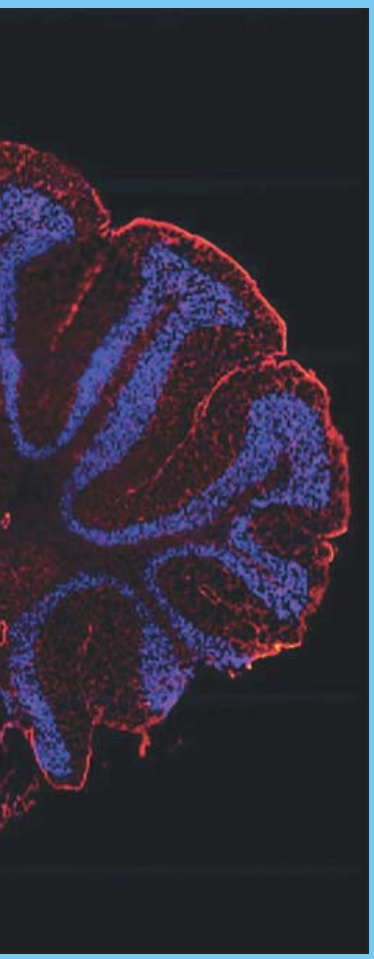

Scientific Report 2015/2016

DEPARTMENT OF MEDICINE

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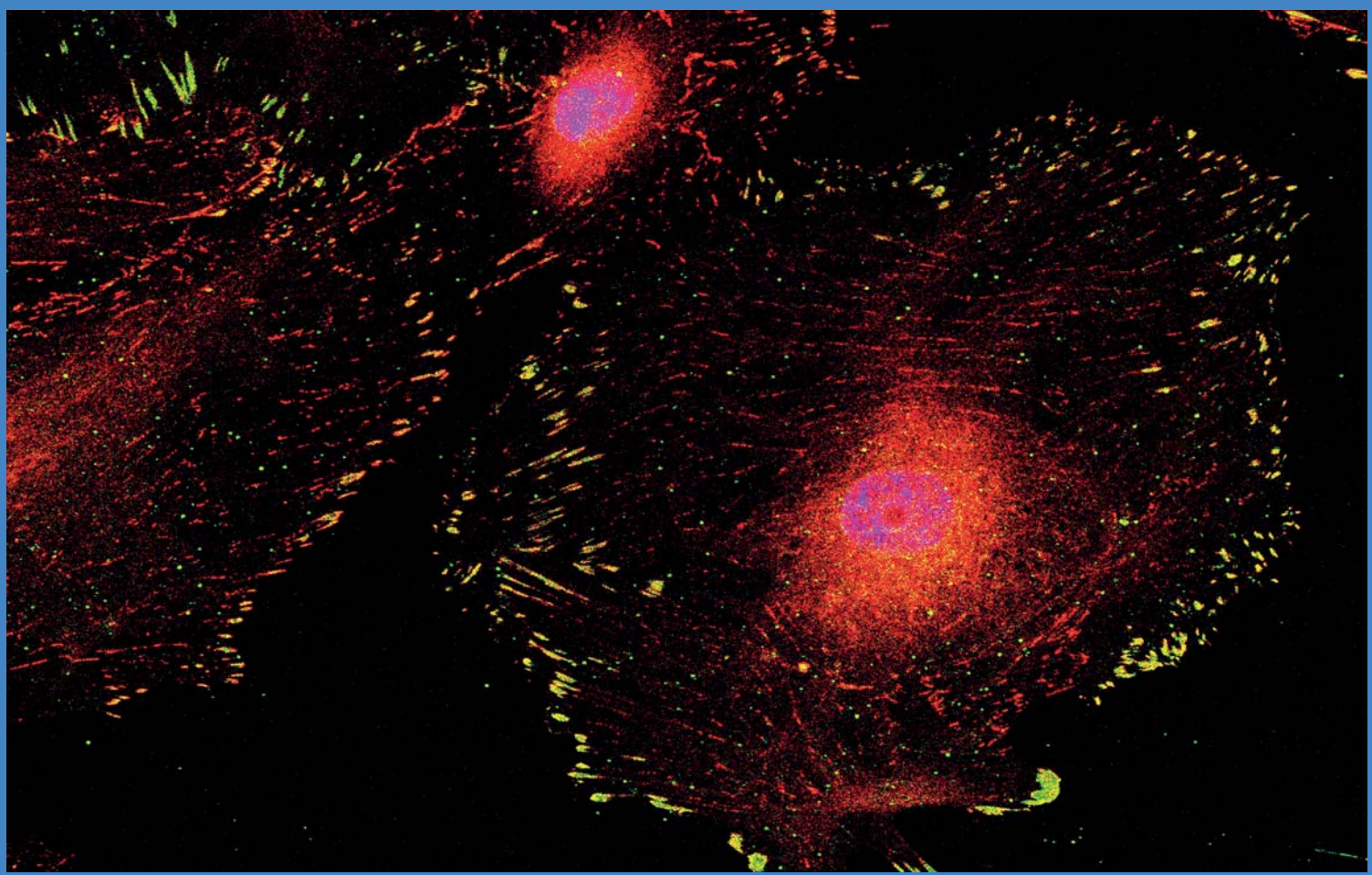

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Contents

This is the third edition of the biannual scientific report published by the **Department of Medicine,** covering the years *2015* and *2016*

Dear Colleagues, dear Readers,

It is our pleasure to present here at a glance the scientific activities of the Department of Medicine of the University of Fribourg for the period of 2015-2016.

Fribourg is a medium size University in the Swiss Academic landscape, but it has a long-standing tradition of quality. Its international visibility and competitiveness is steadily increasing. According to the 2015 ranking of Times Higher Education, the University of Fribourg is a strongly international University. It features as one of the best 100 universities in the world in the category International Outlook. Globally the University of Fribourg is ranked amongst the best 250 of around 17'000 universities worldwide.

As the University does not have a Faculty of Medicine, the Department of Medicine is embedded in the Faculty of Science together with other departments (Mathematics, Computer Science, Physics, Chemistry, Geosciences, Biology and Medicine) and one institute (AM-Institute for Soft Nano- and Material Science), and works in close connection with the Cantonal Hospital of Fribourg (HFR). This situation is unique in medical education and opens interesting opportunities for collaborative research and common goals, but also raises some challenges to find common ground across an ever-broadening spectrum of disciplines, needs and cultures. The research activities of the Department of Medicine are in line with the strategic plan of the University, which has defined Life and Material Sciences as the two priorities of the Faculty of Science.

Professors at the Department of Medicine perform competitive research in many topics, including neurosciences, cardiovascular medicine, metabolism, microbiology, immunology, cancer biology, psychiatry, and medical humanities. The research activities are structured in four clusters:

- Cancer, Microbiology and Immunology
- Neurosciences
- Cardiovascular, Metabolism and Endocrinology
- Medical Humanities

The principal investigators are pursuing research at the molecular, cellular, animal experimental and clinical levels.

The Department of Medicine has invested considerable efforts into promoting and fostering research at all levels. For example in the past two years we have been able to recruit fellows with their own funding (Ambizione, visiting scientists, postdocs, students) and have supported a number of young researches to obtain Swiss and international grants, to develop novel, competitive projects. Acquisition of third party funding has also progressed significantly, with important contributions from the Swiss National Science Foundations, the European Union, and many other foundations or sponsoring organizations. Investigators of the department have acquired important equipment through own funding or R'equip matching funding, including for DNA sequencing, ultrasound small animal imaging, fluorescent-activated cell sorting (FACS), brain activity sensing. In addition, the Swiss Integrative Center in Human Health (SICHH) at the Blue Factory innovation park has established cutting edge technologies and competences now accessible to the

University community, including proteomics, imaging, atomic force microscopy, digital PCR (with the Department of Medicine), ergonomics and bioinformatics. The high quality of research is also demonstrated by the invitation of many investigators of the department to international conferences and seminars, and by the representation in national and international scientific committees and decisional bodies.

The Department of Medicine has participated to the NCCR on bioinspired materials of the University of Fribourg with two projects (Profs. C. Bourquin and C. Rüegg) and the leadership (Prof. C Rüegg, deputy director), as well as to the NCCR Kidney (projects by Profs. J.-P. Montani and Z. Yang). In addition, two specific major achievements have been reached these past two years: the creation of the Swiss Primate Competence Center for Research (SPCCR) in collaboration with the EPFL and the biotech centre (directed by Prof G. Rainer), and the competitive awarding of the National Reference Centre on Antibiotics Emerging Resistance (directed by Prof. P. Nordmann).

In terms of education, the Department of Medicine offers a three-year Bachelor's medical curriculum to around 100 students in Medicine each year. A major development is the approval of the new Master Curriculum in Medicine leading to the Federal Diploma of Medicine. The first cohort of 40 students will enter the curriculum in 2019. The master will be oriented toward primary care medicine and several new positions are being opened in this context. New research opportunities will emerge, especially in collaboration with the hospital and general practitioners.

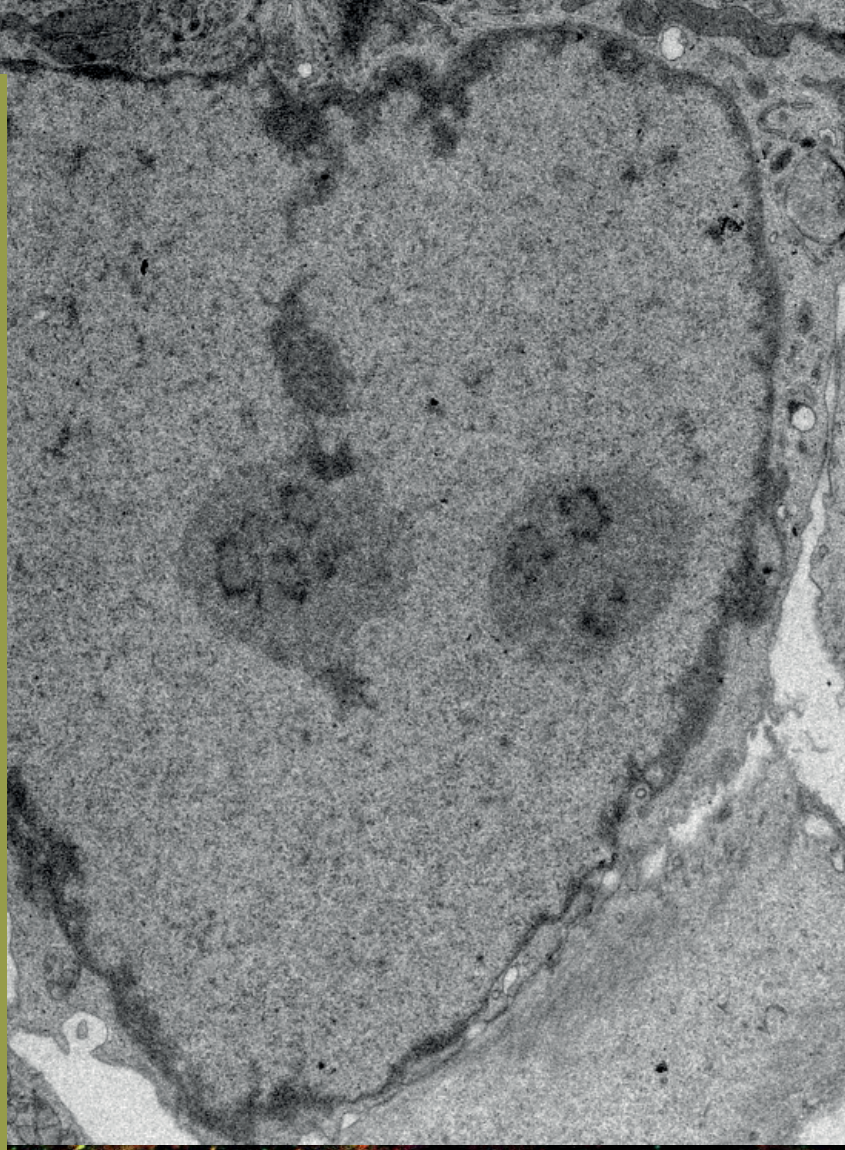
The department also offers a BSc in Biomedical Sciences and BSc in Sport Science and Motor Control. In addition, two 1.5-year Master's Degree curricula are offered: MSc in Sport Science and Motor Control, MSc in Experimental Biomedical Research. Further education at the postgraduate level is offered within «Doctoral Schools» in neurosciences and in immunology and cancer, in conjunction with the universities of Neuchâtel, Bern, Lausanne, Geneva, Southern Switzerland and Basel. At the Bachelor level, French and German are the official languages, while in the Master program the official language is English.

