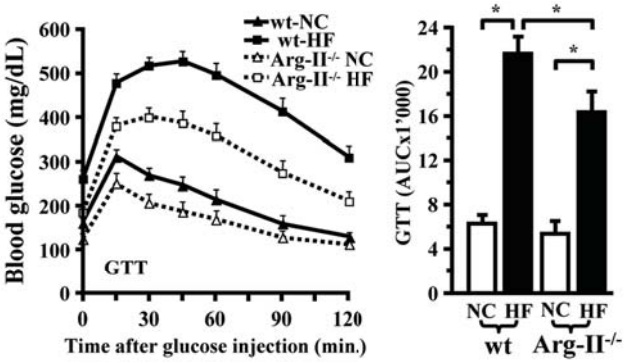

Fig.3 - Improved glucose tolerance in Arg-II$^{-/-}$ mice fed high fat diet as demonstrated by glucose tolerance test (GTT) in the lean and obese wild-type and Arg-II$^{-/-}$ mice. *Data shown are mean±SEM from 14 to 19 individual animals. Area under the curve (AUC) is presented in the corresponding graphs on the right. *P<0.05 between the indicated groups.*

Selected Publications

Yepuri G, Velagapudi S, Xiong Y, Rajapakse AG, Montani JP, Ming XF, ***Yang Z***
Positive crosstalk between arginase-II and S6K1 in vascular endothelial inflammation and aging. Aging Cell, 2012, 11(6):1005-16

Ming X-F, Rajapakse AG, Yepuri G, Xiong Y, Carvas JM, Ruffieux J, Scerri I, Wu Z, Popp K, Li J, Sartori C, Scherrer U, Kwak BR, Montani J-P, ***Yang Z***
Arginase-II promotes macrophage inflammatory responses through mitochondrial reactive oxygen species, contributing to insulin resistance and atherogenesis. JAHA, 2012, 112.000992

Rajapakse AG, Yepuri G, Carvas JM, Stein S, Matter CM, Scerri I, Ruffieux J, Montani JP, Ming XF, ***Yang Z***
Hyperactive S6K1 Mediates Oxidative Stress and Endothelial Dysfunction in Aging: Inhibition by Resveratrol. PLoS One, 2011, 6(4):e19237

Neurosciences **In spite of outstanding recent discoveries in the field, understanding brain function remains nowadays a major challenge for science and society. The brain is the most complex organ of the body, requiring the development of highly sophisticated techniques to study its exquisite function. The brain orchestrates our behavior, it permits our interactions with the environment and other people, and it exerts a prominent control on most body functions. Deciphering the mechanisms underlying brain functions is key to the understanding and treatment of devastating neurological diseases (e.g. Parkinson, Alzheimer, Autism, Epilepsy, etc.) and to restore the function of the nervous system after brain trauma (e.g. stroke) or spinal cord injury.**

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Laboratory for clinical and neurological sciences

Jean-Pierre Bresciani
Perception and control of movement

Marco Celio
Brain circuits for positive emotions

Robert Kretz
Visual neuroscience

Pierre Lavenex
Laboratory of brain and cognitive development

Marco Merlo
Early recognition and treatment of psychic disorders in young adults

Gregor Rainer
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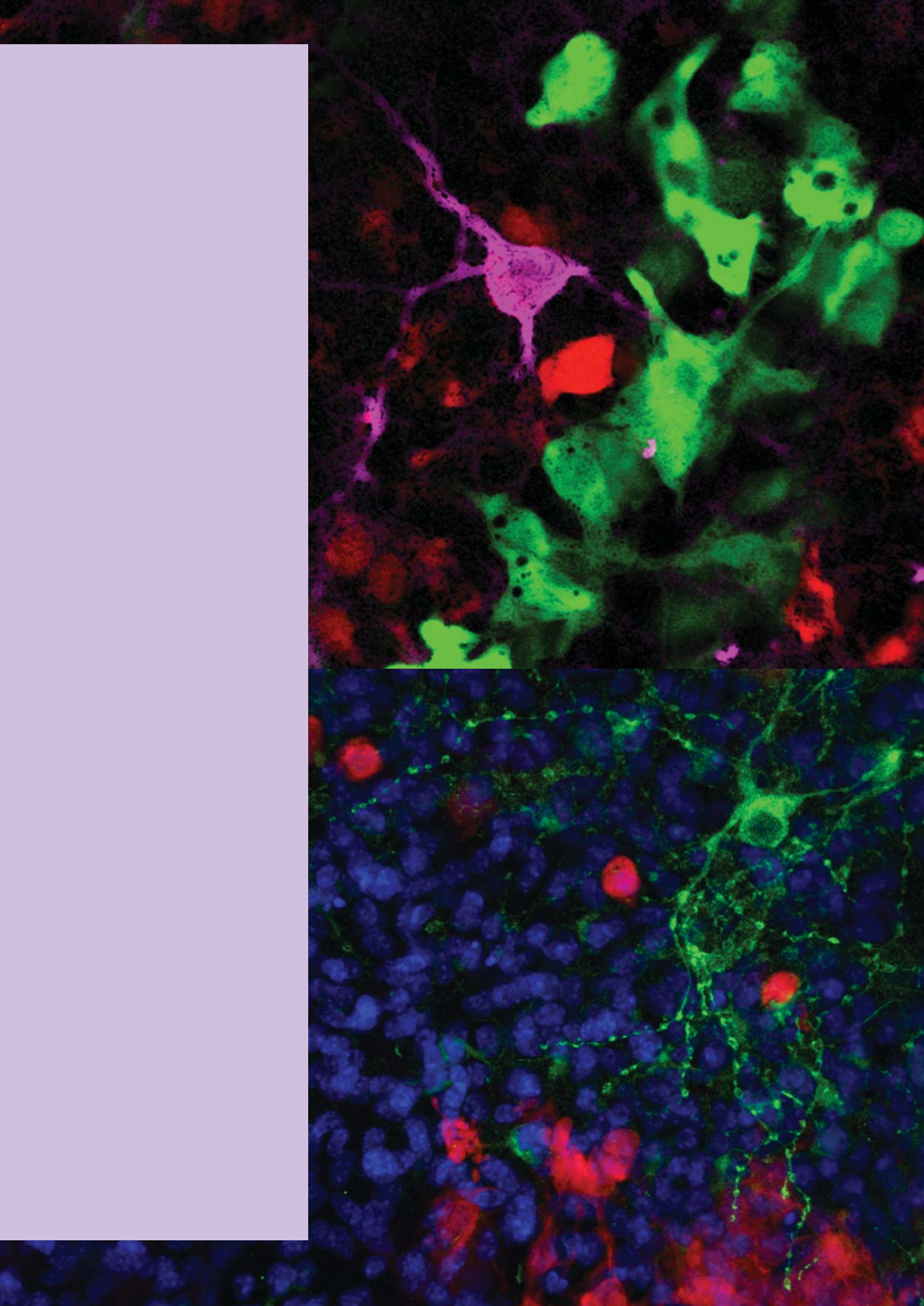
Eric Rouiller
Laboratory of neurophysiology of action and hearing

Beat Schwaller
Calcium signaling in health and disease

Wolfgang Taube
Motor control and motor learning



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INTRODUCTION

Jean-Marie ANNONI

Language selection in the bilingual brain

A major challenge in the field of bilingualism consists of unraveling the neural underpinnings of a bilingual speaker's ability to select and switch between languages depending on constantly changing environmental contexts. Language selection performance depends on many factors that are controlled or manipulated in our studies, in particular: First and second language proficiency, the age of acquisition of the second language, the current linguistic context. In addition, we investigate whether the executive processes involved in language selection share common neurophysiological substrates with those involved in processing non-verbal material, etc.

Reading strategies and bilingualism

A recent and fruitful line of research suggests that higher-order cognitive processes, such as abstract and conceptual thinking, may depend of the context and the expectancy related to this context. The studies of bilingual individuals during reading allow us to investigate the scope and limits of such interactions between language and strategies. In particular, we are interested in whether it could be true that bilinguals explore the world differently whenever they activate their first or they second language.

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LINES OF RESEARCH
- Bilingualism
- Reading strategy
- Brain plasticity
- Executive Functions
- Temporal cognition
- Behavior in Neurological disorders

INTRODUCTION

Lucas SPIERER

The behavioral and brain plasticity of executive functions
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. Lesion-induced deficits of inhibitory control have also important functional consequences including apraxia, a highly prevalent neuropsychological syndrome consisting of impairment in producing communicative gesture in absence of motor or cognitive deficits. The rehabilitation of these pathologies in neurological and psychiatric populations might thus benefit from training-induced reinforcement of inhibitory control functions. The development of efficient inhibitory control training regimens first requires determining whether and how inhibitory control proficiency could be improved in healthy individuals and the underlying neurophysiological mechanisms. A major challenge in this regard is to identify training procedures that will impact on the impaired neurophysiological mechanisms and structures, optimally improve inhibitory control performance and promote the generalization of the effects of the inhibitory control training to untrained conditions and tasks. Although the anatomo-functional organization of inhibitory control has been extensively studied, the behavioral and neural plasticity of this function remains largely unknown. Using psychophysics, transcranial magnetic stimulation and voxel-based lesion-symptom mapping and state-of-the-art electrical and functional resonance neuroimaging approaches, we addressed the behavioral and spatio-temporal brain mechanisms of training-induced plasticity of inhibitory control and the effects of brain lesion on the supporting fronto-striatal brain networks.

e.g. Manuel et al., Journal of Neuroscience, 2010

▶ Jean-Marie ANNONI

Bilingualism, cognition and brain

A first line in this topic is to test highly proficient, bilinguals, taking advantage of the particularity of bilingual Fribourg University. Particularly we sought to integrate some apparently divergent behavioral and EEG studies on the cost of switching language or task. Several neuroimaging studies have shown an overlap of the brain areas involved in language control and domain-general cognitive control. One part of our interests is to measure both behavioral responses and event-related potentials (from bilinguals during mixed-task context). Our current data suggests that bilinguals' language-control mechanism is partly independent from general cognitive control and rely on bilateral frontal-temporal areas. Concerning reading, preliminary results obtained through eye pattern analysis (collaboration with Eyelab, Prof Müri, in Berne) and EEG recording bring some support for different reading strategies in the different language context depending if a language is orthographically opaque or transparent ***(Fig.1)***.

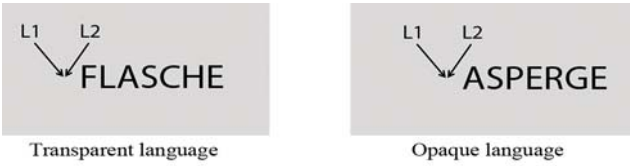

Fig.1 - Landing positions of the first saccade in word reading.

Another, clinical line of our research focuses on degenerative brain disorders and suggest that like in stroke, neurodegenerative disease affects in a parallel manner both languages, which support arguments for a substantially shared L1 and L2 network.

Behavioral and clinical studies

These years were devoted to the analyses of two important mechanisms: Decision making and management of fatigue in neurological disorders. Such questions are important both for medical and social management of neurological patients. Data on medium size cohort (between 70 and 100 patients) showed on one side that the quality of decision making in a gambling task under explicit risk was modified by disease such as MS but in a different manner than would do brain injury.
Secondly an important work showed that post stroke fatigue affects also patients after minor strokes and is a chronic dysfunction. This work has shown for the first time that PSF is related to specific cognitive dysfunction, i.e., attentional and executive impairment. Although we do not know whether the relationship between fatigue and cognitive impairment is causal, and if so, whether fatigue causes cognitive impairment, or vice versa, the study results are consistent with the hypothesis that a stroke lesion affecting the neural circuits involved in regulation of attention and executive function may contribute to the development of tiredness and aversion to effort, and subsequently to the development of the behavioral phenomenon of fatigue.

▶ Lucas SPIERER

In a series of transcranial magnetic stimulation and functional neuroimaging studies, we demonstrated that different inhibitory control training developed either stimulus-driven automatic, bottom-up forms of inhibition within parietal areas or reinforced controlled, top-down inhibitory control in front-striatal brain regions.

We further showed how error detection induces shifts from an automatic to a controlled form of inhibition induced by the detection of errors, and that this mechanisms account for post-error slowing effects ***(Fig.2 & 3)***.

Finally, by applying statistical, voxel-based lesion-symptom mapping in 150 subacute stroke and tumor brain-damaged patients, we showed that brain lesion to left frontal and parietal structures induce different types of ideomotor apraxia errors ***(Fig.4)***.

Manuel et al., Cerebral Cortex, 2012

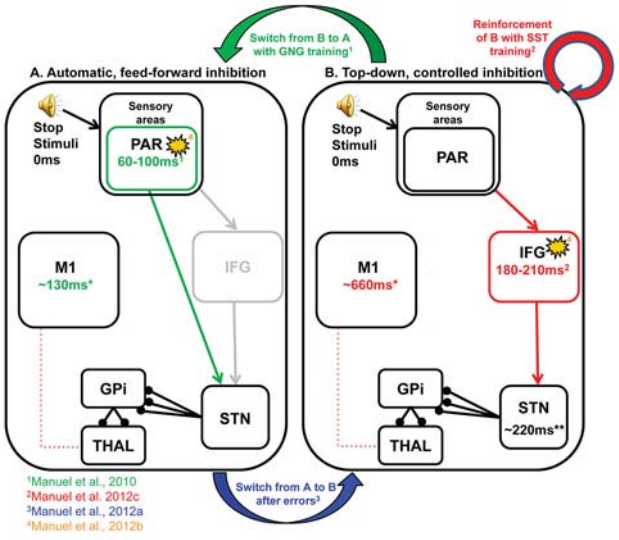

Fig.2 - Modeling the spatio-temporal brain mechanisms of training-induced plasticity of inhibitory control. *The inhibition stimulus is presented at 0ms and is then processed within early sensory areas at ~ 80ms. A. With Go/NoGo training, participants switch from a controlled inhibition mode to an automatic inhibition mode (green arrow). Automatic inhibition develops in PAR around 80ms and shortcuts top-down inputs IFG, in turn leading to faster inhibition. B. During Stop-signal task (SST) training, top-down/controlled inhibition is reinforced around 200ms in the IFG. The IFG then activates STN via the hyperdirect pathway in ca. 10ms. STN then sends output to the GPi to*

inhibit the thalamocortical output which globally suppresses motor execution. If an error occurs during the GNG or SST task, participants engaged in an automatic inhibition mode, switch to a controlled inhibition mode (blue arrow). Finally, lesions underlying motor control deficits in the case of ideomotor apraxia are reported in orange. PAR: parietal; M1: primary motor cortex; IFG: Inferior frontal gyrus; STN: Subthalamic nucleus; GPi: Internal Globus Pallidus; THAL: Thalamus. Arrows indicate excitatory connections and rounds inhibitory connections.

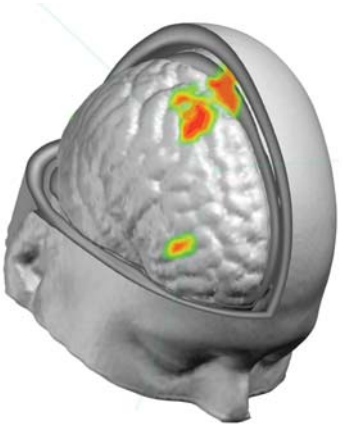

Fig.3 - Electrical source estimations of the right fronto-medial brain network modified by training inhibitory control with a Stop-Signal Task.

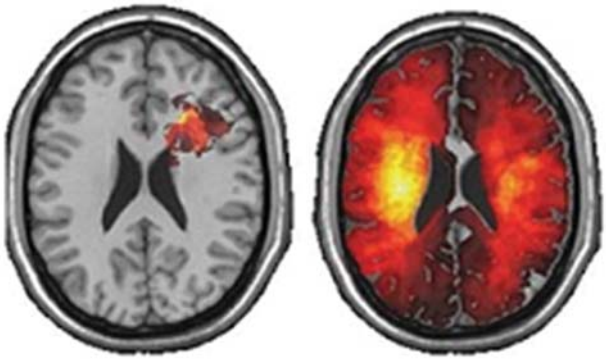

Fig.4 - Left: Example of a voxel-based lesion-symptom mapping result. *P-values of the voxel-wise statistical tests comparing performance between lesioned and intact patients on an apraxia neuropsychological test are color-coded and projected on a template brain. Right: Lesion overlays of 150 hemispheric brain-damaged patients (light yellow= voxels with 26 patients lesioned; dark red: 1 patient).*

Low-level auditory processing (examples)

Auditory motion processing

We identified the neural correlates of auditory motion aftereffects. In vision, the study of motion aftereffects has greatly contributed to our understanding of the neural basis of motion perception. For the auditory system, the basic mechanisms of sound motion perception remain poorly understood, with different models currently being debated. By directly comparing the predictions of different auditory-motion models with the neurophysiological correlates of the auditory motion aftereffect, we found that auditory motion perception relies on direction-selective motion detectors, as found in the visual motion pathway. The electrical brain response to sounds during the aMAE is motion-sensitive, but not direction-selective.

Magezi et al., Journal of Neurophysiology, 2012

The influence of spontaneous brain activity on auditory perception

As another example of our work on low-level auditory processing, we showed that spontaneous variations in brain activity (i.e. internal noise; the main premise of signal detection theory) yields conscious percepts and correlates with discrimination sensitivity. Moreover, we showed that phenomenological sensory experience can be neuroscientifically investigated without any bias induced by variations in the experimental context. To do this, we applied electrical neuroimaging analyses to auditory-evoked potentials in response to identical auditory stimuli spontaneously perceived as being of higher vs. lower pitch. These analyses allowed us to track in real time and throughout the brain volume the spatio-temporal dynamics of the brain's internal noise than engender perception. ■

Bernasconi et al., Journal of Neuroscience, 2011

Selected Publications

Radman N, Staub F, Aboulafia-Brakha T, Berney A, Bogousslavsky J, ***Annoni JM***
Post-stroke fatigue following minor infarcts: a prospective study. Neurology, 2012, 79(14):1422-7

Magezi DA, Khateb A, Mouthon M, Spierer L, ***Annoni JM***
Cognitive control of language production in bilinguals involves a partly independent process within the domain-general cognitive control network: Evidence from task-switching and electrical brain activity. Brain and Language, 2012, 122(1):55-63

Manuel AL, Radman N, Mesot D, Chouiter L, Clarke S, Annoni JM, ***Spierer L***
Inter- and Intrahemispheric Dissociations in Ideomotor Apraxia: A Large-Scale Lesion-Symptom Mapping Study in Subacute Brain-Damaged Patients. Cerebral Cortex, 2012

Jean-Pierre Bresciani
Sport and Motricity

Perception and control of movement

INTRODUCTION

Several sensory channels provide us with information about our body orientation and movements relative to the environment.
We study how this information is integrated for:

1) Perceiving the speed and amplitude of self-motion.

2) Controlling the execution of goal-directed movements such as reaching movements.