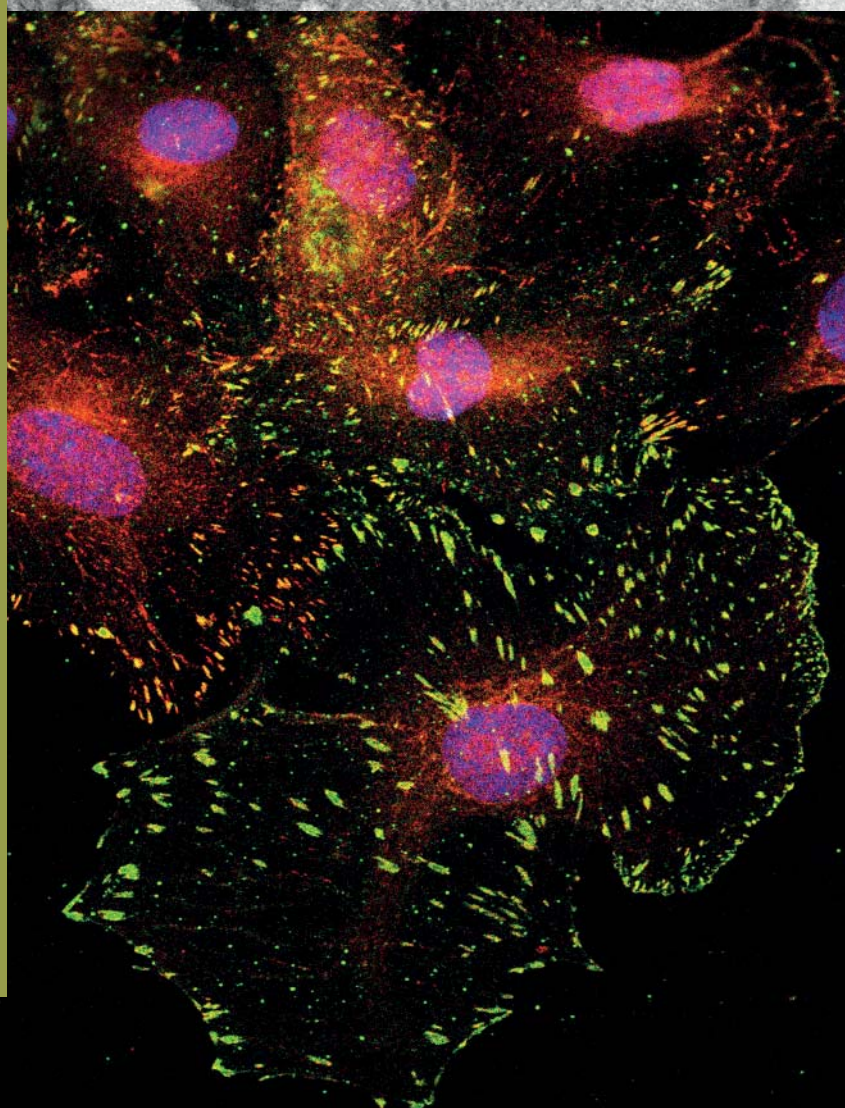
In behalf of all members of the Department of Medicine, I wish you interesting reading in the different fields of medical science and research.

Professor Jean-Marie Annoni
President

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

Cancer, Microbiology and Immunology are research areas highly related from the point of view of pathogenesis, host response and resistance. The research groups working on cancer develop an immunopharmacological approach aimed to enhance the antitumor immune response, and they focus on the study of the microenvironment that may promote the tumor progression. In immunology, topics of interest include the normal immunology of body fluids (breast milk) and the immunological response to viral infections such as that against the Japanese encephalitis virus. A hot area of current medical research is the emerging antibiotic resistance of clinically relevant bacteria analyzed from genetic and biochemical aspects. Several groups focus their research on the development of novel rapid diagnostic tests and novel molecules that may contribute to an early recognition of cancer or infections and optimize their treatment. It can be said therefore that the research groups of the cluster Cancer, Microbiology and Immunology are engaged at the forefront of fundamental and translational medical research.





Carole Bourquin
Immunopharmacology of cancer

Luis Filgueira
Cell biology, immunology, clinical anatomy and educational research

Patrice Nordmann
Emerging antibiotic resistance in bacteria

Curzio Rüegg
Experimental and translational oncology

Albert Santamaria
Cancer stem cells and metastasis

Carole Bourquin
Chair of Pharmacology

Immunopharmacology of cancer

INTRODUCTION

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

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

Fig.1 - Molecular and cellular studies are essential for the rational design of immunotherapy protocols in patients

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The importance of timing for effective immune treatment

We have previously shown that repeated administration of ligands for TLR7 can lead to immune unresponsiveness and low efficacy of cancer therapy (Bourquin et al., Cancer Research 2011). Based on an extensive analysis of molecular signaling pathways, we have developed a sequential treatment of RLR and TLR agonists that prevents unresponsiveness to immune stimulation and leads instead to enhanced immune responses (Hotz et al., J. Immunology 2015). We show that the appropriate sequence and interval between applications is essential for efficacy. We have also elucidated the molecular mechanisms responsible for the time-dependent effect. Using this stimulation sequence, we obtained for the first time a strong CD8 T-cell response that can block cancer progression. We thus contribute to the rational design of immunotherapy protocols, based on molecular and cellular studies, to improve the efficacy of cancer treatments.

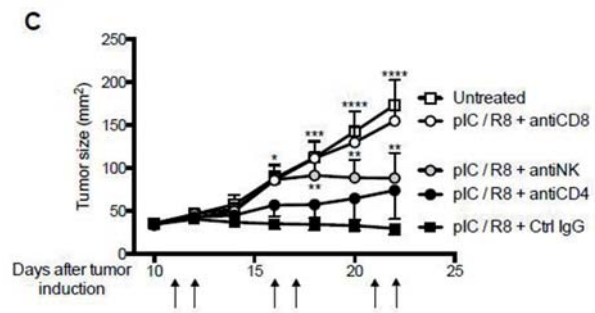


Fig.2 - The outcome of sequential RLR/TLR therapy is CD8 T-cell and NK cell-dependent. *Combination treatment with the RLR and TLR activators pIC and R8 effectively blocks cancer progression. The thera-peutic effect is abolished when CD8 T cells are depleted. (Oncoimmunology, in press)*

Drug delivery systems for cancer immunotherapy

The application of pharmacological agents for cancer immunotherapy faces several challenges: the immune-activating drugs must be delivered either at the tumor site or at the site of induction of an immune response but must not lead to a generalized immune activation. They must be protected against degradation and, as we have shown, timing and sequence of release must be tightly controlled. We have initiated several collaborations within the University of Fribourg as well as with the EPFL and the Ludwig-Maximilian University of Munich to test different types of nanoparticles and their use as vehicles for drug delivery. Our laboratory participates in the NCCR Bio-inspired Materials centered at the Adolf-Merkle Institute in Fribourg. Within this interdisciplinary network we are currently studying drug delivery in cancer immunotherapy by stimuli-responsive materials. ■

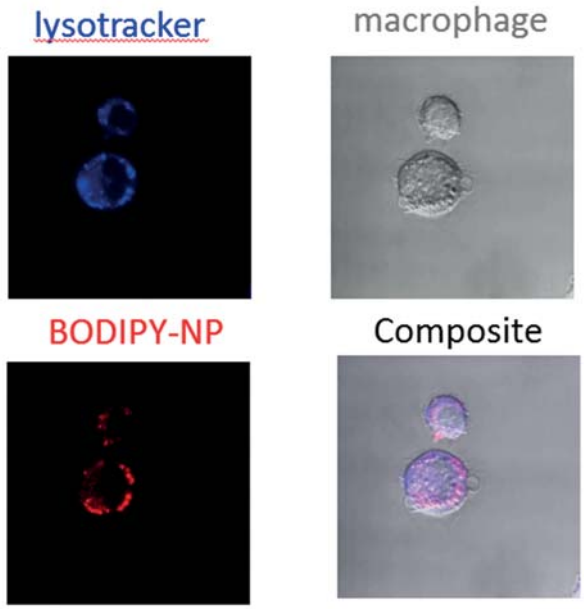


Fig.3 - Red-labeled nanoparticles are taken up by macro-phages. *Blue: endosomal marker; red: nanoparticles (I. Mottas, 2016)*

Selected Publications

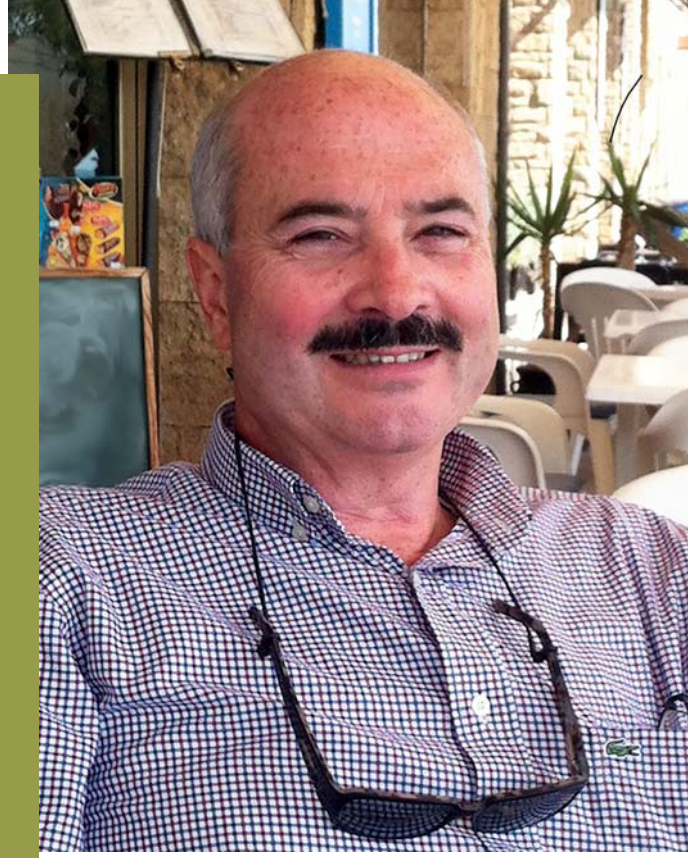
Heidegger S, Gößl D, Schmidt A, Niedermayer S, Argyo C, Endres S, Bein T, ***Bourquin C***
Immune response to functionalized mesoporous silica nanoparticles for targeted drug delivery. Nanoscale, 2016, 8:938-48 (JIF 7.8)

Anz D, Rapp M, Eiber S, Koelzer VH, Thaler R, Haubner S, Knott M, Nagel S, Golic M, Wiedemann GM, Bauernfeind F, Wurzenberger C, Hornung V, Scholz C, Mayr D, Rothenfusser S, Endres S, ***Bourquin C***
Suppression of Intratumoral CCL22 by Type I Interferon Inhibits Migration of Regulatory T Cells and Blocks Cancer Progression. Cancer Res, 2015, 75:4483-93 (JIF 9.3)

Hotz C, Roetzer LC, Huber T, Sailer A, Oberson A, Treinies M, Heidegger S, Herbst T, Endres S, ***Bourquin C***
TLR and RLR Signaling Are Reprogrammed in Opposite Directions after Detection of Viral Infection. J Immunol, 2015, 195:4387-95 (JIF 5.4)

Luis Filgueira
Chair of Anatomy

Cell biology, immunology, clinical anatomy and educational research



INTRODUCTION

The areas of research interest of Luis Filgueira have been cell biology, immunology, clinical anatomy and educational research, addressing various topics. The following report shall focus on 4 research topics that have been addressed during the reporting period.