For instance, we use virtual environments in which we combine actual body motion and simulated motion of the environment to test how parameters such as the size of the field of view or the structure of the visual scene affect motion perception. Concerning the control of goal-directed movements, we investigate how the brain uses afferent signals to modulate 'online' ongoing movements when a discrepancy is detected between the desired and the predicted outcome of the action.

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Effect of visual contrast on perceived visual speed

Classical vision research experiments have shown that speed is underestimated at low contrast. This has been proposed as an explanation of excessive driving speed in fog. Combining psychophysics measurements and driving simulation, we have shown that whereas speed is underestimated when contrast is reduced uniformly for all objects of the visual scene independently of their distance from the viewer, visual speed is actually overestimated when contrast is reduced more for distant objects, as is the case in real fog. With this work, we have demonstrated for the first time that perceived speed depends as much on the spatial distribution of contrast over the visual scene as on the global level of contrast per se.

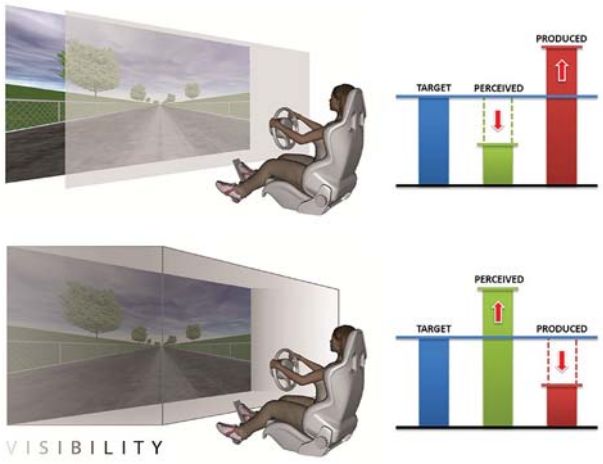

Fig.1 - Visual speed estimation. *When contrast in reduced in a distance-independent manner, as with a foggy windshield (top panel), visual speed is underestimated (green bar) and drivers speed up (red bar). Conversely, distance-dependent contrast reduction similar to that experienced in fog (bottom panel) evokes speed overestimation, prompting drivers to decelerate.*

Contribution of the posterior parietal cortex to the visual control of reaching movements

The posterior parietal cortex (PPC) is known to play an important role in integrating sensory afferents to control voluntary movements. Using a «perturbed» reaching paradigm in which visual information was manipulated, we tested which subregions of the PPC contribute to the processing of target- and body-related visual information. Functional magnetic resonance imaging (fMRI) was used to localize putative target areas involved in online corrections of movements in response to perturbations. The causal contribution of these areas to online correction was tested in subsequent neuronavigated transcranial magnetic stimulation (TMS) experiments. Robust TMS effects were observed at distinct anatomical sites along the anterior intraparietal sulcus (aIPS) and the anterior part of the supramarginal gyrus for both perturbations, whereas TMS over neighboring sites did not affect online control. These results support the hypothesis that the aIPS is more generally involved in visually guided control of movements, independent of body effectors and nature of the visual information. Also, they suggest that the human network of PPC subregions controlling goal-directed visuomotor processes extends more inferiorly than previously thought.

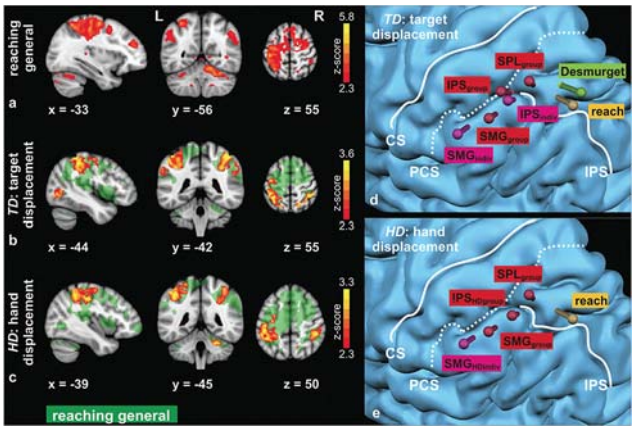

Fig.2 - fMRI activation patterns (left panel) for general reaching (top), target displacement (middle) and displacement of the visual feedback of the hand (bottom). *TMS stimulation sites (right panel) associated to target displacement (top) and displacement of the visual feedback of the hand (bottom).*

Effect of the viewpoint on sensorimotor learning

In everyday life, we always see the world from a first-person view. However, virtual reality techniques allow us to see ourselves interacting with our surroundings from different perspectives. Using a visual–vestibular motor recalibration task in virtual reality, we tested the effect of three different viewpoints on sensorimotor learning. We notably wanted to determine whether the unusual top view, or the addition of a mirror in a first-person view would provide sensorimotor learning advantages with respect to the traditional first-person view. ■ ▸▸

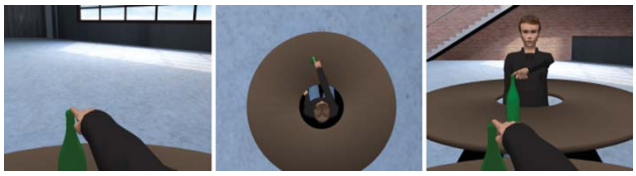

Fig.3 - First-person, top and mirror view used for sensorimotor learning. *For all three viewpoints, significant and quantitatively similar sensorimotor learning occurred. However, only the first-person and mirror view gave rise to a significant decrease in motor variability after learning. These results suggest that the more naturalistic first-person view and the richer mirror view should be preferred when reducing motor variability constitutes an important issue, as for instance for neuro-rehabilitation.*

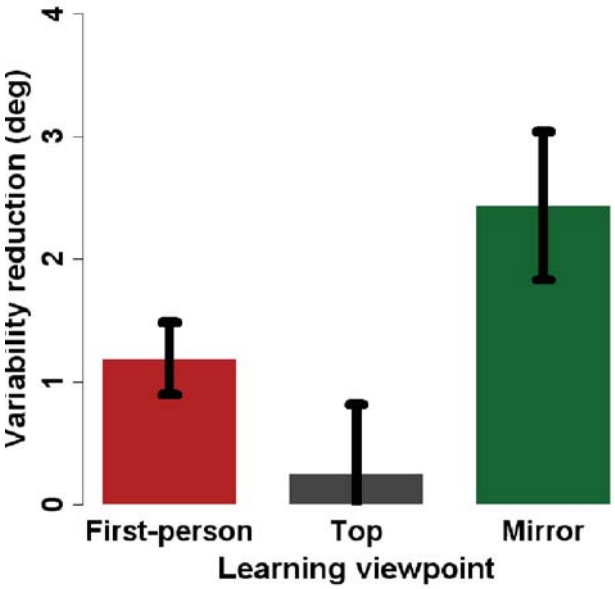

Fig.4 - Only the first-person and mirror view gave rise to a significant reduction of motor variability after learning.

Selected Publications

Pretto P, ***Bresciani JP****, Rainer G, Bülthoff HH*
Foggy perception slows us down. eLife, 2012, 1:e00031

Reichenbach A, ***Bresciani JP****, Peer A, Bülthoff HH, Thielscher A*
Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. Cerebral Cortex, 2011, 21:1602-1612

Schomaker J, Tesch J, Bülthoff HH, ***Bresciani JP***
It is all me: The effect of viewpoint on visual-vestibular recalibration. Experimental Brain Research, 2011, 213:245-256

Marco Celio
Chair of Histology and Embryology
Brain circuits for positive emotions

INTRODUCTION

The hypothalamus *per se* has been long suspected of triggering positive emotions, owing to the circumstance that hamartomas and vascular affections in its tuberal portion provoke bursts of laughter. Electrophysiological studies in various species have indeed confirmed that hypothalamus -as part of the limbic system- contributes to laughter. However, only the rudiments of the neural circuit underlying the expression of positive emotions are known. The medial frontal cortex, the lateral hypothalamus and the periaqueductal grey matter (PAG) are involved; so, too, are centers in the brain stem subserving the mimic, respiratory and laryngeal muscles. The individual components of the circuit, viz., the implicated populations of neurons, have not been defined either anatomically or molecularly.

With our recent discovery of the PV1-nucleus in the medial forebrain bundle of rodents (Meszar et al., 2012) -which we deem to be the counterpart of the lateral tuberal nucleus (LTN) in primates- (Gerig and Celio, 2007; Girard et al., 2011) this situation is now likely to change. Using molecularly-defined nuclei as a centerpiece, the projections and the inputs can be studied with precision. And using an optogenetic approach, it will be possible to selectively manipulate the circuitry with high spatial and temporal precision. By combining this optogenetic approach with electrophysiological recordings in alert, behaviourally unrestrained animals, the functional contribution of subcortical cell populations to neural processing in the «happiness» circuit can be studied. These data can then be used as a basis for fMRI-studies in humans using the laughing paradigm to provoke joyful emotions.

Of the five basic emotions – fear, anger, disgust, sorrow and happiness – only the latter is positive. The lateral hypothalamus may represent the centrepiece for «happiness» as the amygdala is for fear, and the insula for disgust.

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Anatomical studies (in collaboration with the group of Clif B. Saper, Harvard University, Boston)

The PV1-nucleus is located within the ventrolateral division of the medial forebrain bundle. In the horizontal plane, it has a length of 1 mm in mice and 2 mm in rats. PV-immunoreactive perikarya fall into two distinct size categories and number ~900 in rats and ~500 in mice. They are intermingled with PV-negative neurons and coarse axons of the medial forebrain bundle, some of which are PV-positive ***(Fig.1)***. Symmetric and asymmetric synapses, as well as PV-positive and PV-negative terminals, abut on the perikarya of both PV-positive and PV-negative neurons. PV-positive neurons of the PV1-nucleus express glutamate, not GABA - the neurotransmitter that is usually associated with PV-containing nerve cells (Girard et al., 2011; Meszar et al., 2012). Although we could not find evidence that PV1 neurons express either catecholamines or known neuropeptides, they sometimes are interspersed with the fibers and terminals of such cells. From its analogous topographical situation, the PV1-nucleus could correspond to the lateral tuberal nucleus in humans (Gerig and Celio, 2007).

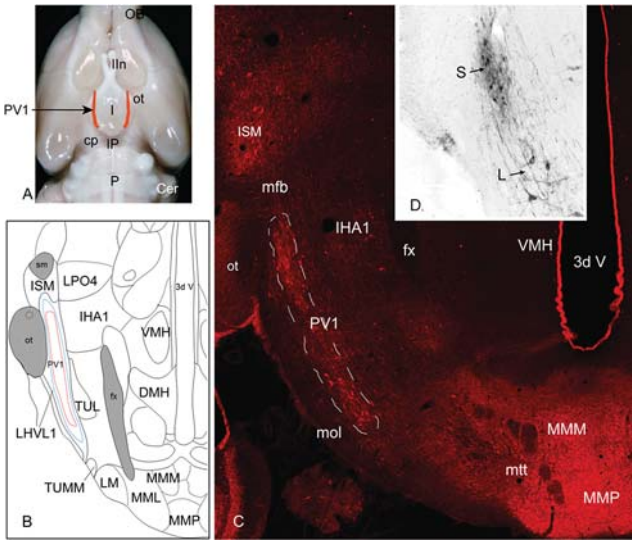

Fig.1 A - Ventral view of a perfusion-fixed rat brain. *The approximate location of the PV1-nucleus is highlighted with two red stripes and indicated with an arrow. See list of abbreviations.* ***1 B -*** *Schematic tracing of a horizontal section at the level of the PV1 nucleus, reproduced in modified form from (Geeraedts et al., 1990b). For abbreviations see table 1. The projected full extent of the PV1 nucleus is highlighted in blue. The contour of the PV1 at this level* (compare with **Fig.1 C**) *is given by the stippled red line.* ***1 C -*** *Horizontal section through the rat hypothalamus at a depth of 8.4 mm (Paxinos and Watson, 2009). The PV1-nucleus is oriented parallel to the fornix (fx), located medial to the optic tract (ot) and separated from the brain surface by the molecular layer (mol). The PV1-nucleus – outlined with a broken white line – is here seen to contain a large number of Pvalb-immunoreactive neurons. The anterior part is rich in small-, the posterior in large neurons* (see also **Fig.1 D**). ***1 D -*** *Higher-magnification view of the PV1 from another experiment (immunoperoxidase staining). In this horizontal plane of section the distinction between the rostrally located, smaller Pvalb-positive neurons (S) and the larger neurons located distally (L) is well visible. The gap between the two cell populations is simply due to the particular inclination of the plane of section. A blood vessel (V) is found in proximity to the small cell cluster.*

Connectivity studies (in collaboration with Silvia Arber and Andreas Lüthi, FMI, Basle)

Projections radiating from the PV1-nucleus to the periaqueductal gray (PAG) and laterodorsal tegmental nucleus (LdTN) have been demonstrated by classical anterograde and retrograde tracing in rats. These experiments also revealed the existence of projections from the infralimbic cortex to the PV1-nucleus. By drawing on the superior targeting precision of the Cre-dependent adenoviral construct (Yonehara et al., 2011) ***(Fig.2 A)***, we have now identified in mice a very discrete terminal region, with a cylindrical form and a length of ~1.5 mm, in the ventromedial portion of PAG ***(Fig.2 B)***. The distal part of this projection impinges upon an unnamed (Franklin and Paxinos, 1997) parvalbumin-positive nucleus ventrolateral to the aqueduct.

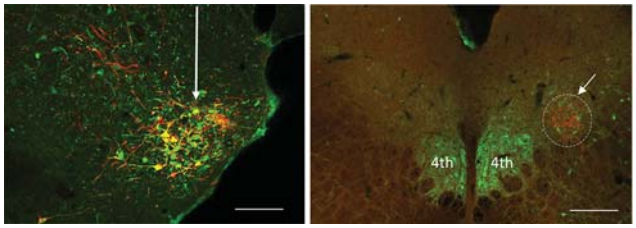

Fig.2 A - Selective infection of neurons within the PV1-nucleus of the laterobasal hypothalamus with a viral construct expressing «cherry» (red). *Immunostaining for parvalbumin is green; double-stained neurons are yellow. The white arrow indicates the position of the injection. Bar = 100 µm.*

Fig.2 B - Terminal field of «cherry»-positive projections from the PV1-nucleus in the lateroventral PAG (arrow). *The adjacent trochlear nucleus (4^{th}) is immunopositive for parvalbumin. Bar = 250 µm.*

Equipped with this knowledge, we now wish to elucidate the functions of this brain area by drawing on classical methodological approaches, e.g. evaluating the behavioral consequences of inactivating or activating the PV1-nucleus in animal experiments. Targeted regions of the brain can be inactivated by the injection of Tetanus- or Diphteria-toxin, which blocks neurotransmission or kill nerve cells. The selective stimulation of specific brain regions can now be effected using a highly sophisticated methodological tool. It involves inducing the neurons to produce in their cell membranes certain molecules (mutated Muscarinic

receptors or Channelrhodopsin) which can then be activated, either with a synthetic drug (DREADD) or with laser light (optogenetic). Both approaches cause a depolarization which stimulates (or inhibits) the neuron. The effects of either inactivating or stimulating the PV1-nucleus of rodents will be evaluated by recording the production of 50-KHz tones («chirps»), by monitoring changes in blood pressure, by gauging the threshold of pain, and by observing the effect of tickling.

fMRI-studies in humans (in collaboration with Martin Lotze, Greifswald)

The postulated homology between the murine PV1-nucleus and the primate lateral tuberal nucleus (LTN) (Gerig and Celio, 2007; Girard et al., 2011) led us to embark on a project aimed at visualizing activity in the lateral tuberal hypothalamus of humans by functional MRI. We conceived an experiment to provoke laughter, a primitive form of vocalization in healthy adults. Functional magnetic resonance imaging (fMRI) was used to explore the brain areas that are activated by instigating laughter through tickling. Eighteen healthy participants were tickled on the sole of the right foot and allowed to laugh. This condition was alternated with an *inhibition of laughter* during tickling and with *voluntary laughter.* During *tickling & laughter*, the lateral hypothalamus, parietal operculum (PO), amygdala and right cerebellum were consistently activated to a greater degree than under the other two conditions. *Tickling & laughter* and *voluntary laughter*, activated regions in the sensory-motor and premotor cortex and in the midbrain periaqueductal grey matter (PAG), whereas *inhibition of laughter* did not ***(Fig.3)*** (Wattendorf et al., 2012). The hypothalamus is known to promote intrinsic behavioral reactions to external stimuli and to project to the PAG, which is itself an important integrative centre of the limbic pathway for vocal control. Our findings suggest that ticklish laughter is typically triggered by hypothalamic activity, which follows a distinguishment of the complex sensory characteristics of the tickling stimulus in the cerebellum and PO (Wattendorf et al., 2012). ■

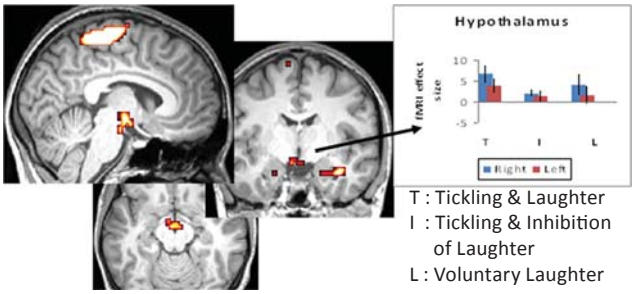

Fig.3 - Tickling & Laughter vs Tickling & Inhibiton of Laughter and Voluntary Laughter. *Increased activity in response to* tickling & laughter *vs.* tickling & inhibition of laughter *vs.* voluntary laughter *in the hypothalamus, the amygdala, the hippocampus and the sensorimotor area representing the foot. Parameter estimates (beta-values) that were derived from peaks in the hypothalamus revealed a higher level of activity in this region alone during* tickling & laughter *than during either* tickling & inhibition of laughter *or* voluntary laughter*. The statistical maps are superimposed on Talairach-normalized images of the brain.*

Selected Publications

Mészár Z, Girard F, Saper CB, ***Celio MR***
The lateral hypothalamic parvalbumin-immunoreactive (PV1) nucleus in rodents. J Comp Neurol, 2012, 520(4):798-815

Girard F, Meszar Z, Marti C, Davis FP, ***Celio MR***
Gene-expression profiles in the parval-bumin-immunoreactive (PV1) nucleus of the mouse lateral hypothalamus. Eur J Neurosci, 2011, 34(12): 1934-43

Wattendorf E, Westermann B, Fiedler KM, Kaza E, Lotze MP, ***Celio MR***
Exploration of the correlates of ticklish laughter by functional magnetic resonance imaging. Cerebral Cortex, 2013, 23,1280-9

Celio MR*, Babalian A, Ha QH, Eichenberger S, Clément L, Marti C, Saper CB*
Efferent connections of the parvalbumin-positive (PV1) nucleus in the lateral hypothalamus of rodents. J Comp Neurol, 2013, Jun 21. doi: 10.1002/cne.23344 [Epub ahead of print]

Robert Kretz
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Visual neuroscience

INTRODUCTION

Robert KRETZ

Our main interests are the visual system and the role of the membrane protein Notch in memory.
For studying the morphological and functional properties of neurons in the visual system I have started in 2009 a collaboration with the group of Gregor Rainer of the physiology unit. Our animal model is the tree shrew *(Tupaia belangeri).* For more details and the research results see the report of G. Rainer.
The second topic about the Notch signaling in the mature brain is the main research field of Lavinia Albéri, a junior group leader from our group.

Lavinia ALBÉRI

Our group is interested in understanding the molecular implications of Notch signaling in the mature brain.
Notch signaling has been extensively studied in neuronal development and increasing evidence is emerging for a role of this signaling pathway in mature brain functions and dysfunctions.
In the mature brain Notch can act as a plasticity molecule and is induced in hippocampal networks upon sensory experience. In this setting Notch modulates synaptic plasticity and spatial learning. Our group is addressing the molecular mechanism by which Notch displays this function.
On the other hand, others and we have observed that following stroke Notch is aberrantly induced. There is emerging evidence that Notch up-regulation may contribute to neuronal demise. By using a loss of function model of Notch pathway component we intend to develop a therapeutic approach towards neuro-protection ***(Fig.1)***.

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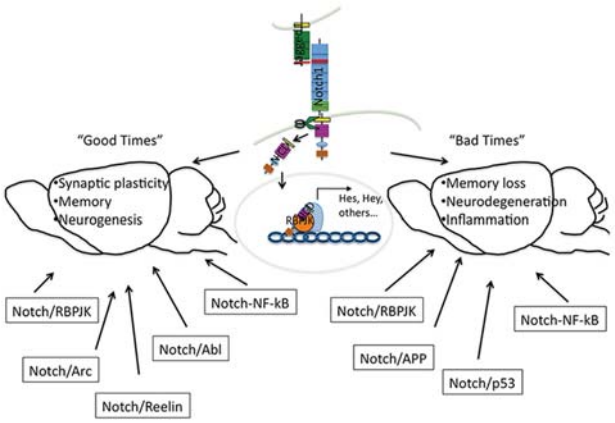

Fig.1 - Brain function and dysfunction through Notch signaling: *Representation of the Notch/RBPJK signaling cascade, which is involved (arrows) in physiological brain functions or pathological conditions in the mature brain.*

Notch and Reelin interaction in memory processing

Notch and Reelin signaling play an essential role in cortical development. Recent evidence has shown that these two molecular pathways crosstalk. In addition, loss of function models for APP, Reelin and Notch signaling have a common denominator in that they affect synaptic plasticity and memory processing. We are interested in understanding whether this interaction occurs also at the synapse and contributes to the function of Notch in synaptic plasticity. In order to address this question we are using loss of function mouse model for Notch (Notch1cKO) to investigate the reciprocal interaction between the pathway components and their function in plasticity. This project is carried out in collaboration with Dr. Kneusel (UniZH), Dr. Scotti (UniBE, UniFR) and Dr. Hoey (UniZH), Prof. Nimpf (& his collaborators).

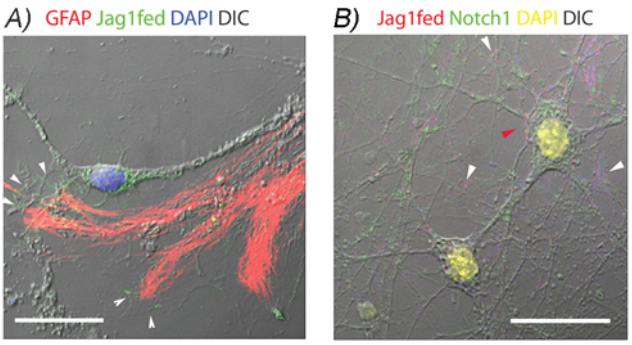

Fig.2 - Jagged1 localizes on glia processes and co-localizes with Notch1 at distal dendrites. *Internalization assay was performed using specific primary antibodies while cells were alive. Proteins bound to the antibodies were visualized post fixation using secondary antibodies conjugated with fluorescent dyes.* ***A)*** *Jagged1 appears localized abundantly at the membrane of the glia processes indicated by GFAP (white arrows). Some Jagged1 can be also observed in the neuron's soma.* ***B)*** *Notch appears mostly internalized and Jagged1 is present on axon-like structure (red arrow) and co-localizes with extracellular Notch mainly on distal dendrites (white arrows).*

Jagged1 a neuronal modulator

It appears that several genetic mutations in Notch pathway components have secondary effects on brain function. An interesting example is «Alagille syndrome», an autosomal dominant disorder with specific mutation in the Jagged1 gene, manifesting beside vertebral deformity and heart malformation also mental retardation. Jagged1 is a cognate ligand of the Notch receptor and it is essential for proper signaling. We have previously observed that Jagged1 is expressed pre-synaptically in neurons and it can be induced by synaptic activity. Neuronal Jagged1 can be also released and act as a paracrine modulator of Notch activity ***(Fig.2 B)***. Interestingly, application of soluble Jagged1 induces Notch processing, increases neuronal activity and can potentiate LTP suggesting that soluble Jagged1 may function as a neuromodulator. We have additional evidence that a pool of Jagged1 is stably residing also in glia cells ***(Fig.2 A)***. The question is whether also the glial-born Jagged1 can contribute to Notch activity/function in memory processing. In order to address these questions we have obtained two loss of function models for Jagged in neurons and glia using the Jagged1 floxed homozygous mouse line (Prof. Taylor, UniBAS) and cre driven specific promoter lines for CamKII and GFAP. This project is carried out in collaboration with Prof. Taylor (UniBAS) and Prof. Csicsvari lab (IST, Vienna).

Modulating learning through optogenetic targeting of Notch positive hippocampal ensembles

In order to gain temporal resolution of Notch activation and better understand how this signaling pathway operates in memory processing we opted for optogenetic manipulation of Notch positive ensembles. We employ adeno-associated construct (AAV) baring a Notch-responsive (RBPJK-RE) element, which drives halorhodopsin tagged with YFP (Halo-EYFP) (AAV-RBPJKRE-DIO-Halo-YFP). Using this construct expression of Halo-YFP occurs only after Notch activation, as a result of a learning experience. Optogenetic silencing of Notch activated ensembles coupled with extracellular recording is achieved through and optotrode shining yellow light during learning and memory trials.
A similar approach is employed using an adeno-associated construct (AAV) baring a Notch-responsive (RBPJK-RE) element driving Channelrhodopsin tagged with YFP (AAV-RBPJKRE-DIO-ChR2-YFP). In this experiment blue light stimulation is utilized in order to elicit specific learning patterns. These experiments allow precise resolution on the recruitment of Notch in hippocampal ensemble and a better understanding of the role of this signaling pathway in spatial memory. This project is carried out in close collaboration with Prof. Csicsvari from IST, Vienna, Austria and the AAV packaging is carried out by Dr. Zentilin and ▸▸

Prof. Giacca at the AAV facility of the ICGEB, Trieste, Italy.

Notch in ischemic Injury: Is it a bad fellow?

Stroke is a frequent cause of death in the developed world and in «non-lethal» cases it produces long term neurological deficits including cognitive, motor impairment, and in some cases seizures. Others and our study has pointed out that, in areas of excitotoxic activity following stroke, Notch signaling is induced and may contribute to cell death. Recent data from our lab point out that, upon ischemic-like injury in primary neurons, there is a strong increase in canonical targets of Notch, which are typically expressed in stem cells. Indeed we observe that RBP-JK conditional knockout (RBPJKcKO) mice, which lack canonical Notch pathway activation, show resistance to neurodegeneration following kainate injection. In addition, kainate induced excitotoxicity is associated with a concomitant Notch-dependent activation of IGF-2 signaling pathway. Interestingly, wild type mice show higher levels of CyclinD1 transcripts following kainate treatment as compared to the RBPJKcKO mice. Thus, we postulate that kainate induced seizures cause neurodegeneration by aberrant cell-cycle initiation through IGF-2 signaling pathway in a Notch-dependent manner ***(Fig.3)***. This project is carried out in close collaboration with Dr. Shuxi Liu (NIH) and Prof. Nick Gaiano (JHMI).

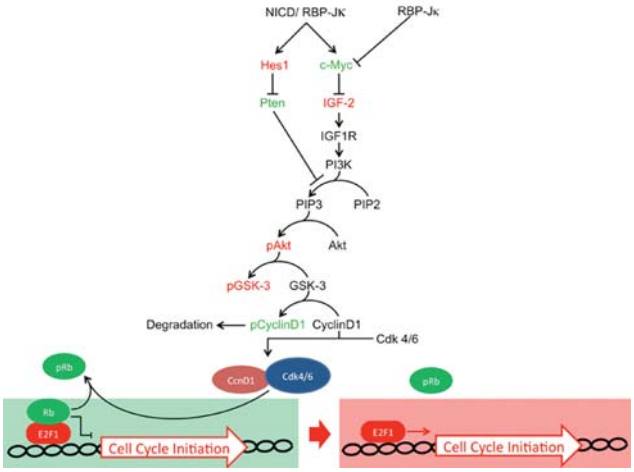

Fig.3 - Notch/RBPJK signaling contributes to cell cycle re-entry in neurons following excitoxicity. *Notch signaling induces IGF2 activation that activates cyclin dependent genes in neurons and contributes to neuronal demise.*

Role of Notch signaling in migration/differentiation and integration of olfactory neurons

In the mature rodent brain olfactory neurons are continuously replenished and are essential for olfaction and animal's behavior. We have observed that Notch expression is spatially regulated in the rostral migratory stream with increasing expression in the olfactory bulb. Based on the evidence that activity is instrumental for Notch activation, in this project, we investigate whether olfaction modulates Notch signaling in developing interneurons and whether this pathway is instrumental in the migration and integration of these neurons in the olfactory bulb circuit. We observe that Notch signaling is prominent in mitral cells of the olfactory bulb and responsive to olfactory stimulation ***(Fig.4)***. Mitral cells receive the primary odor input and project their axons to the sensory cortex. Physiological properties of these cells are investigated in Notch1cKO. This project is carried out in collaboration with Dr. Scotti at University of Fribourg who is an expert in olfactory interneuron development and Prof. Kretz who is an expert in electrophysiology. ■

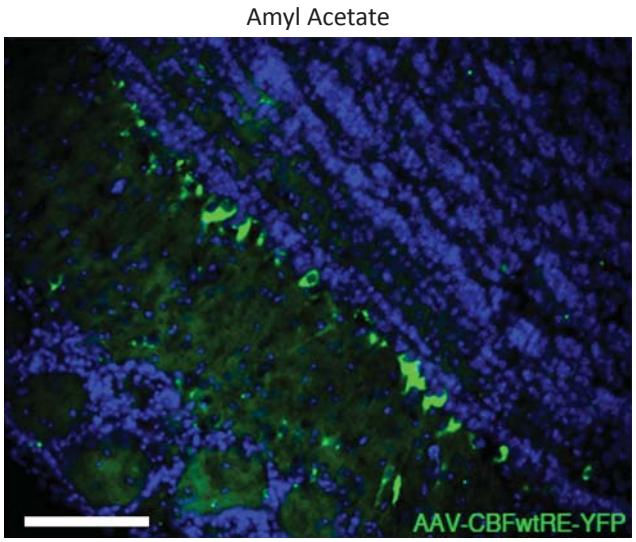

Fig.4 - Notch/RBPJK signaling is activity dependent in Mitral cells of the olfactory bulb (OB). *OB injected with an AAV expressing YFP under Notch transcriptional regulation is induced in sparse mitral cells of the OB in response to odorant stimulation.*

◂◂

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Veit J, Bhattacharyya A, ***Kretz R****, Rainer G*
Neural response dynamics of spiking and local field potential activity depend on CRT monitor refresh rate in the tree shrew primary visual cortex. J Neurophysiol, 2011, 106(5): 2303-2313

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Analysis of Multiple Quaternary Ammonium Compounds in the Brain Using Tandem Capillary Column Separation and High Resolution Mass Spectrometric Detection. J Chrom A, 2012, 1241: 46-51

Fouillen L, Petruzziello F, Veit J, Bhattacharyya A, ***Kretz R****, Rainer G, Zhang X*
Neuropeptide alterations in the tree shrew hypothalamus during volatile anesthesia. J Proteomics, 2013, 80: 311-319

Albéri L*, Hoey S, Brai E, Scotti A, Marathe S*
Notch signaling in the brain: In good and bad times: Aging Research Reviews (Epub)

Albéri L*, Liu S, Wang Y, Badie R, Smith-Hicks C, Wu J, Pierfelice TJ, Abazyan B, Mattson MP, Kuhl D, Pletnikov M, Worley PF, Gaiano N*
Activity-Induced Notch Signaling in Neurons Requires Arc/Arg3.1 and Is Essential for Synaptic Plasticity in Hippocampal Networks. Neuron, 2011, 69:437-444

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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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Developmental regulation of gene expression and astrocytic processes may explain selective hippocampal vulnerability

The hippocampus plays a central role in the brain network that is essential for memory function. Paradoxically, the hippocampus is also the brain structure that is most sensitive to hypoxic-ischemic episodes. Here, we show that the expression of genes associated with glycolysis and glutamate metabolism in astrocytes and the coverage of excitatory synapses by astrocytic processes undergo significant decreases in the CA1 field of the monkey hippocampus during postnatal development. Given the established role of astrocytes in the regulation of glutamate concentration in the synaptic cleft, our findings suggest that a developmental decrease in astrocytic processes could underlie the selective vulnerability of CA1 during hypoxic-ischemic episodes in adulthood, its decreased susceptibility to febrile seizures with age, as well as contribute to the emergence of selective, adultlike memory function.

Hippocampus, 2011, 21:142–149

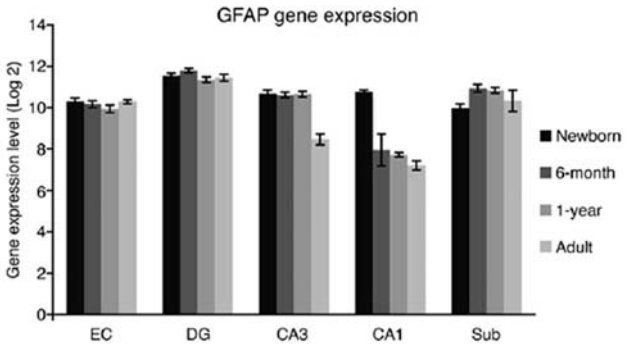

Fig.1 - Microarray analysis: *GFAP gne expression decreased between birth and 6 month of age in CA1. GFAP gene expression decreased between 1 yr of age and adulthood in CA3. GFAP gene expression dit don differ between CA3 udn CA1 at birth, but differed at all other ages. EC, entorhinal cortex; DG, dentate gyrus; CA3 and CA1, fields of the hippocampus; Sub, subiculum.*

Postnatal development of the hippocampal formation: a stereological study in macaque monkeys

We performed a stereological analysis of neuron number, neuronal soma size, and volume of individual regions and layers of the macaque monkey hippocampal formation during early postnatal development. We found a protracted period of neuron addition in the dentate gyrus throughout the first postnatal year and a concomitant late maturation of the granule cell population and individual dentate gyrus layers that extended beyond the first year of life. Although the development of CA3 generally paralleled that of the dentate gyrus, the distal portion of CA3, which receives direct entorhinal cortex projections, matured earlier than the proximal portion of CA3. CA1 matured earlier than the dentate gyrus and CA3. Interestingly, CA1 stratum lacunosum-moleculare, in which direct entorhinal cortex projections terminate, matured earlier than CA1 strata oriens, pyramidale, and radiatum, in which the CA3 projections terminate. The subiculum developed earlier than the dentate gyrus, CA3, and CA1, but not CA2. However, similarly to CA1, the molecular layer of the subiculum, in which the entorhinal cortex projections terminate, was overall more mature in the first postnatal year compared with the stratum pyramidale in which most of the CA1 projections terminate. Unlike other hippocampal fields, volumetric measurements suggested regressive events in the structural maturation of presubicular neurons and circuits. Finally, areal and neuron soma size measurements revealed an early maturation of the parasubiculum. We discuss the functional implications of the differential development of distinct hippocampal circuits for the emergence and maturation of different types of «hippocampus-dependent» memory processes, including spatial and episodic memories.

J Comp Neurol, 2011, 519:1051–1070

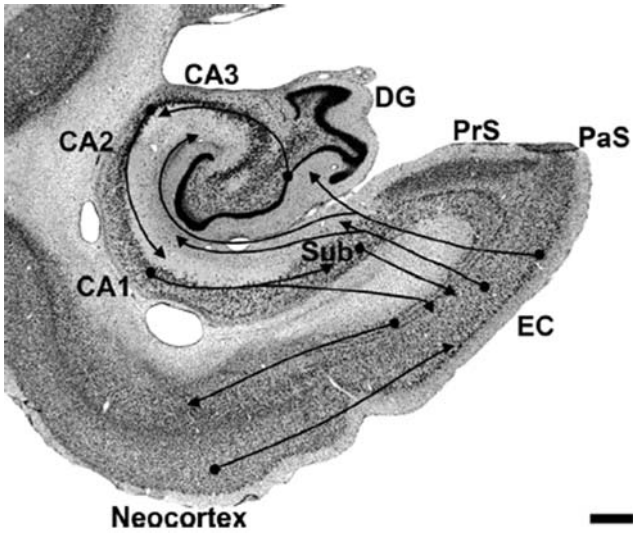

Fig.2 - Hippocampal pathways. *Schematic representation of the hierarchical organization of the main serial and parallel pathways through the different regions of the monkey hippocampal formation. EC, entorhinal cortex; DG, dantate gyrus; CA3, CA2, CA1, fields of the hippocampus; Sub, subiculum; PrS, presubiculum; PaS, parasubiculum. Scale bar = 1 mm.*

Postnatal development of the amygdala: a stereological study in macaque monkeys

Abnormal development of the amygdala has been linked to several neurodevelopmental disorders, including schizophrenia and autism. However, the postnatal development of the amygdala is not easily explored at the cellular level in humans. Here we performed a stereological analysis of the macaque monkey amygdala in order to characterize the cellular changes underlying its normal structural development in primates. The ▸▸

lateral, basal, and accessory basal nuclei exhibited the same developmental pattern, with a large increase in volume between birth and 3 months of age, followed by slower growth continuing beyond 1 year of age. In contrast, the medial nucleus was near adult size at birth. At birth, the volume of the central nucleus was half of the adult value; this nucleus exhibited significant growth even after 1 year of age. Neither neuronal soma size, nor neuron or astrocyte numbers changed during postnatal development. In contrast, oligodendrocyte numbers increased substantially, in parallel with an increase in amygdala volume, after 3 months of age. At birth, the paralaminar nucleus contained a large pool of immature neurons that gradually developed into mature neurons, leading to a late increase in the volume of this nucleus. Our findings revealed that distinct amygdala nuclei exhibit different developmental profiles and that the amygdala is not fully mature for some time postnatally. We identified different periods during which pathogenic factors might lead to the abnormal development of distinct amygdala circuits, which may contribute to different human neurodevelopmental disorders associated with alterations of amygdala structure and functions.