The first topic covers clinical anatomy. Supported by Dr Yotovski, various projects are ongoing in collaboration with orthopaedic surgeons, including Dr K. Grob (St Gallen and University of Western Australia). Most importantly, numerous clinical courses for further education in various medical professions are also hosted.

The second topic covers immune and stem cells derived from human breastmilk (Küffer and Kharoubi Hess), which is done in collaboration with the Lactation Research Group at the University of Western Australia.

The third topic covers infectious immunology, where various models are applied, including Japanese encephalitis virus and microglia (Dr Lannes), various bacterial models (Dr Walch and Lopez) and Malaria (Dr Walch, Dr Mantel, Mbagwu and Kehinde).

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

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Topic 1 - New discoveries in gross anatomy

New approaches in medical imaging and surgical treatment of the skeletal system require verification and discovery of new concepts in clinical anatomy. Here, we report on the outcome of just one of several successful projects that has investigated the anatomy of the quadriceps muscle and its tendon from a clinical perspective, and which has been completed and published (***Fig.1***, Grob et al. Clin Anat, 2016, Grob et al. J Exp Orthop 2016).

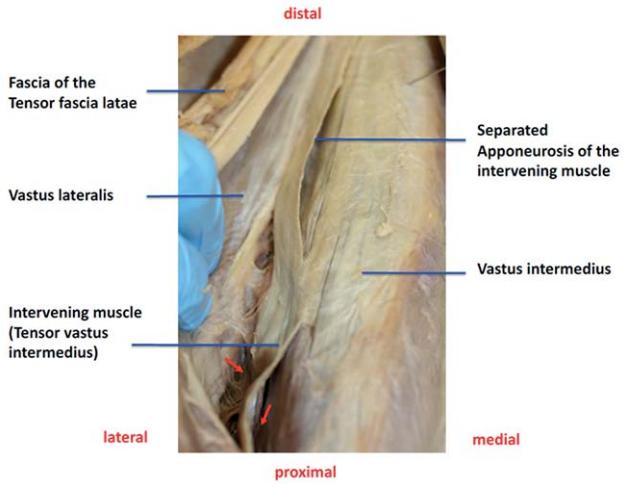

Fig.1 - Exposure by dissection of the newly discovered portion of the human quadriceps muscle *(Intervening muscle: Tensor vastus intermedius), which is relevant under certain clinical conditions, including rehabilitation (Grob et al. Clin Anat, 2016)*

Topic 2 - Immune cells in human breastmilk

We have previously discovered that human breastmilk may contain various types of immune cells (Hassiotou et al. Clin Transl Immunol 2013). During the reporting period, the immune cells and their function has been further investigated (Küffer) confirming that the presence of immune cells in breastmilk depends significantly on the wellbeing of mother and/or child. In addition, we have now discovered that breastmilk immune cells also contain cytotoxic immune proteins, including granzymes, granulysin and perforin. Their role in health and disease of the lactating breast and the baby will be further investigated.

Topic 3 - Infectious Immunology

We have established various infectious models, where the interaction between the immune system and the microbes is investigated at molecular, cellular and systemic level using in vitro human and in vivo mouse models.
For this report, we focus on the proposed entry of Japanese encephalitis virus (JEV) into the brain (***Fig.2***). In that respect, it is important to realise that JEV is transmitted by mosquitos and infects and reproduces in monocytes, dendritic cells, microvascular endothelial cells, microglia, astrocytes and most importantly neurons. The focus of this project has been to further investigate the inflammatory response of JEV-infected microglia. The project will expand into investigating the mechanisms of how JEV gets into the brain, and infects and induces inflammatory responses in various cell types of the brain (Lannes et al. Virol J 2017). ▸▸

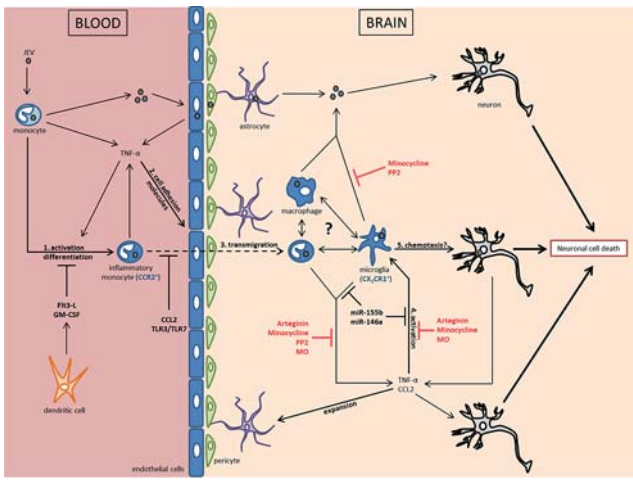

Fig.2 - Proposed entry of Japanese encephalitis virus from the blood circulation through the blood-brain barrier into the brain (Dr Lannes, submitted for publication). *Of note is the fact that JEV infects blood monocytes, dendritic cells, as well as endothelial cells of the microcirculation, a prerequisite for transmission through the blood-brain barrier.*

Topic 4: Educational research in medical and biomedical teaching

We have explored and evaluated new teaching approaches in tertiary anatomy and biomedical teaching, in collaboration with academic members of the University of Western Australia and the University of Basel (Dr E. Eppler). There have been various educational projects that have explored new teaching and learning methods and have been completed and submitted for publication, including a project where feasibility, student satisfaction and enhanced anatomy learning through body painting, ultrasound and clinical investigation have been investigated (***Fig.3***). ■

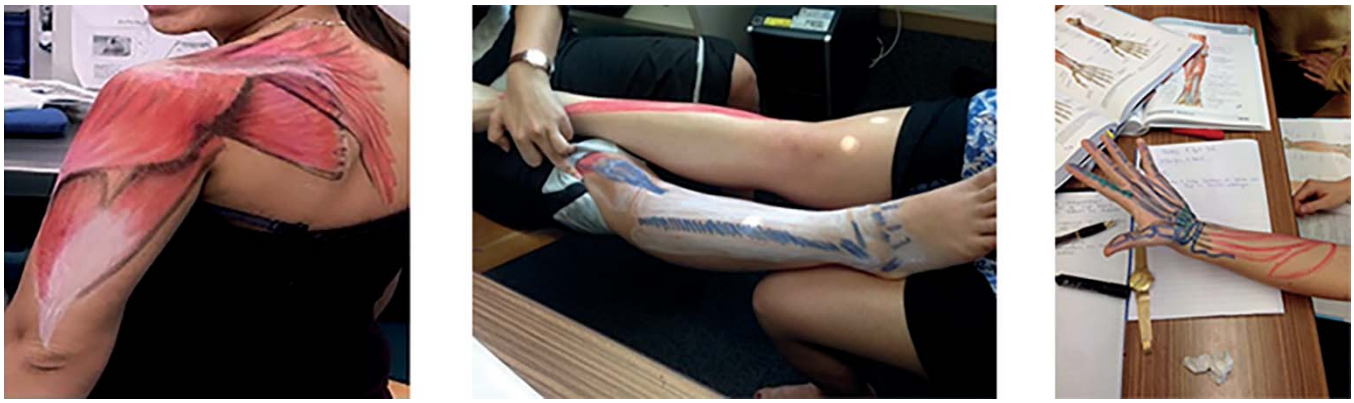

Fig.3 - Examples of body painting done by medical students to explore surface anatomy. *This exercise was part of a new course and an educational research project that has been scientifically evaluated and presented at various conferences and will soon be submitted for publication.*

Selected Publications

Grob K, Manestar M, ***Filgueira L****, Ackland T, Gilbey H, Kuster MS*
New insight in the architecture of the quadriceps tendon. J Exp Orthop, Dec, 2016, 3(1):32

Mantel PY, Hjelmqvist D, Walch M, Kharoubi-Hess S, Nilsson S, Ravel D, Ribeiro M, Grüring C, Ma S, Padmanabhan P, Trachtenberg A, Ankarklev J, Brancucci NM, Huttenhower C, Duraisingh MT, Ghiran I, Kuo WP, ***Filgueira L****, Martinelli R, Marti M*
Infected erythrocyte-derived extracellular vesicles alter vascular function via regulatory Ago2-miRNA complexes in malaria. Nat Commun, Oct 10, 2016, 7:12727. doi: 10.1038/ncomms12727

Grob K, Ackland T, Kuster MS, Manestar M, ***Filgueira L***
A newly discovered muscle: The tensor of the vastus intermedius. Clin Anat, Mar, 2016, 29(2):256-63. doi: 10.1002/ca.22680

Patrice Nordmann
Chair of Microbiology

Emerging antibiotic resistance in bacteria

INTRODUCTION

The rise of antibiotic resistance in human and veterinary medicine can predominately be explained by the spread of antibiotic resistance genes in the environment and their acquisition by clinically relevant micro-organisms. Those resistance genes may be transferred vertically or horizontally. Therefore, early identification of antibiotic resistance genes is becoming mandatory. This includes searching for resistance genes in the environment, including in the food chain and in animals as well as identifying resistance traits among human pathogens and bacterial species acting as the reservoirs of natural resistance genes. Multidrug resistance (MDR) in gram-negatives is currently dominated by the emergence of extended-spectrum ß-lactamase (ESBL) and carbapenemase producers, and more recently, to the last resort antibiotics, polymyxins (colistin). The MDR gram-negatives that are clinically important for human medicine are *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* for which our research focuses. The key elements to control the emergence of antibiotic resistance at the worldwide scale are as follows;

1. rapid detection of emerging antibiotic genes and surveying their spread
2. decrease antibiotic consumption that shall be targeted
3. development of novel rapid diagnostic techniques
4. development of novel antibiotic molecules

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Our research focuses on emerging antibiotic resistance from fundamental genetic/biochemical analysis of emerging antibiotic resistance genes to translational research aimed to develop novel rapid diagnostic techniques and novel antibiotics. This research includes also the identification of the spread of resistance determinants in humans, animals and in the environment. Therefore, a One-Health approach is applied to analyze the emergence of antibiotic resistances of the most clinically-significant Gram-negative bacteria, i.e. *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Collaborations have been established in many countries worldwide. In 2016, research has focused on the analysis of plasmid and chromosome-encoded polymyxin (colistin) resistance and to carbapenemase-mediated resistance.

Plasticity and identification of novel resistance genes

Polymyxins interact with the lipid A moiety of the lipopolysaccharides (LPS) of gram-negative bacteria. It is known that the chromosome-encoded resistance mechanisms involvs covalent additios of phospho-ethanolamine and 4-deoxyaminoarabinose residues to the LPS, leading to a more positively charged LPS that reduces the affinity of positively charged polymyxin molecules. At the end of November 2015, a plasmid-encoded resistance mechanism to polymyxins has been identified for the first time, corresponding to the acquisition of the phoshoethanolamine transferase MCR-1. Then, we identified in December 2015 and January 2016, the first three cases of *E. coli* producing MCR-1 from infected patients in Switzerland, one of them being the first case of multidrug resistance associating MCR-1 and the carbapenemase VIM-1. With colleagues from Zurich and France, we further identified the spread of MCR-1 in *E. coli* in calves and food. Both epidemiological surveys we performed in Lausanne and Geneva, identified a still very low level of diffusion of the MCR-1 gene in bacteremia and urinary tract infections in humans. A detailed analysis of many MCR-1 producers in particular of human origin lead to identify the variety of plasmid backbones as the source of transfer at moderate frequency of the MCR-1 gene among enterobacterial species. We identified this gene being located in a peculiar 2.6 kb cassette (***Fig.1***) that may be the source of its transposon-based mobility. We were also able to determien the reservoir of this novel

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resistance gene being related to MCR-like proteins from *Moraxella* spp. *Moraxella* are commensal bacteria of the environment and of pulmonary tracts from animal, in particular from pigs. In collaboration with US colleagues, we contribute also to characterize to the third dimensional structural analysis of the MCR-1 protein that is a metallo-enzyme with four zinc-ions in its active site.