J Comp Neurol, 2012, 520:1965–1984

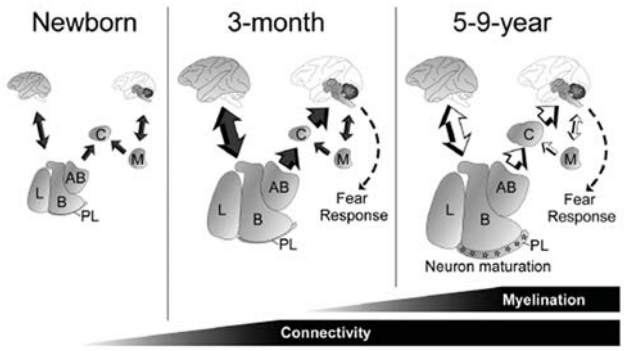

Fig.3 - Schematic representation of the postnatal development of the monkey amygdala circuits. *L: lateral; B: basal; AB: accessory basal; C: central; M: medial; PL: paralaminar. Black arrow: unmyelinated axons; black and white arrow: myelinated axons.*

Developmental regulation of expression of schizophrenia susceptibility genes in the primate hippocampal formation

The hippocampal formation is essential for normal memory function and is implicated in many neurodevelopmental, neurodegenerative and neuropsychiatric disorders. In particular, abnormalities in hippocampal structure and function have been identified in schizophrenic subjects. Schizophrenia has a strong polygenic component, but the role of numerous susceptibility genes in normal brain development and function has yet to be investigated. Here we described the expression of schizophrenia susceptibility genes in distinct regions of the monkey hippocampal formation during early postnatal development. We found that, as compared with other genes, schizophrenia susceptibility genes exhibit a differential regulation of expression in the dentate gyrus, CA3 and CA1, over the course of postnatal development. A number of these genes involved in synaptic transmission and dendritic morphology exhibit a developmental decrease of expression in CA3. Abnormal CA3 synaptic organization observed in schizophrenics might be related to some specific symptoms, such as loosening of association. Interestingly, changes in gene expression in CA3 might occur at a time possibly corresponding to the late appearance of the first clinical symptoms. We also found earlier changes in expression of schizophrenia susceptibility genes in CA1, which might be linked to prodromal psychotic symptoms. A number of schizophrenia susceptibility genes including APOE, BDNF, MTHFR and SLC6A4 are involved in other disorders, and thus likely contribute to nonspecific changes in hippocampal structure and function that must be combined with the dysregulation of other genes in order to lead to schizophrenia pathogenesis.

Transl Psychiatry, 2012, 2, e173

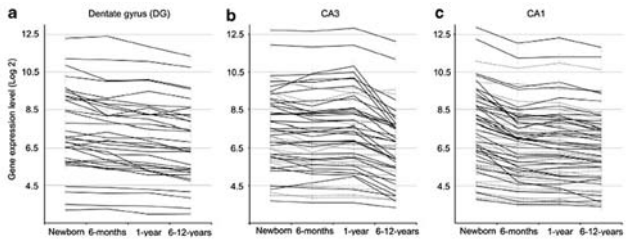

Fig.4 - Gene expression in the dentate gyrus. *Expression patterns of schizophrenia susceptibility genes regulated in the dentate gyrus, CA3 and CA1 from birth to adulthood. (a) Dentate gyrus. (b) CA3: 34 schizophrenia susceptibility genes (63%, solid lines) exhibit a significantly lower expression in adults than at any other ages. (c) CA1: 35 schizophrenia susceptibility genes (52%, solid lines) are significantly more expressed at birth than at any other ages. Error bars represent s.e.*

Selected Publications

Favre G, Banta Lavenex P, ***Lavenex P***
Developmental regulation of expression of schizophrenia susceptibility genes in the primate hippocampal formation. Transl Psychiatry, 2012, 2:e173

Chareyron LJ, Banta Lavenex P, Amaral DG, ***Lavenex P***
Stereological study of the rat and monkey amygdala. Journal of Comparative Neurology, 2011, 519: 3218-3239

Jabès A, Banta Lavenex P, Amaral DG, ***Lavenex P***
Postnatal development of the hippocampal formation: a stereological study in macaque monkeys. Journal of Comparative Neurology, 2011, 519: 1051-1070

Marco C.G. Merlo
Chair of Psychiatry and Psychotherapy
Early recognition and treatment of psychic disorders in young adults

INTRODUCTION

Transition from adolescence to young adulthood is an especially vulnerable phase for developing psychic disorders. Biological and psychosocial stress leads to a dysregulation of HPA axis and particularly the dopamine system involved in evaluating the incoming information («salience») ***(Fig.1)***. This change of information processing can be visualized by EEG technics. For instance, biological stress is related to drug abuse, especially cannabis triggering psychotic-like experiences. On the other hand, research on early and late social adversity, for instance child abuse, neglect and bullying, is also related to psychotic-like experience. This common pathway evolves to a psychosis with a negative impact on pruning and myelination which can be detected by MRI (DTI).

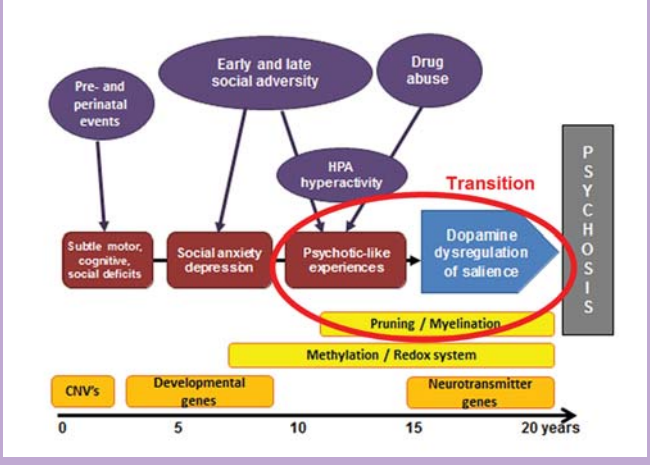

Fig.1 - Bio-psycho-social of evolution to psychosis.

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The main objectives of our research group are to study changes in psychophysiology (EEG) and brain structure (MRI) during transition from a pre-psychotic to a psychotic state. In the same line we intend to develop a bio-psycho-social model in order to evaluate specific psycho- and sociotherapeutic interventions as developed in our international collaboration. Because transition from adolescence to young adulthood is critical, a diachronic investigation of this population is planned.

The presented research work was performed in my previous host institutions. However since my recruitment in September 2012, I already initiated a project at RFSM – Fribourg Network for Mental Health - in collaboration with the division of clinical and health psychology of the University of Fribourg.

Brain structure and early stages of psychosis

Background: Several patterns of grey and white matter changes have been separately described in young adults with first-episode psychosis. Concomitant investigation of grey and white matter densities in patients with first-episode psychosis without other psychiatric comorbidities that include all relevant imaging markers could provide clues to the neurodevelopmental hypothesis in schizophrenia. Methods: We recruited patients with first-episode psychosis diagnosed according to the DSM-IV-TR and matched controls. All participants underwent magnetic resonance imaging (MRI). Voxel-based morphometry (VBM) analysis and mean diffusivity voxel-based analysis (VBA) were used for grey matter data. Fractional anisotropy and axial, radial and mean diffusivity were analyzed using tract-based spatial statistics (TBSS) for white matter data. Results: We included 15 patients and 16 controls. The mean diffusivity VBA showed significantly greater mean diffusivity in the first-episode psychosis than in the control group in the lingual gyrus bilaterally, the occipital fusiform gyrus bilaterally, the right lateral occipital gyrus and the right inferior temporal gyrus. Moreover, the TBSS analysis revealed a lower fractional anisotropy in the first-episode psychosis than in the control group in the genu of the corpus callosum, minor forceps, corticospinal tract, right superior longitudinal fasciculus, left middle cerebellar peduncle, left inferior longitudinal fasciculus and the posterior part of the fronto-occipital fasciculus. This analysis also revealed greater radial diffusivity in the first-episode psychosis than in the control group in the right corticospinal tract, right superior longitudinal fasciculus and left middle cerebellar peduncle. Limitations: The modest sample size and the absence of women in our series could limit the impact of our results. Conclusion: Our results highlight the structural vulnerability of grey matter in posterior areas of the brain among young adult male patients with first-episode psychosis. Moreover, the concomitant greater radial diffusivity within several regions already revealed by the fractional anisotropy analysis supports the idea of a late myelination in patients with first-episode psychosis.

Brain structure, cannabis and early stages of psychosis

Cannabis consumption is temporally associated with the development of first episode psychosis (FEP). Whether or not the chronic use of this substance induces structural brain changes that may be responsible for the cognitive and psychological disturbances in this disorder is still matter of debate. To address this issue, we compared the magnetic resonance imaging (MRI)-assessed grey (GM) and white matter (WM) changes in young FEP patients between users versus non-users of cannabis. This prospective study included 50 consecutive FEP subjects: 33 users (22.7 ± 4.1 years, 4 women) and 17 non-users (23.9 ± 4.2 years, 10 women). Users were further divided into 15 heavy (23.3 ± 4.5 years, 2 women) and 18 light users (22.2 ± 3.8 years, 2 women) according to their lifetime cannabis use. Voxel-based-morphometry (VBM) analysis of GM and tract-based-spatial-statistics (TBSS) analysis of WM were performed. Age and gender were used as non-explanatory co-regressors. There were no supra-threshold differences between user and non-user groups for both GM and WM parameters. This was also the case when only heavy users were compared to non-users. Multivariate models controlling for age and gender confirmed these findings. We found no evidence for cannabis consumption related alterations in GM or WM in FEP subjects. Due to the strict correction for multiple comparisons and sample size, we cannot formally exclude subtle morphometric changes associated with cannabis consumption. However, even if present, such potential alterations would be of low magnitude.

Psychophysiology and early stages of psychosis

Background: Earlier contributions have documented significant changes in sensory, attention-related endogenous event-related potential (ERP) components and θ band oscillatory responses during working memory activation in patients with schizophrenia. In patients with first-episode psychosis, such studies are still scarce and mostly focused on auditory sensory processing. The present study aimed to explore whether subtle deficits of cortical activation are present in these patients before the decline of working memory performance. Methods: We assessed exogenous and endogenous ERPs and frontal θ event-related synchronization (ERS) in patients with first episode psychosis and healthy controls who successfully performed an adapted 2-back working memory task, including 2 visual n-back working memory tasks as well as oddball detection and passive fixation tasks. Results: We included 15 patients with first-episode psychosis and 18 controls in this study. Compared with controls, patients with first-episode psychosis displayed increased latencies of early visual ERPs and phasic θ ERS culmination peak in all conditions. However, they also showed a rapid recruitment of working memory– related neural generators, even in pure attention tasks, as indicated by the decreased N200 latency and increased amplitude of sustained θ ERS in detection compared with controls. Limitations: Owing to the limited sample size, no distinction was made between patients with first-episode psychosis with positive and negative symptoms. Although we controlled for the global load of neuroleptics, medication effect cannot be totally ruled out. Conclusion: The present findings support the concept of a blunted electroencephalographic response in patients with first-episode psychosis who recruit the maximum neural generators in simple attention conditions without being able to modulate their brain activation with increased complexity of working memory tasks.

Toward objective measures of psychotherapy interventions: an integration of EEG as outcome measures of a 1-year dialectical behavior therapy for borderline patients

Background: Emotional dysregulation is a core problem of patients with borderline personality disorder (BPD). ▸▸

They are characterized by instability in various domains such as interpersonal relations, affectivity, impulsivity and self-image. Affective instability results in rapid mood shifts, anger outbursts and chronic feelings of emptiness. Dialectical behavior therapy (DBT) is currently the most validated treatment program for BPD patients. It is based on Linehan's biosocial theory which proposes that BPD symptoms are caused by the interplay of two factors: (1) a biological vulnerability to emotional dysregulation (with high emotional intensity and reactivity, and a slow return to baseline levels after a negative emotion) and (2) an invalidating social environment. DBT posits that problematic behaviors such as anger outbursts and self-harm can be considered as dysfunctional attempts to regulate emotions. Thus, one of the therapeutic targets is skills training to improve emotion regulation and associated problems such as interpersonal difficulties and distress intolerance. Self-report is the classic way to measure treatment outcomes. Adding objective measures of emotional functioning would be a very promising method to see if emotional dysregulation improves with treatment. Previous research of BPD using electroencephalograms (EEG) is still scarce. Marissen et al. (2010) observed altered electrophysiological responses to emotional information, in particular an enhanced emotional cortical reactivity to unpleasant stimuli in BPD patients, compared to controls. Can we confirm this result? If it is the case, is it subject to change after treatment? Is it related to self-reported treatment outcomes? Method: BPD patients admitted to 1-year outpatient DBT treatment program (weekly individual and group therapy, phone coaching, consultation team) complete a set of self-report questionnaires at baseline, three, six, nine months, and at the end of treatment (12 months): diagnosis, depression, hopelessness, and difficulties in emotional regulation, borderline symptoms, and labile emotional and coping and mindfulness skills. Therapists complete the Global Assessment of Functioning and the Clinical Global Impression scales as well as a rating of the quality of working alliance. We are currently working on a research protocol with additional EEG paradigms before and after treatment.

Computer-based interventions – an online program for relatives of individuals with mental illness
www.rfsm-e-motion.ch

Project initiated at the RFSM – Fribourg Network for Mental Health - in collaboration with the division of clinical and health psychology, University of Fribourg.

Background: Mental illness imposes a considerable burden on the patient's families and which place them at risk for adverse mental health outcomes. However, less than 10% of them benefit from specific psychoeducational groups. We have developed an online *minimal contact self-help* skills training and psychoeducational program that promotes caregivers' empowerment through interactive information and skills practice. Method: Participants were 74 patients' relatives, participating either in (a) an online skills training program (about 12-16 weeks, n= 34), or (b) a psychoeducational group (13 weekly sessions, n= 40). They completed baseline and post-intervention questionnaires (measuring e.g. depressive mood, emotion regulation, mindfulness skills). Results: At baseline, patient's relatives in the online condition are significantly younger than those in the group condition. Those in the group condition start with higher mindfulness «non-judgement» skills. Otherwise, both groups had similar depression scores (43.1% of the sample scores above the «depressive» cut-off), difficulties in regulating emotions and other mindfulness skills. They also reported similar levels of burden. After both interventions, there is a significant main effect (medium effect sizes) of time for depression scores (r= 0.47), difficulties in regulation of emotions (r= 0.26) and mindfulness skills (r= 0.46). Also, there are significant group by time interactions for depression (r= 0.31), difficulties in regulation of emotions (r= 0.24) and mindfulness skills (r= 0.36), as the online condition has significantly larger decreases in depression and difficulties in emotion regulation and larger increases in mindfulness skills than the group condition. Conclusion: Based on these promising results, a first randomized controlled trial of this web-based intervention is necessary to establish its effectiveness. Further investigations are needed to better measure the specific benefits of psychoeducational groups.

Selected Publications

Merlo MCG
Philosophie et troubles schizophréniques. Forum Med Suisse, 2012, 12(35):665–667

Ruef A, Curtis L, Moy G, Bessero S, Badan Bâ M, Lazeyras F, Lövblad KO, Haller S, Malafosse A, Giannakopoulos P, ***Merlo MCG***
Magnetic resonance imaging correlates of first-episode psychosis in young adult male patients: combined analysis of grey and white matter. J Psychiatry Neurosci, 2012, 37(5): 305-12

Haller S, Curtis L, Badan M, Bessero S, Albom M, Chantraine F, Alimenti A, Lovblad KO, Giannakopoulos P, ***Merlo MCG***
Combined Grey Matter VBM and White Matter TBSS Analysis in Young First Episode Psychosis Patients With and Without Cannabis Consumption. Brain topography, 2013

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

Salamin V, Martin-Sölch C, Guenot F, Corzani S, ***Merlo MCG***
Empowering those who care: A web-based mental health promotion intervention for relatives of individuals with mental illness. Abstract of the forthcoming presentation at the Swiss Society of Psychology (SSP) Congress, Basel, 2013, September 11-12

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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Laminar specificity of cholinergic neuromodulation in the visual cortex

Acetylcholine is an important neuromodulator involved in cognitive function. The impact of cholinergic neuromodulation on computations within the cortical microcircuit is not well understood. Here we investigate the effects of layer-specific cholinergic drug application in the tree shrew primary visual cortex during visual stimulation with drifting grating stimuli of varying contrast and orientation. We describe differences between muscarinic and nicotinic cholinergic effects dependent on the layer of cortex.

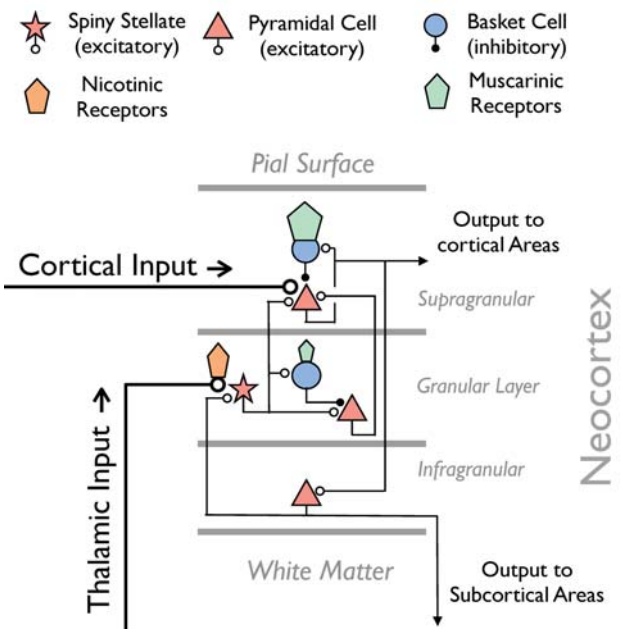

Fig.1 - Laminar location and neuron type for the two main cholinergic receptor classes.

Nicotinic receptor activation enhanced the contrast response in the granular input layer of the cortex, while tending to reduce neural selectivity for orientation across all cortical layers. Muscarinic activation modestly enhanced the contrast response across cortical layers, and tended to improve orientation tuning. This resulted in highest orientation selectivity in the supra- and infragranular layers, where orientation selectivity was already greatest in the absence of pharmacological stimulation. Our results indicate that laminar position plays a crucial part in functional consequences of cholinergic stimulation, consistent with the differential distribution of cholinergic receptors. Nicotinic receptors function to enhance sensory representations arriving in the cortex, whereas muscarinic receptors act to boost the cortical computation of orientation tuning. Our findings suggest close homology between cholinergic mechanisms in tree shrew and primate visual cortices.