By continuing our long term investigation of carbapenemase-mediated resistance, we identified the reservoir of the carbapenemase KPC being likely a *Chromobacterium*-like bacteria. We have also in-vitro evaluated dual carbapenem containing combinations for counteracting the effects of carbapenemase producers and further contributed to the analysis of spread of carbapenemase producers in Europe. We experimentally determined for the first time the transposition of the transposon Tn*125* carrying the blaNDM-1 in Acinetobacter baumannii. Mobilization of that gene is of special importance since this is currently one of the most important carbapenemase and *A. baumannii* acts as an intermediate reservoir in its dissemination.

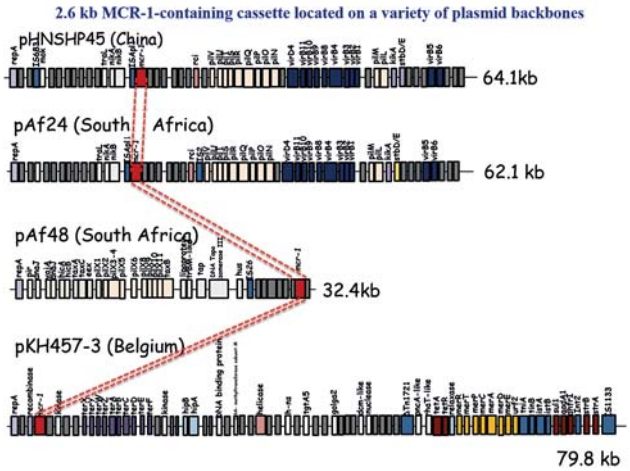


Fig.1

Rapid diagnostic tests and novel antibiotic molecules

Taking into account the importance of the emergence of colistin resistance, we have developed the rapid diagnostic test for its identification. The conventional methods for detection of colistin-resistance isolates such as broth microdilution remain time-consuming (24h to 48h) or not reliable. Therefore, the Rapid Polyxmin NP (Nordmann/Poirel) was developed based on identification of glucose metabolism related to bacterial growth in the presence of a defined concentration of colistin. The formation of acid metabolites is evidenced by a color change of a pH indicator in less than 2h (***Fig.2***). The test is rapid, specific, sensitive, usable with cultured bacteria and blood cultures. It is launched now by ELITech Microbio, being the first marketed product based on a University of Fribourg patent. In addition, we have developed a screening plate, SuperPolymyxin, that can detect growth from any liquid medium (stools, sputum...) of polymyxin resistance bacteria. It will be used for surveying the spread of those resistant bacteria in human and animal settings.

Whereas we have settled the Rapid Carba NP (detection of carbapenemase, Rapidec Carba NP test) a few months ago we have further developed industrially the Rapid ESBL NP test that is aimed to detect extended-spectrum ß-lactamase producer. This latter test is now industrialized by a German company (Senova) and was honored by the obtention of the prize of translational research by Ypsomed in 2015.

In 2016, we have contributed to the evaluation of the in-vitro activity of novel antibiotics such as the aminoglycoside plazomicin, the novel tetracycline, eravacycline, the novel siderophore-cephalosporin and further evaluated internally the antibacterial activity of inhibitors of metallo-carbapenemases such a thiol derivative. ■

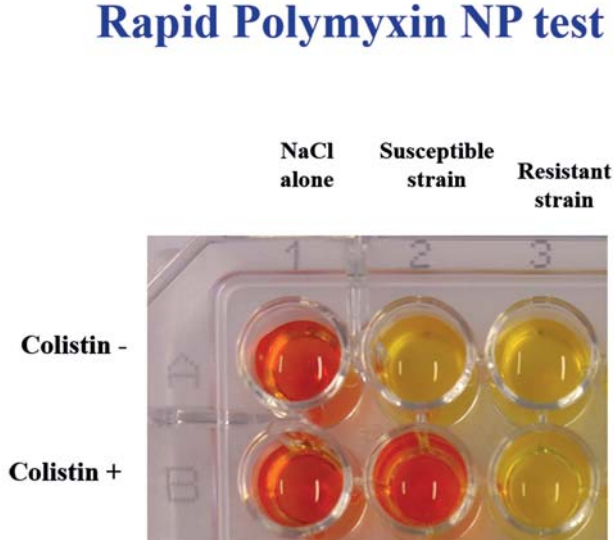


Fig.2

Selected Publications

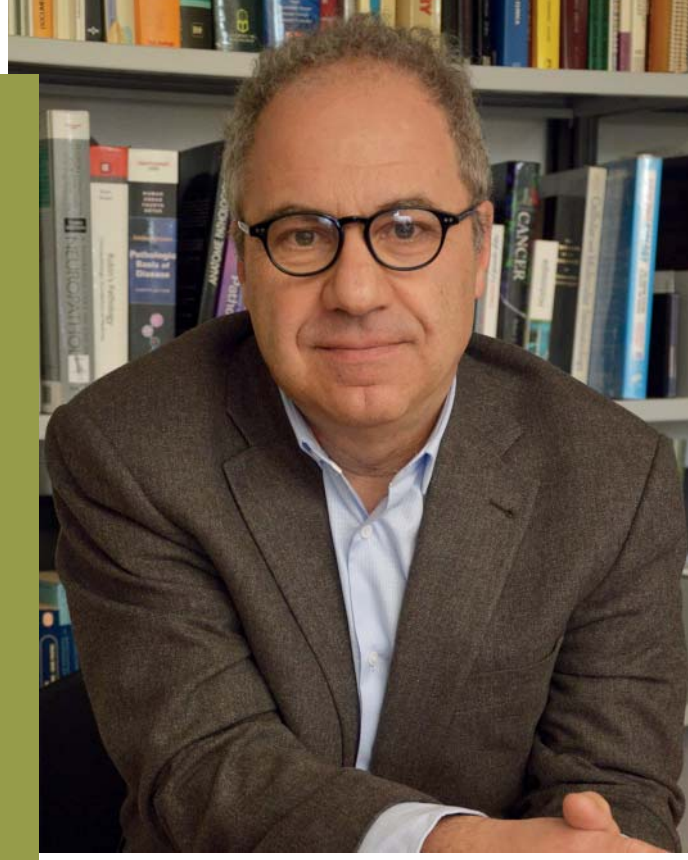
Poirel L, Kieffer N, Brink A, Coetze J, Jayol A, ***Nordmann P***
Genetic Features of MCR-1-producing colistin-resistant Escherichia coli isolates in South Africa. Antimicrob, Agents Chemother, 2016, 60: 4394-4397

Nordmann P*, Jayol A, Poirel L*
Rapid detection of polymyxin resistance in Enterobacteriaceae. Emerg Infect Dis, 2016, 22: 1031-1036

Bontron S, ***Nordmann P****, Poirel L*
Transposition of Tn125 encoding the NDM-1 carbapenemase in Acinetobacter baumannii. Antimicrob Agents Chemotherapy, 2016, 60: 7245-7251

Curzio Rüegg
Chair of Pathology

Experimental and translational oncology



INTRODUCTION

The main focus of the laboratory is the study of the interaction between the tumor and its microenvironment (tumor-host interaction). The tumor microenvironment plays an important role in promoting tumor progression. Tumor angiogenesis and immune / inflammatory cells recruited at tumor sites emerged as critical determinants of tumor progression. Our understanding of the functional relationship between the tumor microenvironment and tumor cells is still limited. This is particularly relevant for three important clinical problems:

- Tumor metastasis. Most cancer-related death are due to metastasis, yet their prevention and control remain difficult.
- Resistance to therapy. This is a major problem for most cancers and therapies.
- Early cancer detection. Early detection is associated with better survival in most cancers, yet it remains a difficult challenge to meet.

In this context, the main questions addressed in the laboratory include:

- What are the mechanisms of tumor metastasis and what is the basis of organ specificity?
- How do inflammatory cells promote tumor progression and metastasis?
- How do cancer cells and the microenvironment react and adapt to anticancer therapies?
- How can we detect and monitor cancer non-invasively?

Although our research is largely experimental, it is always inspired by clinically relevant questions. In addition, we also perform clinical studies in collaborations with clinicians. We are also collaborating with chemists, physicists, and material scientists in the NCCR bioinspired material program to devise novel strategies for cancer detection and treatment.

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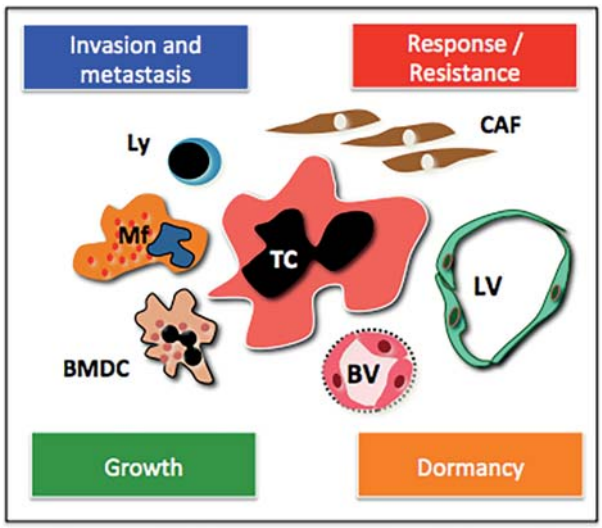

Fig.1 - Tumor host interaction. *Tumor cells growth whitin a tumor microenvironment rich in lymphocytes (Ly), Macrophages (Mf), bone marrow derived cells (BMDC) blood vessels (BV), lymphatic vessels (LV) and fibroblasts (CAF). The interaction with these cells contributes to determine tumor progression and therapy outcome.*

Antiangiogenic therapy prevents breast cancer lung metastasis by reducing angiogenesis and reversing tumor-induced immuno-suppression

Tumor angiogenesis promotes primary tumor growth and metastasis. Anti-angiogenic therapy, mostly in combination with chemotherapy is routinely used for the treatment of advanced and metastatic cancers, including breast cancer. However, therapeutic benefits are limited and transient. Mobilization of myeloid-derived suppressor cells (MDSC) have been implicated in metastasis formation and resistance to anti-angiogenic treatments. We investigated the effect of anti-angiogenic therapy on lung metastasis and immunosuppression using the 4T1 orthotopic mouse model of mammary adenocarcinoma. Teatment with the anti-VEGFR-2 antibody DC101, inhibited primary tumor growth and angiogenesis, lung metastasis and associated angiogenesis. DC101 treatment mobilized monocytic MDSC (mMDSC, $CD11b^{+}Ly6C^{high}$) and induced expression of the immune-suppressive molecule Arginase I (Arg I) in tumor-associated mMDSC, while it globally attenuated MDSC immunosuppressive activity. Treatment with the ▸▸

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Arg I inhibitor Nor-NOHA alone reduced immunosuppression and significantly inhibited lung metastasis formation without affecting primary tumor growth and angiogenesis. In combination with DC101, however, Nor-NOHA treatment did not further improve metastasis control. We conclude that VEGFR-2 inhibition reverses tumor-induced immunosuppression in spite of inducing increase accumulation of mMDSC and Arg I expression. Inhibition of Arg I alone has anti-metastatic effect consistent with a role of T cells in controlling metastasis. When used in combination, this effect is overrun by the dominant anti-metastatic activity of DC101. These observations have potentially clinically relevant implications for the prevention and treatment of metastasis. They also suggest that the combination of anti-angiogenic with immunostimulating agents (ie check point inhibitors) may have clinical benefits.