Novelty preference in tree shrew

Recognition memories are formed during perceptual experience and allow subsequent recognition of previously encountered objects as well as their distinction from novel objects. As a consequence, novel objects are generally explored longer than familiar objects by many species. We have examined novelty preference using the NOR task in tree shrew, a small animal species that is considered to be an intermediary between rodents and primates. Our paradigm consisted of three phases: arena familiarization, object familiarization sessions with two identical objects in the arena and finally a test session following a 24-h retention period with a familiar and a novel object in the arena. After three object familiarization sessions, tree shrews exhibited robust preference for novel objects on the test day.

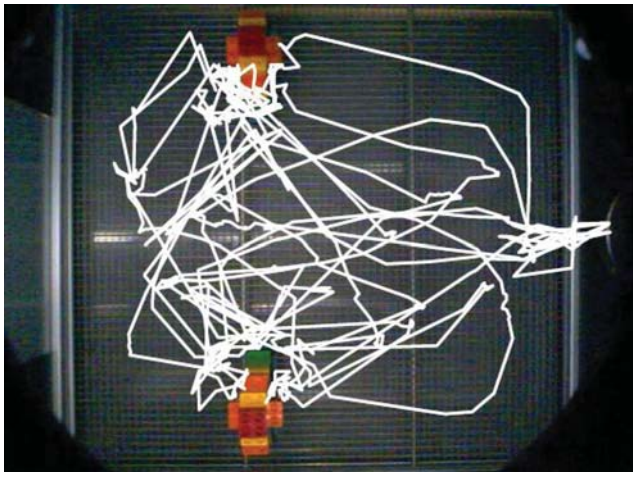

Fig.2 - Animal track exploring familiar and novel objects positioned above and below respectively.

This was accompanied by a significant reduction in familiar object exploration time, occurring largely between the first and second day of object familiarization. By contrast, tree shrews did not show a significant preference for the novel object after a one-session object familiarization. Nonetheless, they spent significantly less time exploring the familiar object on the test day compared to the object familiarization day, indicating that they did maintain a memory trace for the familiar object. Our study revealed different time courses for familiar object habituation and emergence of novelty preference, suggesting that novelty preference is dependent on well-consolidated memory of the competing familiar object. Taken together, our results demonstrate robust novelty preference of tree shrews, in general similarity to previous findings in rodents and primates.

Neuropeptides in the visual system

Endogenous neuropeptides, acting as neurotransmitters or hormones in the brain, carry out important functions including neural plasticity, metabolism and angiogenesis. We have investigated peptides in the visual system, composed of brain regions that are generally less rich in peptides, with the aim of providing the first broad overview of peptides involved in mammalian visual functions. We target three important parts of the visual system: the primary visual cortex (V1), lateral geniculate nucleus (LGN) and superior colliculus (SC). Using a combination of data dependent acquisition and targeted LC-MS/MS based neuropeptidomics, we identified a total of 52 peptides from the tree shrew visual system. A total of 26 peptides, for example GAV and neuropeptide K were identified in the visual system for the first time. Out of the total 52 peptides, 28 peptides with high signal-to-noise-ratio (>10) in extracted ion chromatograms (EIC) were subjected to label-free quantitation. We observed generally lower abundance of peptides in the LGN compared to V1 and SC. Consistently, a number of individual peptides showed high abundance in V1 (such as neuropeptide Y or somatostatin 28) and in SC (such as somatostatin 28 AA1-12). This study provides the first in-depth characterization of peptides in the mammalian visual system. These findings now permit the investigation of neuropeptide-regulated mechanisms of visual perception. ■

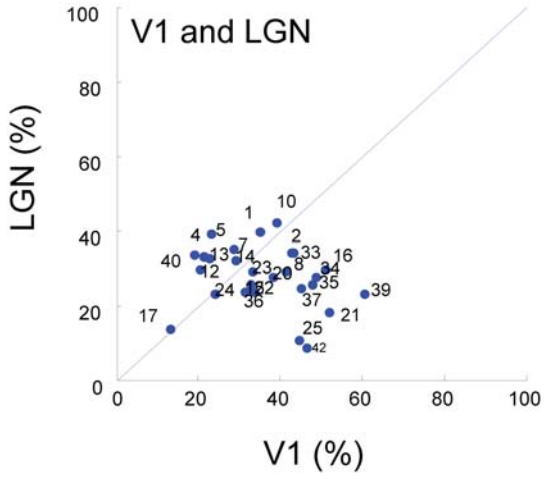

Fig.3 - Relative abundance of peptides in V1 and LGN brain regions.

Selected Publications

Veit J, Bhattacharyya A, Kretz R, ***Rainer G***
Neural response dynamics of spiking and local field potential activity depend on CRT monitor refresh-rate in the tree shrew primary visual cortex. J Neurophysiol, 2011, 106: 2303-2313

Bhattacharyya A, Biessmann F, Veit J, Kretz R, ***Rainer G***
Functional and laminar dissociations between muscarinic and nicotinic cholinergic neuromodulation in the tree shrew primary visual cortex. Eur J Neurosci, 2012, 35(8): 1270-1280

Ranc V, Petruzziello F, Kretz R, Argandona E, Zhang X, ***Rainer G***
Broad characterization of endogenous peptides in the tree shrew visual system. J Prot, 2012, 75(9): 2526-35

Eric M. Rouiller
Chair of Neurophysiology

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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 its behaviour in a constantly changing world, based on a multitude of sensory inputs of different modalities, integrated with the goal to quickly generate the most sophisticated actions in order to efficiently interact with the external world and with other individuals. Our goal is to decipher some mechanisms involved in such sensorimotor integration process, more specifically to identify which brain areas contribute and how. The following questions are addressed:

1) How different senses (vision, hearing, touch, etc) merge in order to form a quick and unified percept?

2) How the simultaneous presentation of two stimuli of different modalities increases the performance (better detection and decreased reaction time), as compared to presentation of the individual stimuli?

3) Which pathways in the brain are responsible for a quick and reliable transfer of multimodal sensory information to motor centers, in order to generate sophisticated hand movements?

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

5) 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?

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.

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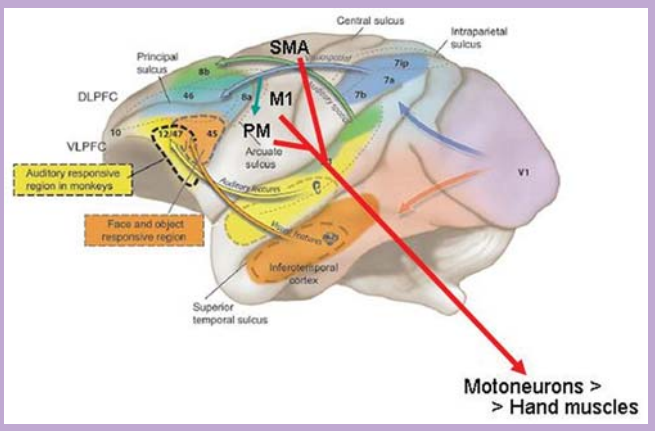

Fig.1 - Schematic survey of multisensory and sensorimotor integration processes in the brain. *Sensory inputs originate here from the visual system (blue and brown arrows) and from the auditory system (yellow and green arrows). Sensorimotor integration is depicted by the transfer of unified sensory percept to motor control brain areas (M1, PM and SMA), sending motor commands to spinal motoneurons, in order to generate voluntary hand movements (redrawn and modified from Romanski, 2007).*

Multisensory integration

In this project, we test in non-human primates (macaques) the hypothesis that the 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. This was true when the stimuli were delivered slightly above their behavioural threshold, but not at higher, comfortable intensities, in line with the inverse effectiveness principle. Single neuron recordings were derived from the premotor cortex (PM) in monkeys performing this detection task: some PM neurons exhibit an activity during the reaction time period reflecting multisensory integration process.

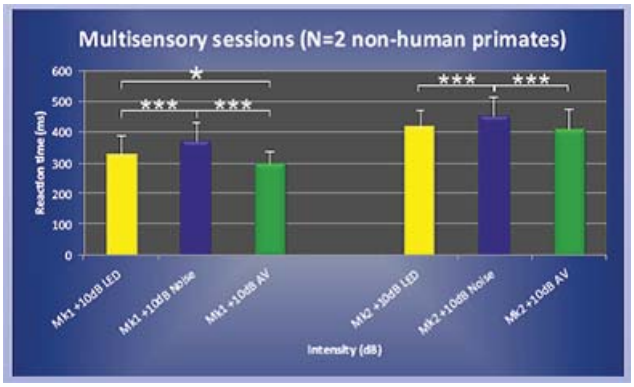

Fig.2 - Reaction times to visual and auditory stimuli. *In two monkeys (Mk1 and Mk2), the reaction times to simultaneous presentation (AV; green bars) of a visual stimulus (LED) **and** an auditory stimulus (noise) were shorter than the reaction times obtained after unimodal presentation of noise alone (blue bars) or the LED alone (yellow bars).*

Sensorimotor integration

In a recent publication, based on video demonstrations of our behavioural methods (Schmidlin et al., 2011; see below), we have presented an exhaustive survey of the multiple motor tasks to which macaque monkeys are subjected, in order to assess manual dexterity. These motor tasks have been refined during the last decade and now they have been validated on a large number of monkeys, including their pertinence to study mechanisms of functional recovery from spinal cord or motor cortex lesion (see below). Three variants of the Brinkman board task, with graded levels of difficulty, are proposed to measure and quantify the ability to manipulate small objects by performing the precision grip (opposition of thumb and index finger). Furthermore, the reach and grasp drawer task is used to assess, in addition to manual dexterity, the ability to develop controlled levels of forces, generated with the forearm and fingers (grip force to pinch the drawer knob and load force to pull the drawer against a resistance).

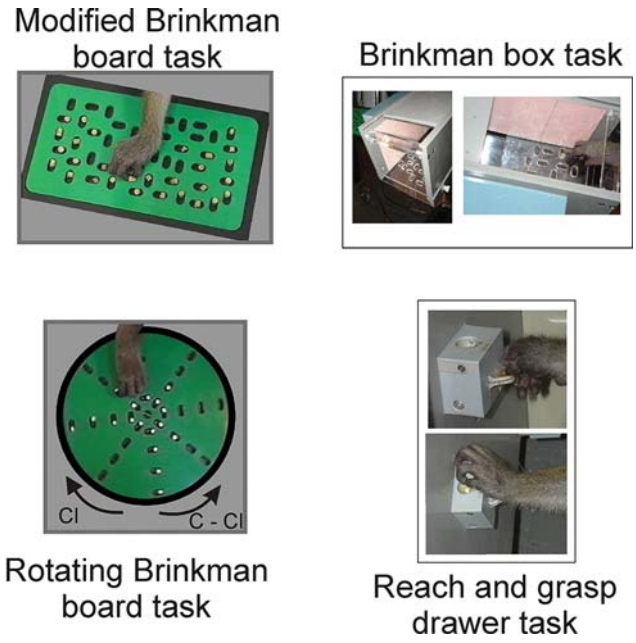

Fig.3 - The four motor tasks to assess manual dexterity in non-human primates (macaque monkeys). *Pictures taken from Schmidlin et al., 2011 (J Vis Exp, 2011, 57, 3258; open access publication).*

More recently, we demonstrated that a motor task like the modified Brinkman board task, representing a kind of motor habit as far as the temporal sequence of grasping the pellets from the 50 slots is concerned, depends on the dorsolateral prefrontal cortex. Indeed, surprisingly for a free will motor sequence, a lesion of the dorsolateral prefrontal cortex led to a disruption of the temporal order according to which the 50 slots are visited by the monkey, as compared to the pre-lesion period (Kaeser et al., 2012; see below).

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 are currently investigating whether the same anti-nogo-A antibody treatment can also promote functional recovery from a unilateral motor cortex lesion (affecting the hand representation in the primary motor cortex). We have obtained preliminary evidence that, as compared to untreated lesioned monkeys, the monkeys subjected to motor cortex lesion and treated with anti-Nogo-A antibody recovered better their manual dexterity (Hamadjida et al., 2012; see below). Furthermore, the anti-Nogo-A antibody treatment enhanced the callosal projection originating from the intact hemisphere and terminating in the ipsilesional premotor cortex, demonstrated to play a

substantial role in functional recovery.

Similarly, another treatment based on autologous cell therapy (adult neural progenitor cells, extracted from the lesioned monkey itself and processed in culture before re-implantation) also promoted better functional recovery after motor cortex lesion (Kaeser et al., 2011; see below). ■

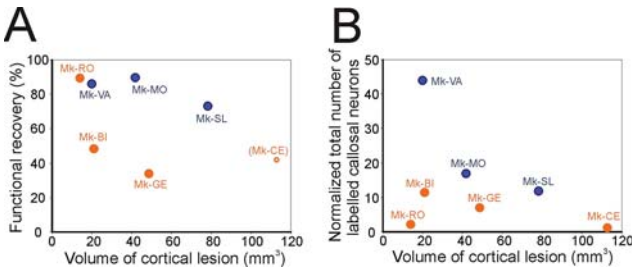

Fig.4 - Functional revovery after motor cortex lesion. *In panel A, plot of functional recovery of manual dexterity after motor cortex lesion, as a function of volume of cortical lesion, showing that anti-Nogo-A antibody treated monkeys (blue circles) recover generally better than untreated monkeys (brown circles). In panel B, as a result of tracing experiments still in monkeys subjected to motor cortex lesion, the callosal projection to the ipsilesional premotor cortex is enhanced in anti-Nogo-A antibody treated monkeys (blue circles), as compared to untreated monkeys (brown circles). Derived from Hamadjida et al., 2012 (Exp. Brain Res. 223; open access publication).*

Selected Publications

Kaeser M, Brunet JF, Wyss AF, Belhaj-Saïf A, Liu Y, ***Rouiller EM****, Bloch J*
Autologous adult cortical cell implantation enhanced functional recovery of manual dexterity after unilateral lesion of motor cortex in non-human primates. Neurosurgery, 2011, 68: 1405-1417

Schmidlin E, Kaeser M, Gindrat AD, Savidan J, Chatagny P, Badoud S, Hamadjida A, Beaud ML, Wannier T, Belhaj-Saif A, ***Rouiller EM***
Behavioral assessment of manual dexterity in non-human primates. J Vis Exp, 2011, 57: 3258; DOI: 10.3791/3258

Kaeser M, Wannier T, Brunet JF, Wyss A, Bloch J, ***Rouiller EM***
Representation of motor habit in a sequence of repetitive reach and grasp movements performed by macaque monkeys: evidence for a contribution of the dorsolateral prefrontal cortex. Cortex, 2012 [Epub ahead of print]

Hamadjida A, Wyss AF, Mir A, Schwab ME, Belhaj-Saif A, ***Rouiller EM***
Influence of anti-Nogo-A antibody treatment on the reorganization of callosal connectivity of the premotor cortical areas following unilateral lesion of primary motor cortex (M1) in adult macaque monkeys. Exp Brain Res, 2012, 223: 321-340

Beat Schwaller
Anatomy

Calcium signaling in health and disease

INTRODUCTION

Together with the ubiquitous calmodulin, the EF-hand containing Ca^{2+}-binding proteins parvalbumin (PV), calbindin D-28k (CB) and calretinin (CR) are the most abundantly expressed members of this family in the brain. Formerly, they were classified as simple buffers serving to «clamp» the intracellular calcium concentration $[Ca^{2+}]_i$. But recent studies also using transgenic mice have revealed these molecules to play pivotal roles in Ca^{2+} homeostasis and signaling and furthermore CB and CR to have Ca^{2+} sensor functions. The three proteins are important for synaptic plasticity and related rhythmic activities within neuronal networks. The lack of any of these proteins in knockout mice induces specific compensation mechanisms including changes in cell morphology and organelle biosynthesis.

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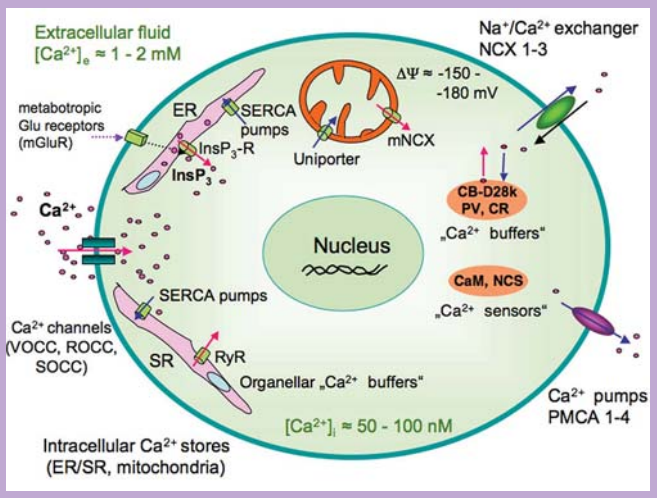

Fig.1 - Components of the Ca^{2+} signaling toolkit. *The extracellular [Ca^{2+}] as well as the intraluminal [Ca^{2+}] are in the order of 1 - 2 mM, while the intracellular (cytosolic) [Ca^{2+}] is approximately 50 - 100 nM. Red arrows indicate systems that lead to a transient increase in [Ca^{2+}]$_i$ including Ca^{2+} channels in the plasma membrane: voltage-operated (VOCC), receptor-operated (ROCC) and store-operated (SOCC) ones. Ca^{2+} ions are also released from organelles including the endoplasmic and sarcoplasmic reticulum (ER and SR), respectively. In the lumen of the ER/SR, large amounts of organellar Ca^{2+} buffers (light blue) including calreticulin are involved in the regulation of Ca^{2+} homoeostasis and ER Ca^{2+} buffering. Release of Ca^{2+} from mitochondria via the mitochondrial Na^+/Ca^{2+} exchanger (mNCX) and from Ca^{2+} buffers increases [$Ca2^+$]$_i$. Mechanisms that decrease [Ca^{2+}]$_i$ (blue arrows) include plasma membrane Ca^{2+}-ATPases (Ca^{2+} pumps; PMCAs), Na^+/Ca^{2+} exchangers, SERCA pumps, the mitochondrial uniporter (MCU) and Ca^{2+} buffers such as CB, PV and CR (taken from Schwaller B, Adv Exp Med Biol, 2012, 740, 1-25).*

Calretinin regulates Ca^{2+}-dependent inactivation and facilitation of $Ca_V2.1$ Ca^{2+} channels through a direct interaction with the $\alpha_1$2.1 subunit

Although indirect evidence suggested that calretinin (CR) might have an additional function as a Ca^{2+} sensor, the putative interaction partner(s) remained elusive. A consensus highly basic CR-binding domain (CRB) was identified from a phage display library screen *in vitro* and revealed the voltage-gated $Ca_V2.1$ Ca^{2+} channel as a putative binding partner. These channels undergo dual modulation by Ca^{2+}, Ca^{2+}-dependent inactivation (CDI), and Ca^{2+}-dependent facilitation (CDF), which can influence synaptic plasticity in the nervous system. Still relatively little is known about the molecular determinants controlling CDI and CDF in neurons. In collaboration with the group of Prof. Amy Lee, University of Iowa, we show that CR, highly expressed in neuron subpopulations including cerebellar granule cells, inhibits CDI and enhances CDF by binding directly to the cytoplasmic linker between domains II and III of the pore-forming alpha subunit $\alpha_1$2.1. In pull-down assays, CR-binding to fusion proteins containing these CRBs was largely Ca^{2+}-dependent. In addition, $\alpha_1$2.1 co-immunoprecipitated with CR antibodies using mouse cerebellar extracts, which confirmed the existence of CR-$Ca_V2.1$ complexes *in vitro* and *in vivo*. Electrophysiology experiments in HEK293T cells revealed that CR significantly decreased $Ca_V2.1$ CDI and increased CDF. For these effects, binding of CR to $\alpha_1$2.1 was required, because they were not observed upon substitution of the II-III linker of $\alpha_1$2.1 with that from the $Ca_V1.2$ α_1 subunit, which doesn't contain the CRBs. In summary, we were the first to show that CR has not only the expected role as a fast Ca^{2+} buffer, but by directly modulating effectors such as $Ca_V2.1$, acts as a Ca^{2+} sensor. The presence of CR in particular neuron subtypes may have major consequences for Ca^{2+} signaling and neuronal excitability. In the next step we will elucidate the region within CR that is responsible for the interaction with $Ca_V2.1$.

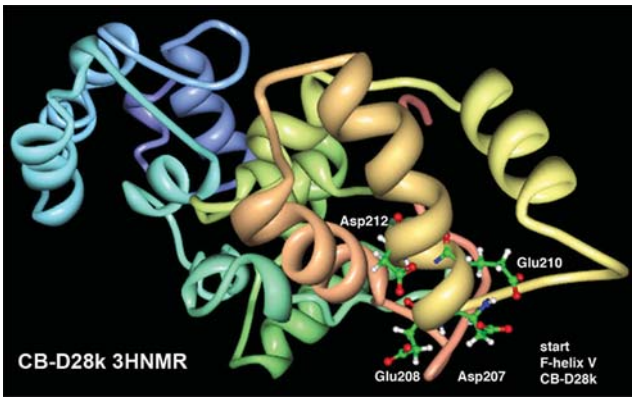

Fig.2 - Putative protein-interaction site in CR based on NMR structure of the closely related protein calbindin-D28k. *EF-hand domains are color-coded (EF1: dark blue; EF2, light blue; EF3: blue/green, EF4: green; EF5: yellow/dark yellow; EF6: orange/red. Surface-exposed acidic residues Asp_{207}, Glu_{208}, Glu_{210}, Asp_{212} are shown and might be part of the region interacting with CRB sequences. Images were generated with PDB ProteinWorkshop 1 (PDB ID: 2G9B).*

Inverse regulation of the cytosolic Ca^{2+}buffer parvalbumin and mitochondrial volume in muscle cells via SIRT1/PGC-1α axis

Deletion of a Ca^{2+}signaling toolkit component leads to homeostatic modulation of the remaining ones. In most cell types expressing PV, PV's absence is compensated by an upregulation of mitochondria as seen in cerebellar Purkinje cells (***Fig.2***). In a more recent study, we investigated the mechanisms regulating PV expression and mitochondrial volume in muscle of $PV^{-/-}$ mice *in vivo* and in C2C12 myotubes *in vitro*. In general, skeletal muscles show a high plasticity to cope with various physiological demands and this is reflected by the different muscle types that can be distinguished e.g. by the force, endurance, contraction/relaxation kinetics, oxidative/glycolytic capacity, and also with respect to Ca^{2+}-signaling components. The absence of PV in fast-twitch muscle *tibialis anterior* (TA) resulted in an increase in the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and of its positive regulator, the deacetylase sirtuin 1 (SIRT1). TA muscles from $PV^{-/-}$ mice also had an increased mitochondrial volume. Mild ionophore treatment of control C2C12 myotubes causing a moderate elevation in $[Ca^{2+}]_c$ resulted in an increase in mitochondrial volume, together with elevated PGC-1α and SIRT1 expression levels. Interestingly in PV-transfected myotubes $[Ca^{2+}]_c$ elevation caused an increase in PV expression levels. In PV-expressing myotubes the mitochondrial volume, PGC-1α and SIRT1 were significantly lower than in control C2C12 myotubes

already at basal conditions and application of ionophore had no effect on either one. SIRT1 activation caused a down-regulation of PV in transfected myotubes, whilst SIRT1 inhibition had the opposite effect. From our results we conclude that PV expression and mitochondrial volume in muscle cells are inversely regulated via a SIRT1/PGC-1α signaling axis. Future experiments should reveal whether such a regulation also occurs in PV-expressing neurons.

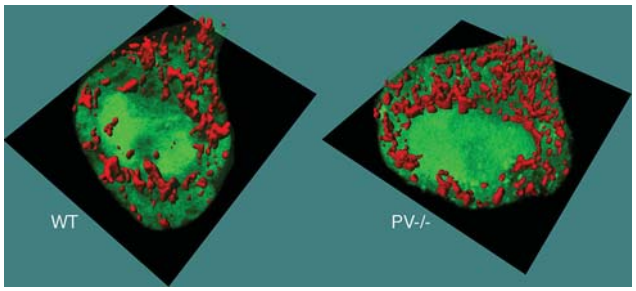

Fig.3 - 3D-reconstruction of confocal images from Purkinje cell somata of a WT and a PV$^{-/-}$ mouse. *Mitochondrial volume (red) is highlighted on a single optical section of the soma. The cytosolic volume (green) was rendered almost transparent. Mitochondria and cytosol were immunostained with anti-COX I and anti-CB antibodies, respectively. Note the increased density of mitochondria close to the plasma membrane in the PV$^{-/-}$ cell (taken from Chen et al., Neuroscience, 2006, 142, 97-105).*

Mechanism of capsaicin receptor TRPV1-mediated toxicity in pain-sensing neurons focusing on the effects of Na^+/Ca^{2+} fluxes and the Ca^{2+}-binding protein calretinin

Transient receptor potential vanilloid subtype 1 (TRPV1) receptor is a pain-sensing, ligand-gated, non-selective cation channel expressed in peripheral sensory neurons. Prolonged activation of TRPV1 by capsaicin leads to cell swelling and formation of membrane blebs in rat dorsal root ganglion (DRG) neurons. In this study we aimed to assessing the contribution of Ca^{2+} and Na^+ ions to TRPV1-mediated changes and furthermore the putative role of CR in this process, since CR is expressed in a subpopulation of DRG neurons. We observed that TRPV1-mediated cell swelling and blebbing was caused by Na^+ influx and concomitant transport of water. While Ca^{2+} influx did not change under these conditions, Na^+ influx was modulated by $[Ca^{2+}]_c$. Ionomycin-induced increase in $[Ca^{2+}]_c$ sensitized TRPV1 channels causing cell swelling. In our study we also observed that capsaicin caused little increase in $[Ca^{2+}]_c$ in the absence of extracellular Ca^{2+} demonstrating that the increase in $[Ca^{2+}]_c$ observed after capsaicin application is derived essentially from the extracellular space. As expected from CR's role as a fast Ca^{2+} buffer, it decreased the amplitude, but slowed down the decay of Ca^{2+} signals evoked by ionomycin. Cells co-expressing TRPV1 and CR were less sensitive to TRPV1-mediated, capsaicin-induced volume increases, cell swelling and cell death. Unexpectedly, CR decreased both the capsaicin-induced Ca^{2+} and Na^+ influx. Our results hint towards a mechanistic explanation for the apoptosis-independent capsaicin-evoked neuronal loss and additionally reveal CR's protective effect. Thus, we hypothesize that CR's Ca^{2+}-buffering capacity reduces the susceptibility of CR-expressing DRG neurons against cell swelling/death caused by overstimulation of TRPV1 channels.

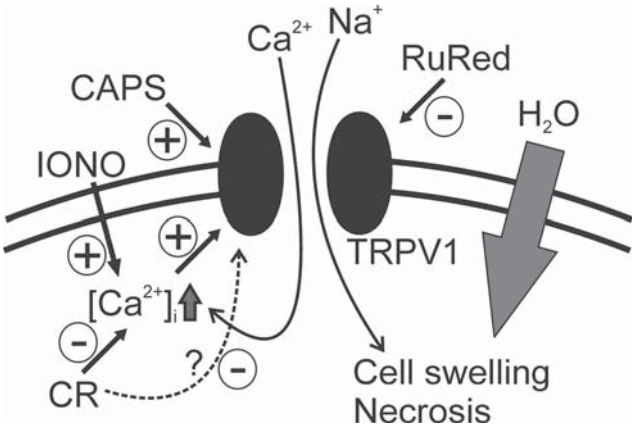

Fig.4 - Proposed model for the molecular mechanism of cell swelling induced by prolonged TRPV1 activation. *The cell swelling is the consequence of Na^+ influx via activated TRPV1 channels and concomitant H_2O transport. The presence of extracellular Ca^{2+} ions might evoke its positive modulating effect on Na^+ influx in at least two ways: i) modifying the TRPV1 pore size to make it more suitable for Na^+ transport or ii) increasing the open-state probability of TRPV1 channels by elevation of $[Ca^{2+}]_i$. Besides the well-known TRPV1 agonist CAPS, an elevation of $[Ca^{2+}]_i$ by the Ca^{2+} ionophore ionomycin (IONO) or other factors can also activate/sensitize TRPV1 channels. This effect can be blocked by the addition of the membrane impermeant Ruthenium Red (RuRed). The presence of CR in the cytosol blunts peak $[Ca^{2+}]_i$ and eliminates/decreases the TRPV1 activation mediated by an increase in $[Ca^{2+}]_i$. Whether the effect of CR is solely the result of CR's Ca^{2+}-buffering properties or indirectly mediated by binding to a TRPV1-modulating protein or directly to TRPV1 channels remains to be determined. Positive modulation of TRPV1 is marked by «+», negative modulation/inhibition by «-». Solid arrows show experimentally proven regulation and the dashed arrow indicates hypothetical modulation of TRPV1, e.g. by CR (taken from Pecze et al., BBA, 2012).*

▸▸

Absence of calretinin, not of calbindin D-28k, causes a permanent impairment of murine adult hippocampal neurogenesis

Calretinin (CR) and calbindin D-28k (CB) function as Ca^{2+} buffers affecting the spatiotemporal aspects of Ca^{2+} transients and also as Ca^{2+} sensors modulating signaling cascades. In the adult hippocampal circuitry, CR and CB are expressed in specific principal neurons and subsets of interneurons. In addition, CR is transiently expressed within the neurogenic dentate gyrus (DG) niche. CR and CB expression during adult neurogenesis mark critical transition stages, onset of differentiation for CR, and the switch to adult-like connectivity for CB. Absence of either protein during these stages in null-mutant mice may have functional consequences and contribute to some aspects of the identified phenotypes. For this, we investigated the impact of CR- and CB-deficiency on the proliferation and differentiation of progenitor cells within the subgranular zone (SGZ) neurogenic niche of the DG. Effects were evaluated (1) two and four weeks postnatally, during the transition period of the proliferative matrix to the adult state, and (2) in 3-month old adult animals to trace possible permanent changes in adult neurogenesis. The absence of CB from differentiated DG granule cells had no retrograde effect on the proliferative activity of progenitor cells, neither affected survival nor migration/differentiation of newborn neurons in the adult DG including the SGZ. On the contrary, lack of CR from immature early postmitotic granule cells caused an early loss in proliferative capacity of the SGZ that was maintained into adult age, when it had a further impact on the migration/survival of newborn granule cells. The transient CR expression at the onset of adult neurogenesis differentiation may thus have two functions: (1) to serve as a self-maintenance signal for the pool of cells at the same stage of neurogenesis contributing to their survival/differentiation, and (2) it may contribute to retrograde signaling required for maintenance of the progenitor pool. ■

Selected Publications

Christel CJ, Schaer R, Wang S, Henzi T, Kreiner L, Grabs D, ***Schwaller B****, Lee A*
Calretinin regulates Ca^{2+}-dependent inactivation and facilitation of $Ca_V2.1$ Ca^{2+} channels through a direct interaction with the $\alpha_1$2.1 subunit. J Biol Chem, 2012, 287: 39766-75

Todkar K, Scotti AL, ***Schwaller B***
Absence of the calcium-binding protein calretinin, not of calbindin D-28k, causes a permanent impairment of murine adult hippocampal neurogenesis. Front Mol Neurosci, 2012, 5: p. 56

Pecze L, Blum W, ***Schwaller B***
Mechanism of capsaicin receptor TRPV1-mediated toxicity in pain-sensing neurons focusing on the effects of Na^+/Ca^{2+} fluxes and the Ca^{2+}-binding protein calretinin. Biochim Biophys Acta, 2013, 1833.1680-91

Ducreux S, Gregory P, ***Schwaller B***
Inverse regulation of mitochondrial volume and the cytosolic Ca^{2+} buffer parvalbumin in muscle cells via SIRT-1/PGC-1α axis. PLoS One, 2012, 7(9): p. e44837

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 five main domains:

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

2) Neural processes in stretch-shortening cycle movements and adaptations in response to plyometric training.

3) Influence of sub- and supraliminal feedback on motor control and motor learning.

4) Prevention and rehabilitation (primarily of back injuries).

5) Neural adaptations in response to strength training and fatiguing strength tasks.

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Neural control of stretch-shortening cycle movements

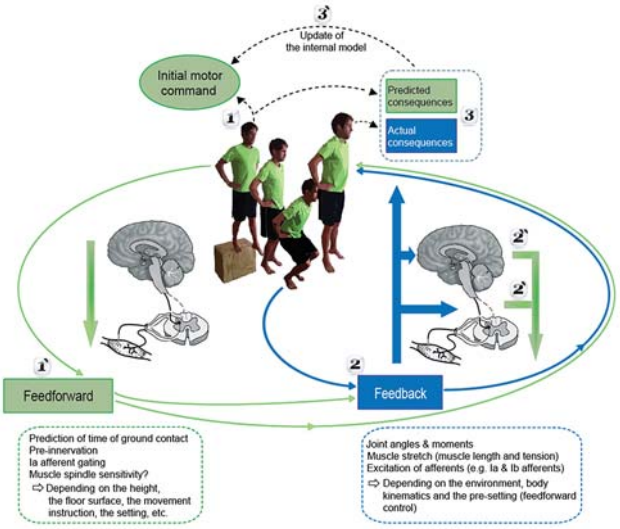

Fig.1 - Neural control of jumping.

Our recent research could contribute to identify basic mechanisms describing the neural control of jumping movements. These results are summarized in a review article (Taube W, Leukel C, Gollhofer A. «How Neurons Make Us Jump» The Neural Control of Stretch-Shortening Cycle Movements. *Exercise and Sport Sciences Reviews,* **2012**, 40(2):106-15). One focus of this article is the close interaction of spinal reflexes and cortical motor commands and thus, the integration of feedforward and feedback mechanisms in order to accomplish complex motor patterns ***(Fig.1)***.

Motor actions in response to subconsciously perceived stimuli

Movements in sports are often extremely fast and it is remarkable how sportsmen such as goalkeepers are able to react in response to very short cues. The question we asked was whether these cues have to be consciously perceived or whether reactions may occur in response to subliminal cues, i.e. cues which were not consciously perceived (Leukel C, Lundbye-Jensen J, Christensen MS, Gollhofer A, Nielsen JB, Taube W. Subconscious visual cues during movement execution allow correct online choice reactions. PloS ONE, 2012, 7(9): e44496).

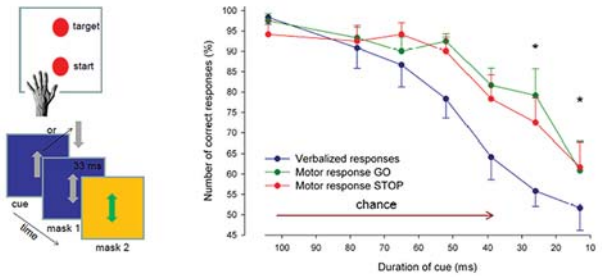

Fig.2 - Motor actions in response to subconscious visual informations.

Subjects should press a start and a target button whenever they perceived an upwards directed arrow on the screen in front of them. However, when they perceived a downwards directed arrow they should only press the start button. We tested subjects in two setups: first, a verbalization protocol (displayed in blue in the image on the right side) where subjects described the direction of the arrow after pressing the start button and second, a motor protocol (displayed in green and red) where subjects had to perform the action i.e. pressing or not pressing the target button after viewing the arrow on the screen.
Our findings imply that the subjects performed correct motor responses to visual cues, which they were not conscious about ***(Fig.2)***. It is therefore concluded that humans may reach decisions based on subconscious visual information in a choice reaction task.

Augmented feedback to improve jump performance and training efficiency

Augmented feedback (aF) has previously been shown to positively influence motor performance in the short (immediate effects) and long term (training over weeks). Despite this knowledge, performance in stretch-shortening cycle, which constitutes one of the most important forms of muscle activation, has never been evaluated under the influence of aF. Therefore, we were interested how aF influenced drop jump performance.

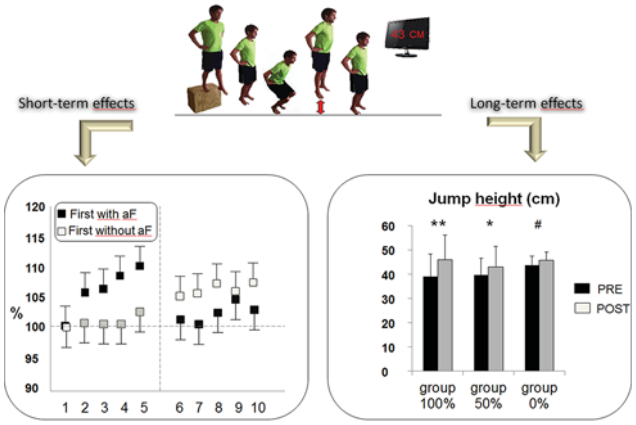

Fig.3 - Augmented feedback improves jump performance.

aF had positive immediate effects on jump height ***(Fig.3** left side of the image)*. Similarly, the group which received most feedback was also most successful in enhancing the jump height in the long-run ***(Fig.3** right side of the image)*. (Paper submitted: Keller, Lauber, Gehring, Leukel, Taube: Augment your jump performances with augmented feedback: immediate and long-term effects).