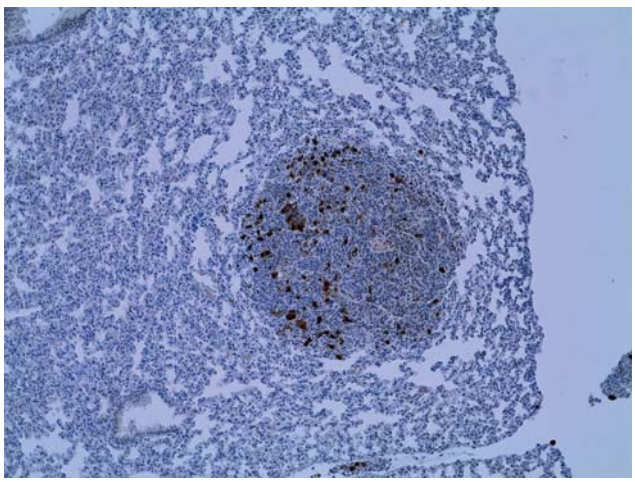

Fig.2 - Expression of Arginase I in lung metastasis. *Expression is restricted to CD11b⁺ cells infiltrating metastatic nodules.*

Anti-angiogenic therapy with Bevacizumab decreases circulating KIT⁺CD11b⁺ cells and IL-10 in metastatic breast cancer patients

Bevacizumab, anti-VEGF-blocking antibody (Avastin™), is currently used in patients with metastatic cancers as anti-angiogenic agent. Whether it exerts its anti-tumor effects beyond local inhibition of angiogenesis, and how these effects can be monitored in patients, remains largely elusive. To address these questions, we investigated myelo-monocytic cells and cytokines in the peripheral blood of metastatic breast cancer patients undergoing therapy with bevacizumab. Circulating endothelial cells (CEC), endothelial progenitor (CEP) and CD11b⁺ cells before and during therapy with chemotherapy alone or in combination with bevacizumab were characterized using flow cytometry, real time PCR and RNASeq. Aged-matched healthy donors were used as baseline controls. Breast cancer patients had elevated frequencies of CEC, CEP, TIE2⁺CD11b⁺ and KIT⁺CD11b⁺ cell subsets. Of those cells, only KIT⁺CD11b⁺ cells decreased in response to bevacizumab. Cancer patients expressed higher mRNA levels of the M2 polarization markers CD163, ARG1 and IL-10 in CD11b⁺ cells and increased levels of the M2 cytokines IL-10 and CCL20 in plasma. Therapy with bevacizumab, significantly decreased IL-10 mRNA in CD11b⁺ cells and IL-10 protein in plasma. This pilot study provides evidence of systemic immunomodulatory effects of bevacizumab and identified circulating KIT⁺CD11b⁺ cells and IL-10 as candidate biomarkers of bevacizumab activity in metastatic breast cancer patients. A follow up study is planned. It also validates some of the results observed in the above preclinical study.

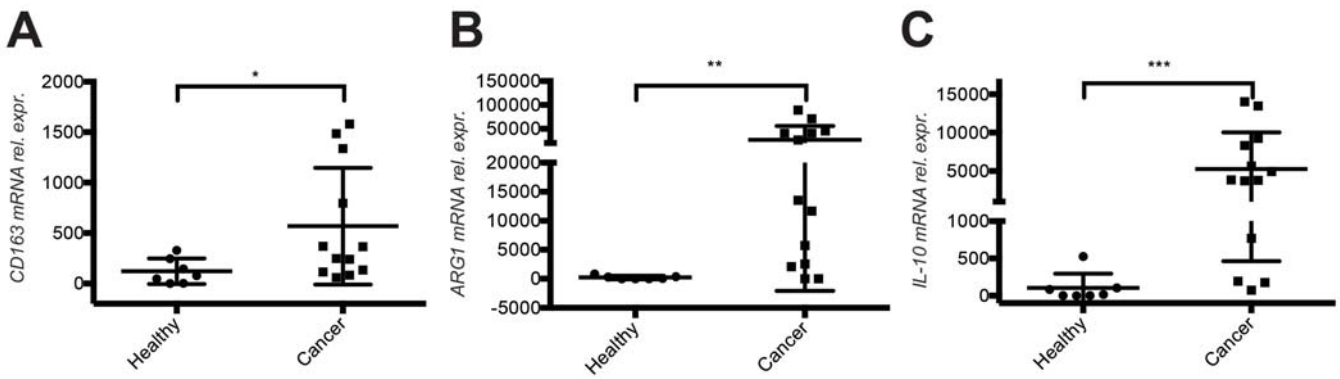

Fig.3 - Circulating CD11b⁺ monocytes in cancer patients have a M2 polarization phenotype. *CD11b⁺ cells were isolated from the blood of healthy donors and cancer patients and mRNA expression for the M2 markers CD163 (**A**), ARG1 (**B**) and IL-10 (**C**) in CD11b⁺ cells analyzed by qPCR.*

The matricellular protein CYR61 promotes breast cancer lung metastasis by facilitating tumor cell extravasation and suppressing anoikis

Matricellular proteins play multiple roles in tumor growth, invasion and angiogenesis, while their contribution to metastasis and the putative mechanisms involved are less well characterized. In ER-negative human breast cancer, elevated expression levels of the matricellular protein Cysteine-rich angiogenic inducer 61 (CYR61) are associated with more aggressive progression. We investigated the role of CYR61 in breast cancer lung metastasis using the triple negative human breast cancer cell lines MDA-MB-231 and SUM159. Silencing of CYR61 significantly decreased lung metastasis from tumors orthotopically implanted in mammary tissue and upon tail vein injection. CYR61 silencing impaired cancer cell extravasation to the lung during, but only during, the first 24 hours after tail vein injection. *In vitro* experiments revealed that CYR61 promotes cancer cell transendothelial migration and motility and promoted cancer cell resistance to anoikis. CYR61-dependent cell survival under non-adhesive conditions relied, at least partially, on β_1 integrin ligation by cell surface-associated CYR61 and AMPKα signaling. Our data provide the first evidence that CYR61 promotes breast cancer lung metastasis by facilitating tumor cell extravasation and protecting from anoikis during initial seeding to the lung. ■

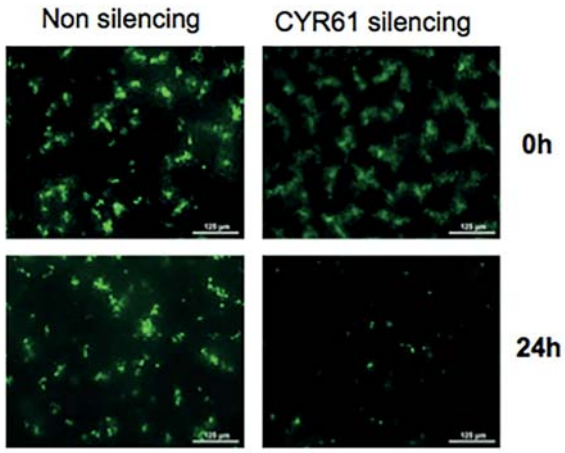

Fig.4 - CYR61 promotes early steps of lung metastasis. *Fluorescent signal from Green Cell Tracker-labeled 4T1 cancer cells imaged at the lung surface immediately (0 hour) after injection in the tail vein or 24 hours later (24h). After 24 hours there are significantly less cells with silenced CYR61 expression compared to control cells.*

Selected Publications

Cattin S, Fellay B, Pradervand S, Trojan A, Ruhstaller T, ***Rüegg C*****, Fürstenberger G**
Effects of Bevacizumab on circulating CD11b$^+$ myelomonocytic cell populations in metastatic breast cancer. Oncotarget, Mar 8, 2016, 7(10):11137-50
(* equal contribution)

Huang YT, Lan Q, Lorusso G, Duffey N, ***Rüegg C***
The matricellular protein CYR61 promotes breast cancer lung metastasis by facilitating tumor cell extravasation and suppressing anoikis. Oncotarget, Feb 7, 2017, 8(6):9200-9215.

Secondini C, Spagnuolo L, Coquoz O, Ciarloni L, Spinetti T, Botta F, Bourquin C, ***Rüegg C***
VEGFR-2 inhibition reverses immunosuppression and reduces lung metastasis in the 4T1 breast cancer model despite MDSC mobilization and Arg-1 induction. Oncoimmunology, in press

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Pathology Laboratory
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Cancer stem cells and metastasis

INTRODUCTION

Breast cancer is organized as a hierarchy in which cancer stem cells (CSC) are at the apex. It has been recently shown that CSC are not only responsible for tumor development and resistance to therapy but they are also the cell-of-origin of metastasis. Since metastasis accounts for over 90% of cancer-related deaths, understanding the mechanisms that CSC use in order to colonize secondary organs is essential to the field of cancer biology. We focus our efforts on understanding the interactions that CSC establish with their lineage, other populations of cells and the environment and how these factors affect tumor progression. Our aim is to shed some light on the current comprehension of the metastatic process and to help to improve current therapies.

Fig. 1 - Ms. Flavia Fico pulverizing a mammary gland tumor to perform chromatin immuno-precipitation.

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Cancer is a disease characterized by uncontrolled cellular proliferation and spread/invasion of other organs different from that of origin. Cancer affects most animals on Earth, including birds and reptiles; and in fact, even plants develop tumors too, although these are unable to metastasize due to the physical restrictions of the cell wall matrix. Independently of the fact that at least some cancer rates in humans have increased in modern times due to environmental conditions and life-style changes, cancer is a disease that has affected humans and their ancestors for thousands of years. Given that bigger animals have more cells, one would expect that they would present higher incidences of cancer (because it should have higher chances to suffer mutations that will eventually derive in the formation of a tumor). However, there seems to be a lack of correlation between body size and cancer incidence between species, a phenomenon known as Peto's paradox. Is cancer evolutionary conserved? Could cancer represent evolutionary failed attempts to produce new morphologic structures? There is no doubt that these and other observations rise so many interesting questions that make cancer research not only a necessary field of study, but also an extremely intriguing and exciting one.

Over the last years a great deal of experimental and clinical data has accumulated supporting the notion that many cancers are organized as their normal tissue counterparts, i.e. as a pyramidal hierarchy, with the so-called cancer stem cells (CSC) at the apex. According to the CSC hypothesis, cancer is originated from a progenitor-like cell or a transformed cell acquires stem cell characteristics. CSCs therefore are long-lived and are able to self-renew and differentiate. Furthermore, these cells are known to possess various escape and survival mechanisms. The CSC hypothesis states that it is necessary and sufficient to kill CSCs in order to eradicate a whole tumor. However, their intrinsic singularities make CSCs especially difficult to target and therefore many aspects of the model remain to be proved experimentally.

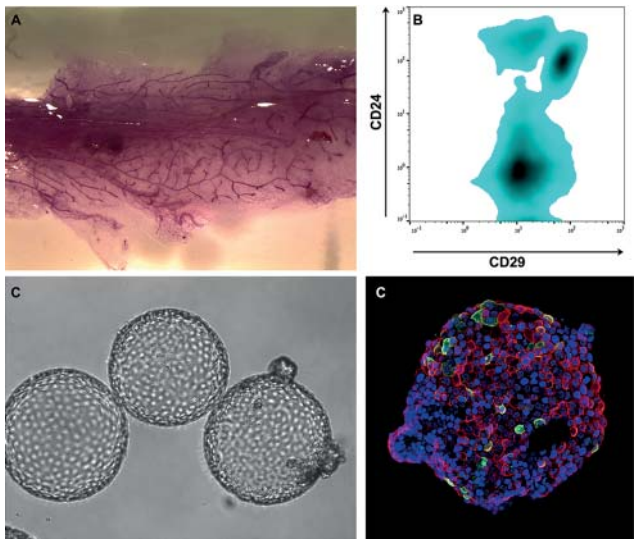


Fig.2 - Carmine aluminum staining of the mouse mammary gland showing the ducts (A). *Fluorescent Activated Cell Sorting (FACS) is a common technique to identify and collect distinct cell populations, in this case showing the typical profile used to identify subsets of mammary gland stem cells (B). Breast cancer stem cells can be grown in ultra-low attachment conditions, in which they form floating structures imaginatively called mammospheres (C). Tumor mammospheres can be stained with fluorescent conjugated antibodies to identify particular subsets of cells (D).*