Biomechanical difference of over ground versus treadmill human locomotion

Different locomotion modes (walk, run, hop) show a braking-acceleration of the center of mass (COM) direction during each step, which translates into a kinetic energy fluctuation. The aim of this study was to analyze if the energy fluctuation and muscle activity are altered when different locomotion modes are performed over ground (OG) or on a treadmill (TM). Based on the foot marker, the contact phase was determined and different COM energy fluctuations were determined for each step: The kinetic vertical, kinetic forward, the potential and the total external mechanical energy fluctuations (ΔEkv, ΔEkf, ΔEp and ΔEm). ΔEkf and ΔEp showed no effect between OG and TM, whereas ΔEkf was systematically reduced for all TM locomotion modes. Despite this systematic reduction no difference in ΔEm and muscle activity was found for walking. Here the body is expected to vault over a straight leg, where the leg muscles have limited possibilities to adjust the biomechanical demands. For running and hopping not only a reduction in ΔEkf was found, but also a reduction in ΔEm (-9%, -5%, respectively) and muscular activity. In these locomotion modes the knee is flexed during contact phase and the muscles have the capacity to alter the biomechanical action on the TM. The general mechanical difference is that a reduction in breaking-acceleration of the COM occurs on the TM, which may be related to a reduced landing angle over TM. Walking shows comparable overall energetic demands between OG and TM, whereas running and hopping display reduced energetic demands on the TM. ■

Selected Publications

Keller M, Pfusterschmied J, Buchecker M, Müller E, ***Taube W***
Improved postural control after slackline training is accompanied by reduced H-reflexes. Scand J Med Sci Sports, 2012, 22(4): 471-477

Leukel C, Lundbye-Jensen J, Christensen MS, Gollhofer A, Nielsen JB, ***Taube W***
Subconscious visual cues during movement execution allow correct online choice reactions. PloS ONE, 2012, 7(9): e44496

***Taube W**, Leukel C, Gollhofer A*
«How Neurons Make Us Jump» The Neural Control of Stretch-Shortening Cycle Movements. Exercise and Sport Sciences Reviews, 2012, 40(2):106-15 (Pick of the week; BIOMECH-L, April 12-25, 2012)

Medical Humanities Medical practice and medical science evolve quickly. Their value is dependent on social, cultural and historical context. *Medicine and society* is a research and teaching program which makes use of human and social sciences in order to promote reflection on the issues (ethical, legal, economic, literary, etc.) raised by such an evolution. *Medicine and society* is part of an innovative field, organized around newly created international journals. The aim is to encourage constructive confrontation between various disciplinary viewpoints, in order to foster reflection on the complexity of the patient-doctor relation.

Alexandre Wenger

Medicine, social sciences and the humanities

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Veuillez Monsieur, par Complaisance, et un peu aussi par charité, Compâtir aux Maux dun Malade Dune espece nouvelle et particuliere et Laider Du Secours bien fortant de vos Lumieres. elles sont si généralement Connues, et vous paroissez par vos ouvrages avoir un tel amour pour L'humanité, que j'ay cru ne pas etr Etranger de vous rien que de vous offrir une occasion de La Soulager. il Sagit plus ici des Maux de L'esprit que de ceux du Corps; ou si le reste des organes y a quelque part, et même La principalle, Comme je Le crois, Les effets ne Sont absolument Sensibles que Sur Les opérations de L'esprit; perception, Mémoire, entendement, &c. Sans plus Long preambule j'entre en Matiere, Daignez Maccorder un moment dattention.

Je suis garçon, de L'âge de 42. ans; mon temperament Sans etre Robuste, ou plutost etant un peu délicat, est pourtant assez bon; il est vray que je Le ménage et tres Souvent je fais des excez: j'entends même de ceux qui ne furent que Relatifs, Car telle chose qui ne nuisoit point Du tout a un autre

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.

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DOCTORAL CANDIDATE
Bénédicte Prot

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.

During the 2012-2013 academic year, 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; Thierry Collaud, UniFr, Markus Zimmermann-Acklin, UniFr)
- ***Public health*** (Pierre-Alain Raeber, UniFr)
- ***History of Medicne*** (Hubert Steinke, UniBe)
- ***Literature, cinema and medicine*** (Alexander Wenger, UniFr)
- ***Psycho-social Medicine*** (Marco Merlo, UniFr)
- ***Medical Law*** (Jean-François Dumoulin, UniFr; Christiana Fountoulakis, UniFr; Alexis Overney UniFr; Franz Werro, UniFr)
- ***Medical Anthropology*** (Corina Salis Gross, UniBe)
- ***Health Economics*** (Pierre Stadelmann, UniL, Stéphane Guérard, UZh)
- ***Health geography*** (Olivier Graefe, UniFf; 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)

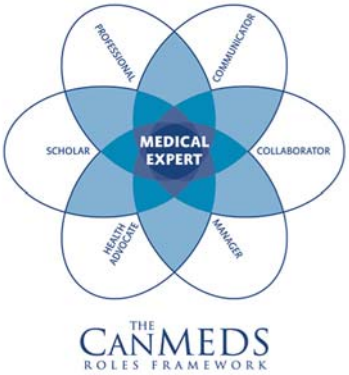

Fig.1 - Seminars. *Every year, a seminar is organised as part of the program around a current or controversial subject related to medicine and society (e.g. DRGs, e-health, etc). The lectures and seminars prepare students to better understand their future roles within the medical community. In this respect, the Medicine and Society program follows closely the* Swiss Catalogue of Learning Objectives for Undergraduate Medical Training *as well as the* CanMEDS Roles Framework.

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)

Fig. 2 - The Four Guises of the Doctor. *Anonymous, Netherlands, 17thc. (© Museum Boerhaave, National Museum of the History of Science and Medicine, Leiden, Netherlands).*

The painting reveals a patient awaiting the physician as if he would wait for the **Messiah**. Arriving at the patient's bedside, the doctor is welcomed as a **savior angel**. Once the patient is cured, the doctor is perceived as a **mere mortal**. When the latter requests his fee, he is seen as a **devil**.

Ongoing Projects

The preparations for a **digital museum on medicine and society** are currently underway. Thematic exhibitions of an academic level will be presented on a dedicated website in a playful and eye-catching format to attract a wider audience and raise awareness of the Medicine and Society courses. Each exhibition will engage cross-disciplinary views from medical **specialists**, health-care professionals, but also from art historians in an attempt to underline the social complexity and cultural richness of the medical ▸▸

topics discussed.

The Medicine and Society team members are involved in a number of research projects related to the *literature and medicine* research field. Julien Knebusch conducts a research on interactions between **french poetry** and **medicine** in the 20th Century by studying 1) the ways medical knowledge has been reinvested and explored by poet-physicians and poets linked to physicians and 2) the ways physicians have approached poetical knowledge. Benedicte Prot works on the medico-literary representations of nudity in the 18th Century. ■

Fig.3 - Research Meetings. *Alexandre Wenger and Radu Suciu, in collaboration with the Triangle Azur, organized The World Knowledge Dialogue symposium, held at Villars-sur-Ollon (Switzerland) from 14 to 17 October 2012. Its aim was to foster interdisciplinary discussions around* medicine, literature *and the* **digital humanities**. *The symposium brought together some 50 IT experts, physicians and literary scholars to set up a digital database around medicine and literature.*
More on www.wkd2012.ch

Recently Published Books

Julien Knebusch, Poésie planétaire ***L'ouverture au(x) monde(s) dans la poésie française au début du 20è siècle****, Paris, Presses de la Sorbonne Nouvelle, 2012*

Alexandre Wenger, ***Le Médecin et le Philosophe. Théophile de Bordeu selon Diderot****, Paris, Hermann, 2012*

Radu Suciu, André Du Laurens. ***Discours des maladies mélancoliques****, Paris, Klincksieck, 2012 (edition critique)*

Third party funding to group leaders

BASPO
(Bundesamt für Sport)

Biotech Industry

Center for Integrative Human Physiology (ZIHP), Cooperative Grant

Christopher Reeves Foundation

Commission for Technology and Innovation (CTI/KTI)

CSC

DFG
(Deutsche Forschungsgemeinschaft)

ESF EURYI Program
(European Science Foundation
- European Young Investigator Awards)

European Commission
Seventh Framework Program - Initial training Network

European Commission
Seventh Framework Program - Large integrated Project

IP-SCOPES
(Swiss National Science Foundation)

ISREC Foundation

ITI Research Grant

Medic Foundation

NCCR Molecular Oncology
(Swiss National Science Foundation)

NCCR Neuro
(Swiss National Science Foundation)

NCCR-Kidney.CH
(Swiss National Science Foundation)

Novartis Foundation for Biomedical Research

Novartis Pharma

Oncosuisse / Swiss Cancer League

Research Funds of the University of Fribourg

San Salvatore Foundation

Swiss Heart Association

Swiss Heart Foundation

Swiss League Against Epilepsy

Swiss National Science Foundation - Equipment Grant 'R'Equip'

Swiss National Science Foundation - Individual research grants

Swiss National Science Foundation - Prodoc Program - ProDoc, research module

Swiss National Science Foundation - Prodoc Program - ProDoc, teaching module

Synapsis Foundation

Various Private Foundations

Publications

Group Jean-Marie Annoni
(with Lucas Spierer)

Jean-Marie Annoni

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Group Beat Schwaller

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Group Wolfgang Taube

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Book

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Group Franziska Theilig

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Group Alexandre Wenger

Livres

Alexandre Wenger
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Direction d'ouvrages collectifs

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Wenger A
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Group Zhihong Yang

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Dissertations

Group Jean-Marie Annoni

PHD THESES
Aurélie Manuel
Michael Mouthon

Group Marco Celio

BIOMED MASTER THESES
Daniele Milani
Gioele Albisetti

MASTER OF MEDICINE THESES
Valentina Imstepf

MD THESES
Severin Rossi

Group Stéphane Cook & Mario Togni

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Géraldine Guex
University of Bern

MASTER OF MEDICINE THESES
Jeanette Mollet
University of Bern
Linus Schoepke
University of Bern
Damien Casagrande
University of Lausanne
Guillaume Aeby
University of Bern
Lucie Kalberer
University of Bern
Christian Cerehetti
University of Basel
Daniele Gozzoli
University of Basel
Noé Corpataux
University of Lausanne
Franziska Kocher
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Dominique Birrer
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Gayathri Yepuri
Helena Marcelino

Group Luis Filgueira

HONOURS OF SCIENCE THESES
Felipe Souza Duque
Alecia-Jane Twigger

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Mansur Abdullah Alghamdi
Ahmaed Saeed Baashar

PHD THESES
Dieter Cadosch
Foteini Hassiotou

Group Pierre Lavenex

PHD THESES
Adeline Jabès
Loïc Chareyron

MASTER OF SCIENCE THESES
Typhaine Juvet

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Erik G. Grasser

MASTER OF MEDICINE THESES
Luc Barberini

Group Eric M. Rouiller

PHD THESES
Adjia Hamadjida
Marie-Laure Beaud

MASTER OF SCIENCE THESES
Pauline Chatagny
Simon Badoud

MASTER OF MEDICINE THESES
Florence Hoogewoud

Group Curzio Rüegg

MASTER OF SCIENCE THESES
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BMS, University of Bern
Nersine Gharbi
Master 2, University of Toulouse

MASTER OF MEDICINE THESES
Marisa Blanquet
University of Zurich
Katharina Burmeister
University oif Basel
Philippe Herzog
University of Lausanne
Gregoire Humair
University of Lausanne
Maristella Santi
University of Lausanne

Group Wolfgang Taube

PHD THESES
Evelyne Kloter
She is the first recipient of a PhD in this domain in Fribourg

MASTER OF SCIENCE THESES
Page Frédéric
Julien Pasquier
Laurence Gogniat
Fabian Rüffli
Alain Bondallaz

Group Zhihong Yang

PHD THESES
Angana Gupta Rajapakse
Gautham Yepuri

MASTER OF SCIENCE THESES
Srividya Velagapudi

Meetings organised by Department members

Group Stéphane Cook & Mario Togni

Co-organization (with Mrs. S. El Mkhenter) des Journées Romandes de formation continue pour le personnel paramédical travaillant en salle de cathétérisme cardiaque, June 15-16, 2011, Lausanne

Co-organization (with the working group) of the «Swiss Session» held at EuroPCR 2011 (Paris Course on Revascularization), May 20-23, 2011, Paris

Co-organization (with the working group) of the «business meeting» of the working group. at the Annual Meeting of the Swiss Cardiology Society, June 8-10, 2011, Basel

Co-organization (with the working group) of the «Swiss Session» held at TCT 2011 (Transcatheter Therapeutics), November 7-11, 2011, San Francisco

Organization of the 1st journée Fribourgeoise de cardiologie, December 1, 2011, Fribourg

Organization of the 20th Anniversary Winter Meeting of the Working Group «Interventional Cardiology and Acute Coronary Syndromes» January 20-21, 2012, Suisse Majestic Grand Hotel, Montreux

Co-organization (with PD Dr. O. Müller) of the FFR-OCT, May 3-4, 2012, Fribourg

Co-organization (with the working group) of the «Swiss Session» held at EuroPCR 2012 (Paris Course on Revascularization), May 15-18, 2012, Paris

Co-organization (together with PD Dr. G. Sütsch) of the «CTO and DRG» symposium and the «business meeting» (with the working group) at the Annual Meeting of the Swiss Cardiology Society, June 13-15, 2012, Lausanne

Co-organization (with the working group) of the «Swiss Session» held at TCT 2012 (Transcatheter Therapeutics), October 22-26, 2012, Miami

Co-organization (course director: Dr. V. Gupka) of the 6th Indo-European Course on Revscularization (6th IECR). November 21-22, 2012, Zurich

Organization of the 2nd journée Fribourgeoise de cardiologie, December 6, 2012, Fribourg

Co-organization (with the working group) of the «business meeting» held during the Winter Meeting of the Working Group «Interventional Cardiology and Acute Coronary Syndromes» January 15-17, 2013, Feusisberg

Organization of the 1st ICAR Meeting, March 22-24, 2013, Champéry

Group Abdul Dulloo

Fribourg Obesity Research Conference (FORC)-2011
Body composition, Thermogenesis & Inflammation in Pathogenesis of Obesity & Metabolic Syndrome
Organising Committee (AG Dulloo, JP Montani)

European Congress on Obesity (ECO) 2011 Istanbul International Scientific Committee member (AG Dulloo et al.)

Group Pierre Lavenex

Tag der Forschung für Leben - Von der Grunlagenforschung bis zur Therapie. Fondation Recherche pour la Vie. Université de Fribourg, February 2012

Group Jean-Pierre Montani

USGEB meeting, Zurich
Organizing and chairing symposium «Unraveling mechanisms of cancer progression by imaging techniques» January 28, 2011, Zurich

FORC-2011, Fribourg
Co-organizer of the 6th Fribourg Obesity Research Conference, September 23, 2011, Fribourg

Organization of the Annual meeting of the Swiss Physiological Society, September 13, 2012, Fribourg

Group Curzio Rüegg

Vascular Progenitors in Biology and Medicine (FP7 SmArt program conference)
Fribourg, Switzerland; September 2012 (with Q. Xu, King's College, London)

«Research day» DepMed and HFR
May 2012 (with J.M. Annoni UNIFR, and D. Hayoz / HFR, Fribourg)

Group Zhihong Yang

17th Cardiovascular Research & Clinical Implications Meeting, 6 / 7 October 2011, Murten, Switzerland, Marijke Brink (Basel), Beat Kaufmann (Basel), Thomas Dieterle (Basel); Brenda R Kwak (Geneva), Pierre Fontana (Geneva), Christian M. Matter (Zurich), Ulf Landmesser (Zürich), Hugues Abriel (Bern), Christian Zuppinger (Bern), Daniel Hayoz (Fribourg), Zhihong Yang (Fribourg), Thierry Pedrazzini (Lausanne), Nicolas Rodondi (Lausanne)

AGLA & Cardiovascular Biology Meeting, March 8, 2012, Zurich: Arnold von Eckardstein, Zurich; Brenda Kwak, Geneva; Ernst Niggli, Berne; Christian Zuppinger, Berne; Christian Matter, Zurich; Zhihong Yang, Fribourg

AGLA & Cardiovascular Biology 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)

Lectures and seminars given by Department members

Group Stéphane Cook & Mario Togni

Cook S, Resténose Intrastent, High Tech, January, 26, 2011, Marseille

Cook S, Infarctus du myocarde et ses complications, formation postgraduée en médecine interne, colloque de médecine, February, 1, 2011, Fribourg

Cook S, Heart rate in the center of the cardiovascular continuum, Program Cardiology Update 2011, Dinner Session 2: Satellite Symposium Servier, February, 15, 2011, Davos

Cook S, Cardiovascular Interventions in Europe 2009/2010, EAPCI General Assembly, EuroPCR, May, 17, 2011, Paris

Cook S, Take-Home Message, Microvascular function after PCI, Abstract Session, EuroPCR, May, 18, 2011, Paris

Cook S, Breaking the link between stenting and dual antiplatelet therapy, Symposium, EuroPCR, May, 18, 2011, Paris

Cook S, Native and induced coronary aneurysm: from the imaging to the treatment, How should I treat?, EuroPCR, May 19, 2011, Paris

Cook S, How Did I Treat ? EuroPCR, May, 19, 2011, Paris

Cook S, Chest pain, B.P. Koirala Institute of Health Sciences, May, 30, 2011, Dharan - Nepal

Cook S, Myocardial infarction and Complication, B.P. Koirala Institute of Health Sciences, May, 31, 2011, Dharan - Nepal

Cook S, Clinical Cases, B.P. Koirala Institute of Health Sciences, June, 1, 2011, Dharan - Nepal

Cook S, Infective Endocarditis, Short Term Training in Tropical & Infectious Disease, B.P. Koirala Institute of Health Sciences, June, 1, 2011, Dharan - Nepal

Cook S, Financial report/ budget WM/ financial consulting result, Swiss Working Group Interventional Cardiology, Business Meeting, SGK 2011, June 8, 2011

Cook S, Website, Working Group, Swiss Working Group Interventional Cardiology, Business Meeting, SGK, June 8, 2011

Cook S, Interventional training, Swiss Working Group Interventional Cardiology, Business Meeting, SGK, June 8, 2011

Cook S, Platinum Program - Evaluation of the PROMUS™ Element™ Everolimus-Eluting Coronary Stent, Boston Scientific Symposium, SGK, June 8, 2011

Cook S, Physiopathologie de la maladie coronarienne et urgences cardiologiques: Aspects importants pour le personnel paramédical, Journées Romandes de formation continue pour le personnel paramédical travaillant en salle de cathétérisme cardiaque, June, 15, 2011, Lausanne

Cook S, Lire et comprendre les études sur le DES – les informations essentielles. Journées Romandes de formation continue pour le personnel paramédical travaillant en salle de cathétérisme cardiaque, June, 15, 2011, Lausanne

Cook S, Progrès Thérapeutiques, Les Thérapies du future: scaffold bioresorbable- ABSORB, Journées Romandes de formation continue pour le personnel paramédical travaillant en salle de cathétérisme cardiaque, June, 15, 2011, Lausanne

Cook S, DEB; Latest results after EuroPCR 2011, Endovascular Complications; »up-date minutes« be up-dated & make the right choice, June, 16, 2011, Lausanne

Cook S, A-Propos de 2 cas, Colloque Morbidity-Mortality, SICO, June, 17, 2011, Fribourg

Cook S, TV et series TV: Risque et Enseignements en Cardiologie, Colloque Servier, June, 23, 2011, Neuchâtel

Cook S, Docteur, j'ai mal au coeur, Formation continue en cardiologie, Parc Hôtel, September, 27, 2011, Fribourg

Cook S, Urgences cardiologiques, Colloque formation continue infirmière, soins intensifs et anesthésiologie, October, 27, 2011

Cook S, Maman, j'ai dilaté les artères, MedAlumni, November, 17, 2011, Fribourg

Cook S, Cardiomyopathies, Formation continue en cardiologie, November, 22, 2011

Cook S, Cardiologie: Peut-on apprendre la médecine en regardant les séries TV?, Journées des Gymnasiens, November, 23, 2011

Cook S, Dénervation sympathique rénale: Aspects pratiques, Colloque formation infirmière, cardiologie, November, 24, 2011

Cook S, Syndromes coronariens aigus - Physiopathologie et prise en charges, Colloque formation infirmière, soins continus, November, 25, 2011

Cook S, Antiplaquettaires - Mise au point 2011, 1ère journée Fribourgeoise de cardiologie, December, 1, 2011, Fribourg

Cook S, PCI vs. CABG in multivessel diabetic patient, Diabetes and ACS, Masterclass 2012 State-of-the-Art Management of Acute Coronary Syndromes, ACS MasterClass, December, 8-9, 2011, Geneva

MN Giraud, Cardiac stem cells and regenerative medicine, Stem Cells & Regenerative Medicine Course Graduate School, University of Bern. Avril, 2011

MN Giraud, Engineering a muscle graft for myocardial recovery, 3rd UCL_RFH Cardiovascular Diseases Workshop, Imperial College, May, 20, 2011 London

Cook S, Interventions Coronariennes Percutanées, 2012, Rencontre Eli-Lilly, January, 2012, Fribourg

Cook S, Financial report/ budget WM/ financial consulting result, Swiss Working Group Interventional Cardiology, Business Meeting, Wintermeeting, January, 20, 2012

Cook S, Website, Working Group, Swiss Working Group Interventional Cardiology, Business Meeting, Wintermeeting, January, 20, 2012

Cook S, Résultats à long terme des stents actifs, High Tech 2012, January, 27, 2012, Marseille

Cook S, Le Foramen Ovale Perméable: Implications pour le Plongeur, rapport annuel des plongeurs PolCant, February, 2, 2012, Grange-Paccot - Fribourg

Cook S, Humanmedizin, Forum Job-Info 2012, UniFribourg, February, 15, 2012

Cook S, Insuffisance cardiaque aigüe - Prise en charge invasive, Colloque de formation du service de cardiologie, CHUV, February, 16, 2012, Lausanne

Cook S, Cardiology Update 2012, Midis Pratiques, February, 28, 2012, Fribourg

Cook S, Endocardite, Colloque de Médecine Interne, HFR Hôpital cantonal, March, 6, 2012, Fribourg

Cook S, Intravaskuläre Bildgebung - Was haben wir von Stentthrombose gelernt?, Kardio Lunch, March, 8, 2012, Basel

Cook S, Syndrome coronarien aigu - Prise en charge 2012, Colloque de Formation CSSC – HOPITAL DE SAINTE-CROIX, March, 20, 2012, Grandson

Cook S, Quid de la dénervation rénale percutanée, Colloque d'angiologie, HFR, March, 21, 2012, Fribourg

Cook S, Imagerie Intravasculaire - Qu'avons-nous appris des thromboses de stent?, Rencontres Franco-Suisses, March, 22, 2012, Geneva

Cook S, Remplacement valvulaire aortique percutané, Colloque SICO, HFR, March, 23, 2012, Fribourg

Cook S, Introduction, cours FFR-OCT, May, 3-4, 2012, Fribourg

Cook S. Imagerie intravasculaire en 2012, cours FFR-OCT, May, 3-4, 2012, Fribourg

Cook S, Syndrome coronarien aigu - Prise en charge, May, 8, 2012, Sentier

Cook S, Recherche translationnelle en cardiologie, R-days, UniFR/HFR, May, 10, 2012, Fribourg

Cook S, Complications: Balades Suisses, ACIPACCA, June, 1-3, 2012, Saint Endréol

Cook S., Ballons Actifs: Découvrez de Nouveaux Horizons, APPAC, June, 6, 2012, Biarritz

Cook S, Take-Home Messages, APPAC, June, 6, 2012, Biarritz

Cook S, Financial report/ budget WM/ financial consulting result, Swiss Working Group Interventional Cardiology, Business Meeting, SGK, June, 13, 2012, Lausanne

Cook S, Cardiovascular Risk Management in 2012, Symposium satellite, SSC, June 14, 2012, Lausanne

Cook S, Take-Home Messages, Symposium satellite, SSC, June 14, 2012, Lausanne

Cook S, Summary & Conlcusion CTO 2012 and DRG, SSC, June 15, 2012, Lausanne

Cook S, Opical Coherence Tomography, 7th Interventional Course On High Risk Coronary Interventions «Meet The Experts», June, 27, 2012, Lugano

Cook S, Herzinsuffizienz, Prevention Summit / USZ, August, 30, 2012

Cook S, Traitement antithrombotique du syndrome coronarien aigu – quoi de neuf? September, 6, 2012, Billens

Cook S, Prise en charge du syndrome coronarien aigu en 2012, September, 11, 2012, Riaz

Cook S., Quid du syndrome coronarien et des antiplaquettaires en 2012, HiB, September, 19, 2012, Payerne

Cook S., Dénervation rénale en pratique, 20 ans de la cardiologie interventionnelle du CHU d'Avignon, Palais des Papes, September, 29, 2012

Cook S., Left Ventricular Perforation by a Pigtail Catheter, Swiss Complication Pearls (Sponsored by the Swiss Society of Cardiology Working Group on Interventional Cardiology and Acute Coronary Syndrome), TCT 2012, October, 24, 2012 , 9:00 am - 10:00 am, Miami

Myocardial tissue engineering for heart function recovery, European mini-symposium on Cardiovascular Regenerative Medicine, September, 13, 2012, Strasbourg-Ilkirch - France

Group Abdul Dulloo

GlaxoSmithKline Workshop on «Fat burning for weight loss»; University Birmingham, UK, January, 2011
Lecture: The search for compounds that stimulate thermogenesis in obesity management: from pharmaceuticals to functional food ingredients

18th European Congress on Obesity - ECO 2011; Istanbul, Turkey, May, 2011
Session: Neuronal & Metabolic programming
Lecture: Thrifty metabolism in catch-up growth trajectories to obesity and metabolic syndrome

33rd European Society for Parenteral & Enteral Nutrition (ESPEN) Congress, Gothenburg, September, 2011
Symposium: Paediatric Nutrition - Challenges for the future adult
Lecture: Adipose plasticity in catch-up growth

6th Fribourg Obesity Research Conference, September, 2011
Symposium: Body composition, Thermogenesis & Inflammation in Pathogenesis of Obesity & Metabolic Syndrome
Lecture: What constitutes adaptive thermogenesis in body composition regulation?

Oskar Kellner Symposium 2011, Warnemünde, Germany, September, 2011
Session: Metabolic flexibility & Regulation
Lecture: Pathways from weight fluctuations to obesity

Recent Advances & Controversies in Measuring Energy Metabolism, Maastricht, Netherlands, November, 2011
Session: Adaptive thermogenesis
Keynote Lecture: What constitutes adaptive thermogenesis in human body composition regulation?

19th European Congress on Obesity - ECO 2012 Lyon, France, May, 2012
Session: Beyond BMI: Body Composition Analysis in Obesity
Lecture: Looking at the other side of the coin: Relevance of fat-free mass in energy homeostasis

7th Annual Meeting of the Swiss Association for Study of Obesity (ASEMO/SAMO) Bern, November 2012
Lecture: How dieting makes some fatter: from a perspective of body composition autoregulation

Group Robert Kretz

Experimental Biology, San Diego, USA, 2012

The Notch Meeting, Athens, Greece, 2012

Group Anna Lauber

Regulation of Sex Development: Paradigm shifts?
23rd European Society for Pediatric Urology (ESPU) Meeting, Zurich (CH), May, 9-10, 2012

Alternatives to testosterone: the human (out)back-door pathway.
International Adrenal Cortex Meeting, Houston (USA), June, 20-22, 2012

Why boys will be boys and girls will be girls: human sex development and its defects.
26th Conference of European Comparative Endocrinologists, Zurich (CH), August, 21-25, 2012

Wenn das Geschlecht beim Kind unklar ist. 42. SVA-Davoser Kongress, Davos (CH), November, 2-4, 2012

Group Pierre Lavenex

Building a brain to learn and remember? Lavenex, P. 50 year jubille of the Brain Reearch Institute, Zurich, November 2012

Differential maturation of distinct hippocampal circuits underlies the emergence of distinct memory processes Lavenex, P. Functional architecture of memory conference, Ruhr University Bochum, May 2012

How does one build a brain to learn and remember? Lavenex, P. Institut des Neurosciences, Université Joseph Fourier, Grenoble, March 2012

Postnatal development of the primate hippocampus; from genes, to brain, to behavior. Lavenex, P. Spring Hippocampal Research Conference, Verona, June 2011

How does one build a brain to learn and remember? Lavenex, P. Seminars in Neuroscience, Institute of Neuroinformatics, ETHZ-University of Zurich, April 2011

A la découverte de la mémoire. Lavenex, P. Société Fribourgeoise des Sciences Naturelles, December 2012

Tag der Forschung für Leben – Les animaux en recherche. Bloch J. Vergauwen G. Yerly, C., Lavenex, P. Fondation Recherche pour la Vie. Université de Fribourg, February 2011

Group Jean-Pierre Montani

NCCR-Kidney.CH, Annual Retreat, Beatenberg «Energy metabolism regulation by the kidney», January, 21, 2011

Fribourg Obesity Research Conference (FORC-2011), «Body composition, Thermogenesis & Inflammation in Pathogenesis of Obesity and Metabolic Syndrome», introductory talk, September, 23, 2011

Annual meeting of the Italian Society of Physiology, Sorrento/Italy «Caloric restriction, weight cycling and health» (invited symposium lecture, September, 25, 2011

Annual meeting of Swiss Society of Nephrology, Montreux, «Metabolic consequences of experimental uninephrectomy», invited symposium speaker, December, 2, 2011

Faculty of Medicine of Lisbon, «Role of soft drinks in the pathogenesis of cardiovascular diseases», invited seminar, January, 12, 2012

NCCR-Kidney.CH, Annual Retreat, Spiez «Protective role of the kidney against diet-induced metabolic and cardiovascular disorders», January, 27, 2012

University of Bern, Faculty of Medicine, Master-seminar «Water Balance and hypertension», February, 8, 2012

National Institute for Physiological Sciences, Okazaki, Japan, «Autonomic nervous control during soft drink ingestion», invited seminar, March, 26, 2012

International Fellowship Programme on Integrative Kidney Physiology and Pathophysiology, University of Bern, «Homeostatic Kidney Functions: Control of Blood Pressure», main lecture, May, 4, 2012

University of Geneva, 2nd International Symposium on Sodium and potassium homeostasis in health and disease «A Guytonian view of sodium homeostasis and blood pressure control», invited symposium lecture, June, 14, 2012

University of Latvia, Riga, «Role of soft drinks in the pathogenesis of cardiovascular diseases», invited seminar, June, 28, 2012

Health Sciences eTraining Foundation, Bern symposium, «Hypertension, Sodium Transport and Guyton's Hypothesis», September, 12, 2012

Joint meeting of the Swiss Society of Hypertension and the Belgian Hypertension Committee, Lausanne, «Mechanisms of obesity-induced hypertension», invited plenary lecture, October, 13, 2012

Group Curzio Rüegg

SAMO workshop on anti-angiogenic therapies, Lucerne, February, 4-5, 2011

Research seminar, Institut für Pathologie, UNIBE, March, 21, 2011

Meting on Tumor Angiogenesis, Bern, April, 14, 2011

FMI, Basel; Switzerland, April, 14, 2011

Center for Physiology and Pharmacology, Dept. of Vascular Biology, University of Vienna, Vienna, May, 20, 2011

8th International Symposium on the Biology of Endothelial Cells, Zürich, June, 15-18, 2011

INSERM Unit 682, Strasbourg, France, June, 20, 2011

TUMIC closure conference on metastasis, Lisbon, Portugal, June, 25-29, 2011

MaNGO Workshop on gynecological cancers, Mario Negri Institute, Milano, Italy, July, 1, 2011

FriMat Day, University of Fribourg, Switzerland, July, 4, 2011

2011 ISREC cancer meeting, EPFL, Lausanne, Switzerland, September, 7-11, 2011

Radiobiology conference, Seoul, South Korea, September 30, October, 1, 2011

Swiss research days, Public Lecture, Fribourg, February, 6, 2012

ICTR2012, Fifth International Conference on Translational Research in Radiation Oncology, Geneva, Switzerland February, 28 - March, 3, 2012

1st St.Gallen EORTC Gastrointestinal Cancer Conference, St Gallen, Switzerland, March, 22-24, 2012

European SmArt Workshop on Proteomics and Vascular Biology London, March, 27-29, 2012

Café scientifique, Fribourg, April, 19, 2012

Research Days in medicine, University of Fribourg, May, 10-11, 2012; HFR and UNIFR

Angiogenesis Priority Programm SSP1190, closure meeting, Usedom, Germany, May, 12-15, 2012

Friedrich Mischer Institute - FMI, Basel, June, 12, 2012

Oncology Department, University Hospitals Geneva, HUG, Geneva, June, 27, 2012

ENT Department, CHUV, Lausanne, Switzerland, August, 30, 2012

DKFZ Heidelberg and Mannheim University, Germany, September, 4, 2012

IRB, Bellinzona, Switzerland, October, 12, 2012

Institute of Anatomy, University of Bern, November, 15, 2012

2012 MedAlumni Day, University of Fribourg, Switzerland, November, 17, 2012

Group Franziska Theilig

Invited Overview Talk at the Kongress of the American Society of Nephrology in San Diego 2012
«Corin in Proteinuric Kidney Diseases»

Group Zhihong Yang

Yang. Z. Modulating endothelial and macrophage Functions in cardiovascular disease. AGLA update meeting, March, 31, 2011

Yang Z. The vascular endothelium and macrophages in metabolic diseases. 6th Fribourg Obesity Research Conference (FORC-2011). September, 23, Fribourg, Switzerland

Yang Z. Oxidative Stress and Inflammation: The Common Soil for Aging, Obesity, and Atherosclerosis, Depart Medicine Seminar, April, 24, 2012

Yang Z. Targeting Vascular Disease Signalling. Department Research Day. May, 11, 2012

Further achievements

Group Stéphane Cook & Mario Togni

Board member of the working group «Acute coronary syndromes and PCI» of the Swiss Society of cardiology

Board member of the EAPCI Training & Education Committee

Group Abdul Dulloo

Serge Summermatter, who obtained his doctoral degree in 2007 from our laboratory for his thesis work on skeletal muscle metabolism and fat storage during weight recovery, has recently joined Novartis (Basel) as head of the Muscle Diseases research group

External committee member for nomination of Dr Frederic Preitner asMER, Metabolic Platform, Univ. of Lausanne

External expert for nomination of Assistant Professor Sean Adams for promotion to rank of Associate Professor in the Dept.of Nutrition, University of California, Davis (USA)

Group Luis Filgueira

Member of NHMRC Panel in 2011

Reviewer of Austalian NHMRC and ARC in 2011 and 2012

Group Robert Kretz

Guest Editor for Frontiers Neuroscience

Group Pierre Lavenex

Associate Professor, Institute of Psychology, University of Lausanne, August 2012

Secretary of the Swiss Society for Neuroscience, 2011-present

NS Bulletin Editorial Board Member, 2011-present

Group Jean-Pierre Montani

External expert for the position of Assistant Professor in Computational Modelling, Faculty of Medicine, University of Zurich (2011)

Associate Editor for «Frontiers in Integrative Physiology» (effective 1.1.2011)

Group Curzio Rüegg

Board member of the Scientific Committee of the Swiss Cancer League

Group Wolfgang Taube

Denis Golliard received the «Freiburger Sportpreis» for his achievements in establishing the Bachelor-Studies in Movement and Sport Science in Fribourg and his commitment to promote sport and sport science

Wolfgang Taube was nominated as executive member of the SGS (Sportwissenschaftliche Gesellschaft der Schweiz)

Group Zhihong Yang

Mss Srividya Velagapudi received the Prix Vigener 2012 at the Dies academicus for her Master thesis work

The work by Ming X-F, et al., «Arginase-II promotes macrophage inflammatory responses through mitochondrial reactive oxygen species, contributing to insulin resistance and atherogenesis. JAHA 2012;1:e000992doi:10.1161/JAHA.112.000992» was selected by European Society of Cardiology's working group «Atherosclerosis and Vascular Biology» as the interview article of October 2012. http://www.escardio.org/communities/Working-Groups/atherosclerosis-vascular-biology/publications/Pages/arginase-II.aspx and was also recommended as being of special significance in its field by Amira Klip and Nicolas Pillon from the F1000 Faculty: http://f1000.com/prime/717967456

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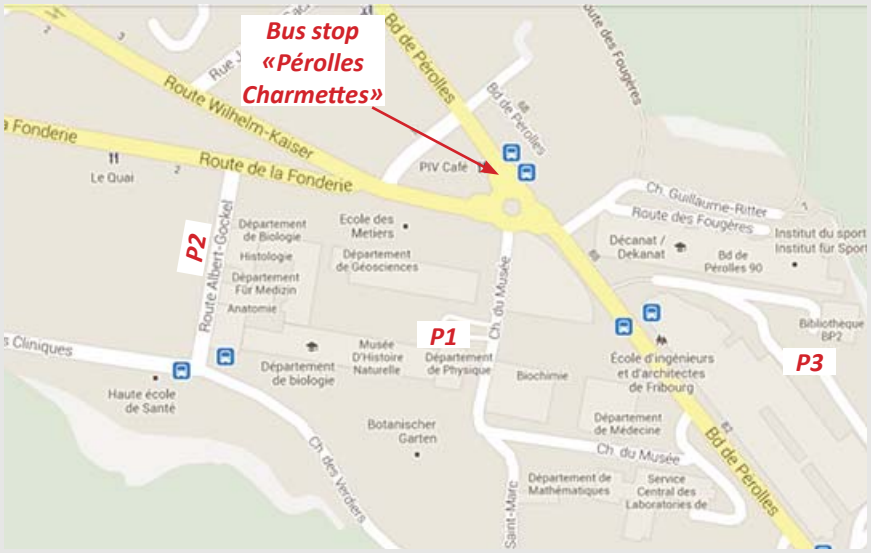
Visiting the Department of Medicine at UNIFR

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

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- Pathology

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- Anatomy
- Medical Humanities

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- Microbiology

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- Cardiology
- Endocrinology
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- Physiology
- Psychiatry

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- Movement and Sport Science (PER08 - Laboratories)

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