Over 90% of cancer-related deaths are due to metastatic disease. Metastasis is the process through which a cell in a given tumor abandons it, enters the circulation and finally colonizes a different organ. This colonization ultimately means the destruction of the host tissue and the disruption of the organ's function. It was not until very recently that our group and others showed that CSCs are not only at the origin of primary tumors, but also at that of metastasis. In ecological terms, the arrival of a new species to a different habitat can lead to competition for the available resources. Resource exploitation or/and interference will result in a decrease of the biological fitness of one species, thus affecting its dynamics. In a tumor, competition between ▸▸

proliferating tumor cells for the same resources is fierce because the tissue is proliferating at higher rates. At some point, resources become scarce and less competitive cells start dying by apoptosis or necrosis. However, most adult somatic cells are quiescent or have very slow rates of proliferation. Therefore, while intratumor competition is intense, metastatic cancer cells will have most of the times a competitive advantage in the new site and will act as supercompetitors - provided that they are able to exploit the resources of the new environment and evade the immune system. Our group is interested in understanding the relationships between breast cancer-derived CSCs and their lineage and the interactions they establish with the surrounding microenvironment, including the immune system. We use an array of cellular and molecular biology approaches (***Fig.2***) and state-of-the-art technology to study how CSCs are able to make themselves at home in a new tissue when they metastasize. Our aim is to use this knowledge to design effective therapeutic tools to treat metastatic disease (***Fig.3***). ■

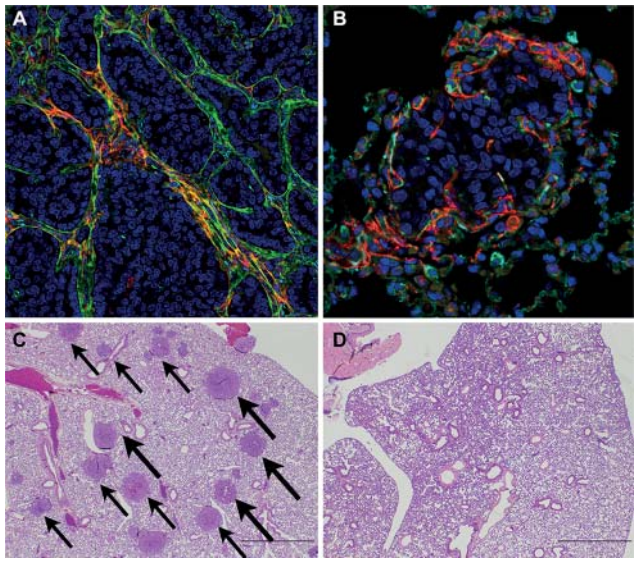
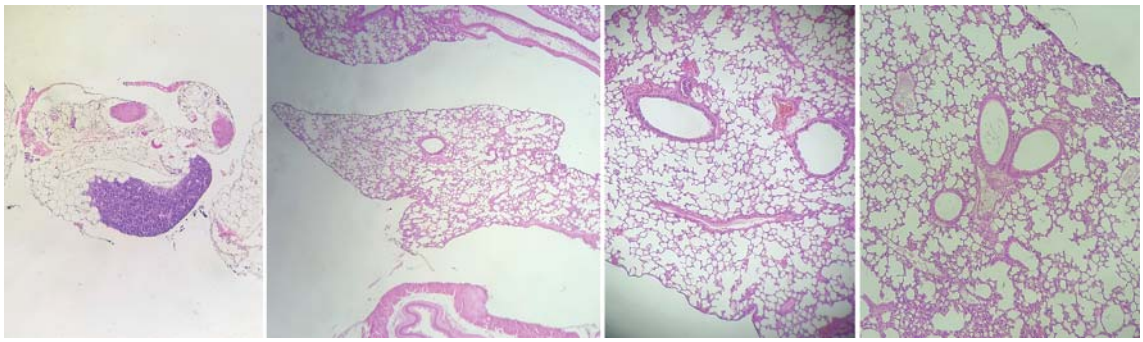


Fig.3 - Components of the extracellular matrix detected by immunofluorescent staining (red and green) are secreted by both CSCs and host tissue (cyan) in the primary tumor (A) and in metastatic colonies, where they play a crucial role (B). *We have found that small molecules that target metabolic particularities of cancer stem cells are able to completely prevent metastasis to the lungs. Cells treated with this inhibitor are unable to form metastatic colonies (D) compared to the controls (C, where arrows point metastatic foci).*

It's amazing what one can find in the microscopic world



Selected Publications

Khurana S, Schouteden S, Manesia JK, ***Santamaria-Martinez A****, Huelsken J, Lacy-Hulbert A, Verfaillie CM*
Outside-in integrin signalling regulates haematopoietic stem cells function via Periostin-Itgav axis. Nature Communications, 2016

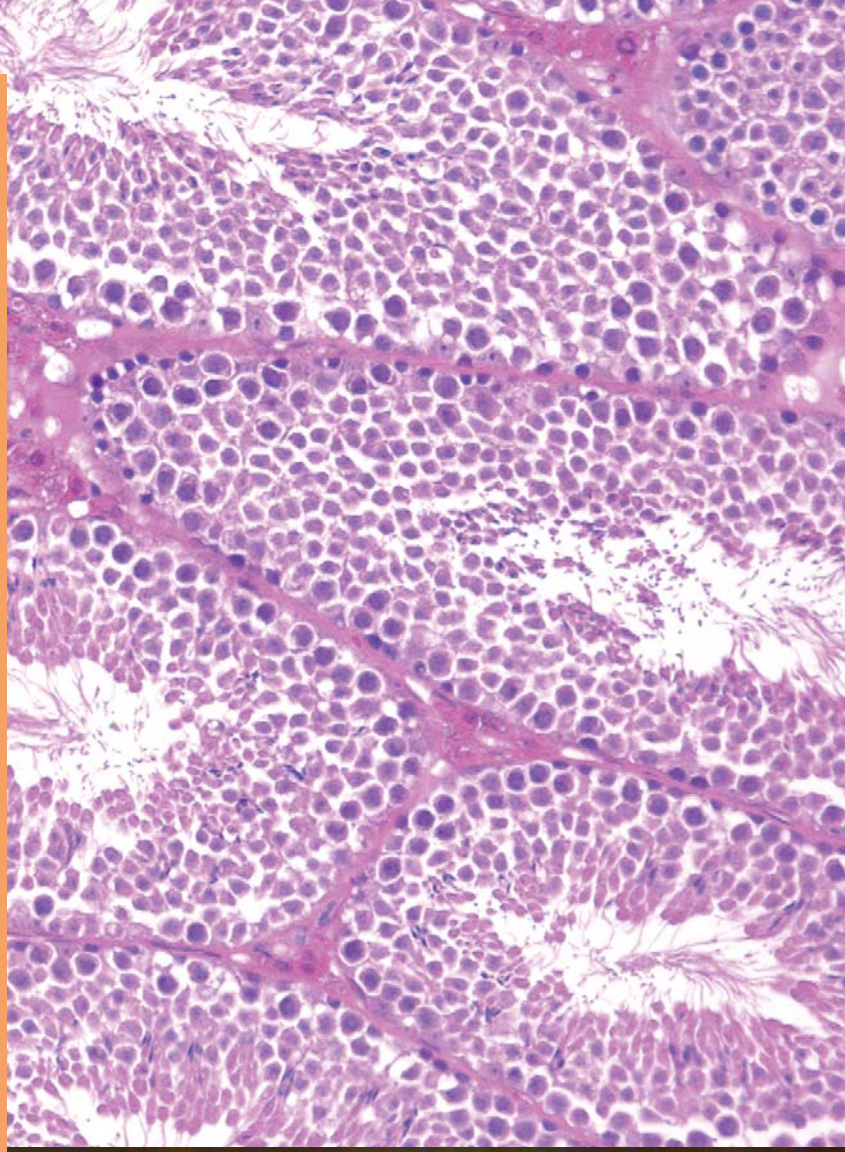
Santamaria-Martinez A*, Irmisch A, Allen EA, Huelsken J*
Therapeutic overactivation of the oxidative pentose phosphate pathway depletes breast cancer stem cells. In preparation

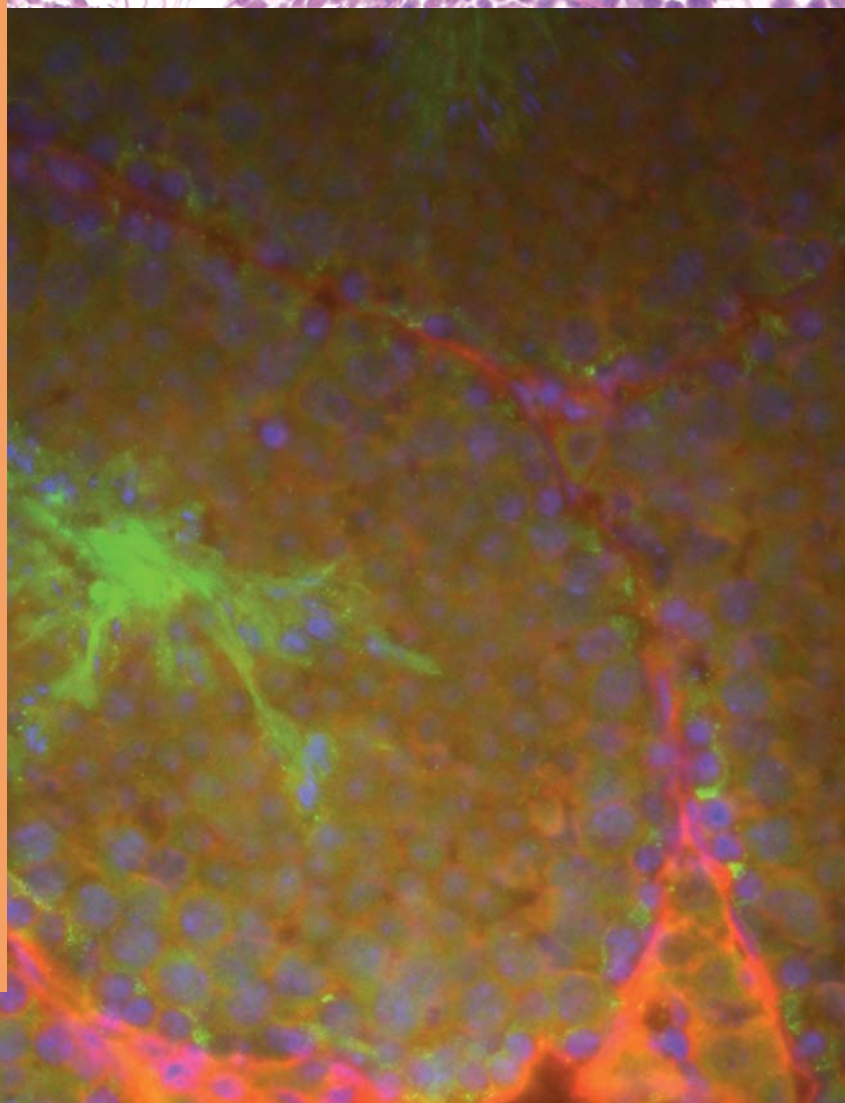
Cardiovascular, Metabolism and Endocrinology

Cardiovascular diseases, metabolic disorders, endocrine dysfunctions and kidney diseases together represent the major part of medical problems of our society. The prevalence of these diseases are increasing exponentially with aging. Many aspects including risk factors, nutritional status and pathophysiological mechanisms are common among these diseases.

The cluster «Cardiovascular, Metabolism and Endocrinology» therefore aims to understand physio-pathological and clinical therapeutic aspects of the diseases for medical and biomedical education as well as research. This cluster intends to make much effort towards vertical (from genes to whole body) and horizontal (organ-organ interactions) integration and/or translational approaches to understand biological process of human health and diseases as well as risk factors using appropriate experimental models.

The basic research on the impact of nutrition, diet, growth development and aging on cardiovascular injury and repair, metabolic diseases, hepatic and renal diseases is strengthened by the research theme on mechanisms of cellular adaptation to hypoxia and by clinical cardiovascular medicine. The research of this cluster is complemented by the research topic on endocrine hormonal factors in sexual differentiation and development.





Abdul Dulloo
Nutritional energetics and body composition regulation

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Pre-clinical cardiology

David Hoogewijs
Integrative oxygen physiology

Anna Lauber-Biason
Experimental and translational endocrinology

Jean-Pierre Montani
Cardiovascular and metabolic physiology

Zhihong Yang
Cardiovascular and aging research

Abdul G. Dulloo
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Nutritional energetics and body composition regulation

INTRODUCTION

It is well documented - from longitudinal studies of starvation and caloric restriction - that mammals are able to adapt to food scarcity by increasing the efficiency of energy utilization, i.e. by switching to a thrifty metabolism for conserving energy. There is also evidence that this thrifty metabolism persists during weight recovery upon refeeding and that the energy thus conserved is directed at accelerating specifically the recovery of the body's adipose mass rather than that of lean tissues. This preference for «catch-up fat» is viewed as a result of a feedback loop between adipose tissue and thermogenesis; it probably evolved to optimize survival capacity during an ancestral life characterized by periodic food shortage. Nowadays, it is a key factor causing higher body fat gain relative to lean tissue and is commonly observed in adults after malnutrition, weight loss cures, anorexia nervosa and cancer-cachexia. This thrifty catch-up fat phenomenon has also been linked to the hyperinsulinemic state of catch-up growth and the associated risks for later development of type 2 diabetes and cardiovascular diseases. Understanding the mechanisms of the thrifty metabolism underlying catch-up fat and how they cross-link with insulin resistance is a main focus of our research.

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During the last few years, our laboratory has been investigating whether thrifty mechanisms operate in skeletal muscle in response to caloric restriction in animals. In parallel, we have also been validating, in humans, novel approaches for phenotyping thrifty metabolic traits expressed in energy expenditure (EE) or in the resetting of the set-point for core body temperature regulation (***Fig.1***).

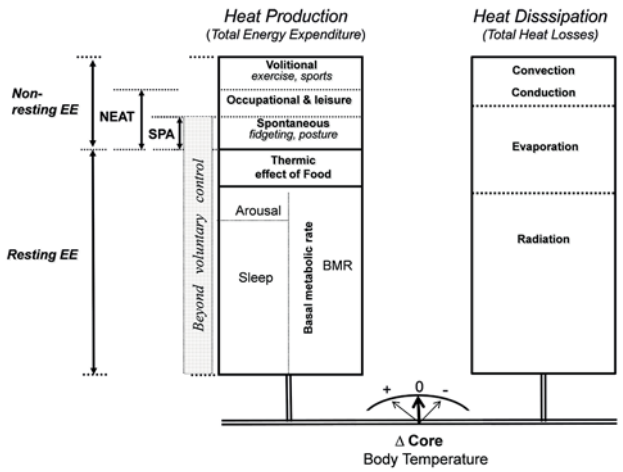

Fig.1 - The various compartments and sub-compartments of human daily energy expenditure (EE) from a perspective of thermal balance. *Note that (i) non-resting EE is divided into volitional and non-exercise-activity thermogenesis (NEAT), which in turn is subdivided into occupational/ leisure activity and spontaneous physical activity (SPA), the latter being essentially subsconscious, and (ii) the Δ core body temperature reflects the balance between total EE (heat production) and total heat dissipation (heat loss). From Dulloo and Schutz. Current Obesity Report (2015)*

Animal studies: unravelling thrifty mechanisms in skeletal muscle

Using a validated rat model of semistarvation-refeeding, we found that during caloric restriction as well as during the catch-up fat phase of refeeding, hindlimb muscles showed delayed contraction-relaxation kinetics, which correlated with increased proportion of slow at the expense of fast muscle fibers. From a molecular point of view, semistarvation-refeeding caused major changes in the muscular expression of transcription factors that control slow vs. fast fiber phenotype (namely calcineurin, PGC1-α, and FoxO1), and of the deiodinases DIO1, DIO2, and DIO3, which is in agreement with decreased availability of skeletal muscle T3, the active thyroid hormone (***Fig.2***). Collectively, altered muscle thyroid hormone metabolism, fiber type composition and contractile properties constitute mechanisms by which diminished skeletal muscle thermogenesis could contribute to energy conservation during weight loss and weight recovery, and hence contribute to the thrifty metabolism that drives catch-up fat during refeeding. Furthermore, through the use of abdominally-implanted telemetry pills (which allow continuous monitoring of core body temperature over weeks) we have found that the fall in core body temperature in response to caloric restriction persists during the catch-up fat phase of refeeding, and hence in line with the notion that a lower set point for body temperature regulation (which conserves energy) could contribute to the thrifty catch-up fat phenotype. ▸▸

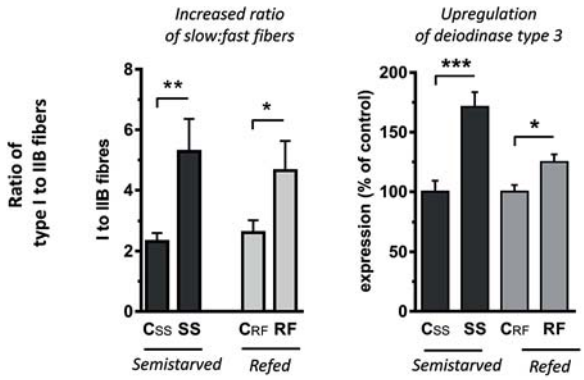

Fig.2 - Alterations in skeletal muscle fiber composition and protein expression of deiodinase type 3 (DIO3) *- in hindlimb gastrocnemius muscle of caloric-restricted, i.e. semistarved (SS), and refed (RF) rats, and their respective controls (C_{SS} and C_{RF}). *P ≤ 0.05; **P ≤ 0.01, ***P ≤ 0.001. Note that deiodinase type 3 (DIO3) upregulation leads to diminished muscle thyroid hormone (T3) availability. From Andrade et al. Frontiers in Physiology (2015)*

Human studies: novel approaches to phenotype thrifty metabolic traits

In humans, there is considerable uncertainty as to whether the thrifty metabolism operating to conserve energy operate primarily in EE at rest or in non-resting compartments of EE, and whether such thrifty metabolism can be expressed through a lower core body temperature (***Fig.1***). In line with our findings in animals for skeletal muscle to be a major site for such thrifty metabolism, in part expressed through altered energetics of contractile processes, we have developed standardized approaches to assess the specific energy cost (or efficiency) of performing low-level physical activities in untrained sedentary people (***Fig.3***). Overall, the assessment by linear regression of the energy cost of low-intensity intermittent leg press (isometric) exercise or during low power cycling (dynamic) exercise – conducted within the range of the increase in EE for low-intensity movements of everyday life – extends the capacity for metabolic phenotyping in the general population. They are performed in the seated position, hence are non-weight-bearing activities and well-tolerated. Furthermore, we have recently completed validation tests of the accuracy, repeatability and feasibility of continuous core temperature monitoring over 24 hours using ingested pill telemetry.

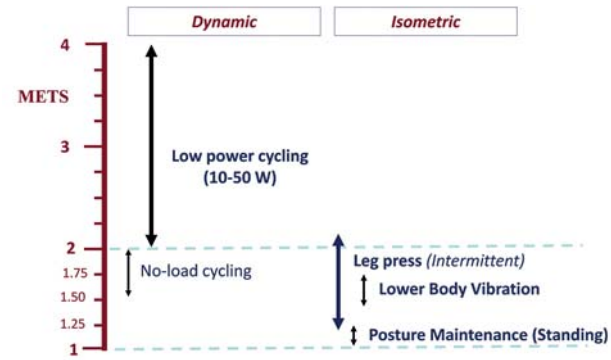

Fig.3 - Standardized tests recently developed and validated for assessing human variability in the energy cost of low-level dynamic and isometric physical activities. *For each test, the double-headed arrow indicates the range for the measured relative increases in energy expenditure, expressed in METs (i.e. fold increases above resting values) across the varying intensity of the physical activity test. From Dulloo et al. Obesity Reviews (2016)*

Perspectives

These novel approaches open up new avenues for research in human EE phenotyping and diagnosis of thrifty metabolic traits, with implications for the role of altered set point of body temperature and altered efficiency of performing low-level work (dynamic or isometric) in metabolic predisposition to fatness. ■

Selected Publications

***Dulloo AG**, Miles-Chan JL, Montani JP, Schutz Y*
Isometric thermogenesis at rest and during movement: a neglected variable in energy expenditure and obesity predisposition. Obesity Reviews, 2016, in press

***Dulloo AG**, Schutz Y*
Adaptive Thermogenesis in Resistance to Obesity Therapies: Issues in Quantifying Thrifty Energy Expenditure Phenotypes in Humans. Current Obesity Report, 2015, 4:230-40

De Andrade PB, Neff LA, Strosova MK, Arsenijevic D, Patthey-Vuadens O, Scapozza L, Montani JP, Ruegg UT, ***Dulloo AG**, Dorchies OM*
Caloric restriction induces energy-sparing alterations in skeletal muscle contraction, fiber composition and local thyroid hormone metabolism that persist during catch-up fat upon refeeding. Frontiers in Physiology, 2015, 6:254. doi: 10.3389/fphys.2015.00254

Marie-Noëlle Giraud
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Pre-clinical cardiology

INTRODUCTION

Diseases related to the heart can cause extreme health conditions and cardiovascular diseases represent the most frequent causes of death worldwide with coronary artery disease (CAD) as the main etiology. During the last decades, the identification and early treatment of risk factors, improved medical and interventional strategies lowered cardiovascular mortality and delayed the progression of chronic heart failure by reducing the left ventricular remodelling. These therapies efficiently improve the clinical outcome and the quality of life of patients suffering acute myocardial infarction (MI). Nevertheless, despite these significant technological advances, the morbidity and mortality due to the progression of heart failure is still growing.
Indeed, currently, no curative treatment exists for degenerative diseases such as MI that lead to significant loss of functional tissue and ultimately to heart failure. Therefore, patients that survived acute MI face an excessiv risk of further cardiovascular events. The urgent need for new therapies fostered the development of strategies that focus on the recovery of the cardiac structure and function.

Our pre-clinical research focuses on 3 aspects:

1. The evaluation of curative treatment and regenerative capacity of the myocardium, using stem cell and tissue engineering approaches for heart regeneration

2. New preventive approaches to limit CAD and rupture of vulnerable atherosclerotic plaque

3. New therapeutic approach for CAD

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BMS UniFR

Evaluation of curative treatment and regenerative capacity of the myocardium

Cell and matrix combination to form biological patches has gained increasing interest for the treatment of myocardial infarction. It consists of the delivery of a large number of the cells entrapped in a substrate and aims at re-vascularising and regenerating damaged cardiac tissue via the secretion of cytoprotective factors that stimulate intrinsic cardiac repair capacity. Nevertheless, the mechanism of action and insight on the emerging regenerative capacity of the myocardium are missing.

We investigated the potential of biological patches to restore cardiac function. We succeeded in stabilizing the heart function. The actual challenge is the regeneration of the myocardium. Promising results were obtained showing improvement of the myocardial contractile capacity and reduction of the fibrotic area (***Fig.1***).

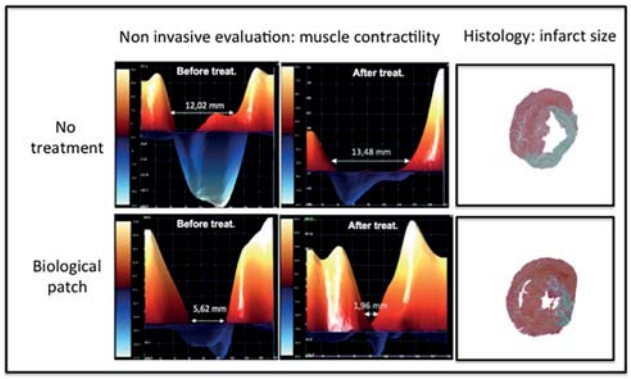

Fig.1 - We assess the efficacy of the treatment using non-invasive high resolution echocardiography and obtained imaging of the regional contractility. *Contractile muscle is represented in red and stretched muscle in blue. Non-contractile area was reduced 4 weeks after treatment administration. Histological sections of the heart corroborate this finding, showing a reduced infarct after trichromatic staining where healthy muscle is in red and fibrotic tissue in green.*

New preventive approaches for coronary diseases

We investigated in a pre-clinical study the local delivery of photodynamic therapy (PDT) to induce plaque regression (***Fig.2***). The principle relies on a photo-sensible drug after intravascular delivery and on-site activated with light induction (***Fig.3/Fig.4***) (in collaboration with Dr. G. Wagnieres, EPFL).

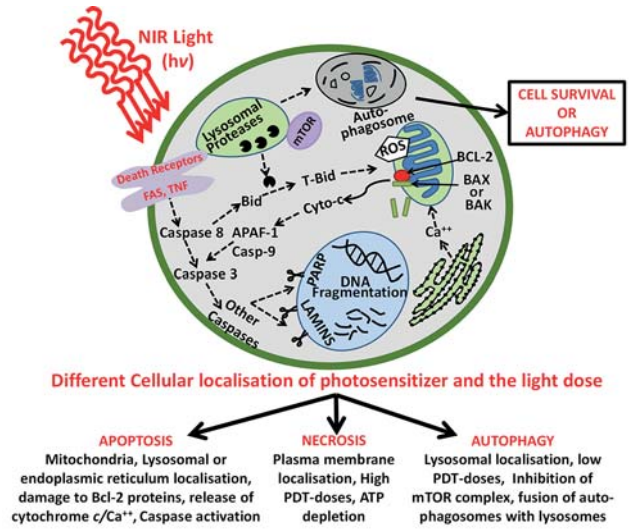

Fig.2 - Overview of the cell death pathways associated with PDT: *PDT induced cell death occurs by different pathways. (1) Mitochondrial pathway-release of cytochrome c and activation of caspases. (2) Activation of death receptors (FAS, TNF)-activates caspase-8. (3) Endoplasmic reticulum pathway- release of Ca++. (4) Lysosomal pathway-formation of autophagosome, inhibition of mTOR complex, may promote or inhibit the process of apoptosis. In addition PDT may lead to necrosis if the light dose is sufficiently high.*

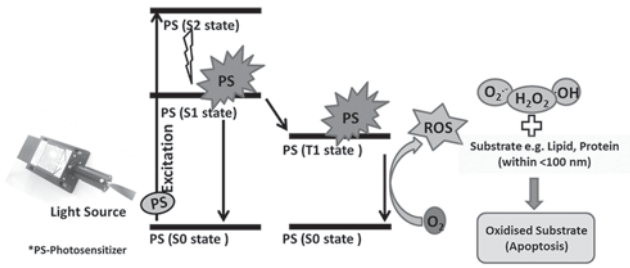

Fig.3 - Jablonski diagram of the photosensitized singlet oxygen production: *Ground state (S0) photosensitizer molecule absorbs light that excites it to the low lying (S1) or higher lying excited state (S2) which subsequently reaches the excited triplet state (T1) via intersystem crossing. Subsequently it leads to the production of reactive oxygen species (ROS) that oxidises cellular components to induce apoptosis*

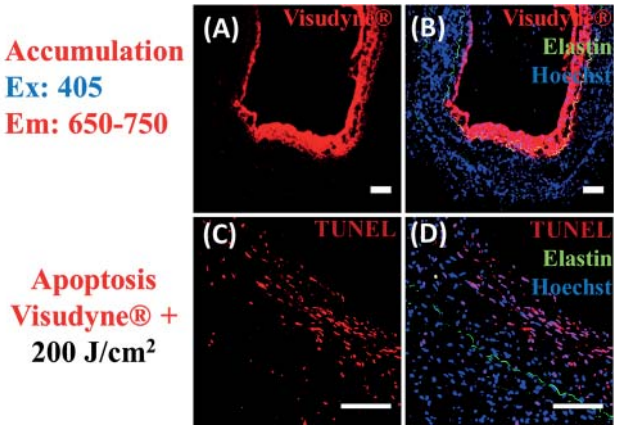

Fig.4 - Figure illustrating the (A, B) accumulation of the PS liposomal verteporfin (Visudyne®) following ex-vivo perfusion in rabbit atherosclerotic iliac artery and (C, D) Intra-arterial PDT induced apoptosis of plaque cells. Scale bar: 100 µm

In parallel, we tested the proof of concept of using Ultrafast laser pulses for atherosclerotic plaque sub-ablation. Femtolaser aims at the destruction of the necrotic and lipidic core of the plaque. The endothelium and fibrous cap will therefore be preserved while the plaques are disrupted (in collaboration with Prof. Psaltis, EPFL).

A new generation of coronary stents

Recent advances for the treatment of acute coronary syndromes focus on new non-permanent stents with increased biocompatibility, reduce side effect and allows metal-free vessel regeneration.
We are developing within a large interdisciplinary project the next generation of stents, and focus on (i) new materials and designs presenting optimal mechanical, biocompatibility and bioresorbability properties and (ii) innovative methods to foster rapid healing or re-endothelialisation of injured vessels. ■

Selected Publications

Jain M, Zellweger M, Frobert A, Valentin J, Van dem Berggh H, Wagnièers G, Cook S, ***Giraud MN***
Intra-arterial drug and light delivery for photodynamic therapy using Visudyne: implication for atherosclerotic plaque treatment. Front Physiol, Sep 12, 2016, 7:400

Giraud MN*, Borrego I*
Myocardial Tissue Engineering: a 5 year-update. Stem cells in Clinical Application vol3: Liver, Lung and heart regeneration. Editor: Phuc Van Pham, Springer, 2016, ISBN 978-3-319-46692-7

Frobert A, Valentin J, Magnin JL, Riedo E, Cook S, ***Giraud MN***
Prognostic Value of Troponin I for Infarct Size to Improve Preclinical Myocardial Infarction Small Animal Models. Front Physiol, Nov 27, 2015, 6:353

David Hoogewijs
Physiology

Integrative oxygen physiology

INTRODUCTION

The maintenance of oxygen homeostasis is an essential physiological challenge for all large animals. Reduced oxygen supply (hypoxia) induces alterations in the gene expression pattern, serving for the adaptation to the environmental conditions at the cellular, local and systemic level. Apart from physiological and pathophysiological processes, including embryonic development, high-altitude adaptation, wound healing and inflammation, the mechanisms of adaptation to hypoxia are of crucial importance for clinically relevant diseases such as anemia and cancer as well as ischemic heart disease.

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

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

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MASTER THESIS
Maarten Chantillon
Biochem Uni Duisburg-Essen, 2015

BACHELOR THESIS
Ozan Karaman
Biomed Uni Duisburg-Essen, 2016

The globin gene family

Globins are small globular metallo-proteins consisting of about 150 amino acids, which comprise eight α-helical segments in a characteristical 3-over-3 α-helical sandwich structure. This conserved «globin fold» identifies them as members of a large protein superfamily. Globins contain a heme prosthetic group, by which they can reversibly bind gaseous ligands like O_2, CO and NO. Historically, the familiar vertebrate O_2-binding hemoglobin, a tetramer of α- and β-globins, and myoglobin were among the first proteins whose sequences and structures were determined over 50 years ago. Most known globins fulfil respiratory functions, supplying the cell with adequate amounts of O_2 for aerobic energy production via the respiratory chain in the mitochondria. However, over the last two decades evidence has accrued indicating that globins exhibit additional, novel functions as enzymes, sensors and signaling molecules.

Genomic analyses have considerably altered and extended our view of the globin family in mammals, leading to the discovery of novel globin types like neuroglobin and cytoglobin, which are expressed in nerve and fibroblast-like cells, respectively. Both globin types perform yet-to-be-illuminated functions, which possibly reside in antioxidant defense, ROS signaling or even lipid metabolism. Recently, we identified a novel family of large (>1600 amino acids), chimeric proteins containing a globin-like domain and a calpain-like protease domain (Hoogewijs et al. 2012). Intriguingly, its internal globin domain is circular permuted, an unprecedented feature in the globin field (***Fig.1***). This evolutionary ancient globin type was found strongly conserved from early metazoans to humans and was named androglobin based on its preferential expression in mammalian testis tissue. Hexacoordination of the androglobin heme iron and lack of transcriptional induction in hypoxia indicates a function independent of classical O_2 supply. Androglobin expression is associated with postmeiotic stages of spermatogenesis and analysis of a newly generated androglobin-deficient mouse model suggests a crucial role in reproduction, in line with the observation of higher androglobin expression levels in spermatozoa from fertile vs. infertile males. Ongoing research, funded in 2016 by the German Research Foundation (DFG), aims at elucidating the physiological role, regulation and biomedical implications of this fifth mammalian globin type.

Additional mammalian globin studies, funded by the NCCR Kidney.CH, identified cytoglobin as implicated in chronic kidney disease. Using numerous renal cellular models we could demonstrate that cytoglobin-deficient cells display an increase in cell death and upregulation of multiple genes involved in apoptosis and redox balance, indicating an anti-oxidative role of cytoglobin in the kidney. Current investigations focus on the *in vivo* analysis of the renal role of cytoglobin employing cytoglobin-deficient mice.

The increasing availability of numerous sequenced genomes has also facilitated the identification of novel putative globins in non-mammalian organisms, ranging from bacteria to vertebrates. Recent explorations of the globin gene repertoire of for example echinoderms, marine organisms closely related to vertebrates, identified androglobin, neuroglobin and cytoglobin orthologs in these species. Molecular phylogenetic analyses indicated that the split between neuroglobins and cytoglobins occurred in the deuterostome ancestor shared by echinoderms and vertebrates (Christensen et al. 2015).

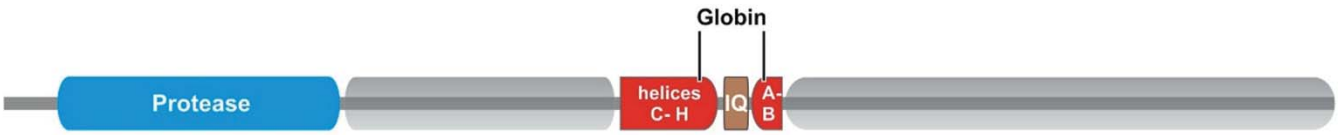

Fig.1 - The chimeric domain structure of human androglobin. *The calpain-like protease domain, the rearranged globin domain and the IQ motif are indicated (Hoogewijs et al. 2012).*

Cellular oxygen sensing

The ability of cells to sense and respond to a decrease in tissue oxygenation (hypoxia) is fundamental to multiple physiological and pathophysiological processes. Hypoxia stabilizes hypoxia-inducible factor α subunits (HIFα) which together with the constitutive HIFβ subunit form the active HIF-1 and HIF-2 transcriptions factors. HIFs induce several hundred genes following a drop in oxygen availability. While HIF-1α is ubiquitously expressed and regulates a wide variety of target genes, HIF-2α expression is more specific and its downstream functions are less well known, but include some target genes of major physiological relevance, including erythropoietin (Epo) and iron transporters. We discovered the transmembrane adaptor protein PAG1 as a novel HIF-2 target gene (Schörg et al. 2015). These studies demonstrated that a single hypoxia response element (HRE), 82 kb upstream of the PAG1 gene, is responsible for its hypoxic regulation (***Fig.2***). TALEN-mediated destruction of the distal endogenous HRE-containing genomic locus abolished the HIF-mediated hypoxic induction, indicating that this site is necessary

and sufficient for hypoxic PAG1 regulation. Chromosome conformation capture assays further confirmed the physical association between the remote PAG1 enhancer and its promoter, and indicate that the promoter-enhancer physical interaction occurs independent of the disrupted locus and HIF, confirming pre-existing longe-range chromatin looping at remote HREs.

On the level of *EPO* gene regulation the most relevant research line included the *in silico* discovery and functional validation using reporter gene and chromatin immunoprecipitation assays of a distant element ▸ regulating renal oxygen-dependent Epo transcription, which likely represents the long sought-for Epo kidney-inducible element (***Fig.3***). Additionally, we contributed to the investigations of the role of EphA2/ephrinA1 signaling in kidney repair after hypoxic injury on Epo production (Rodriguez et al. 2016), we studied the oxygen-dependent regulation of aquaporin-3 (Hoogewijs et al. 2016) and investigated hypoxia-regulated lincRNAs (Lelli et al. 2015). Finally, HIF-2 upstream investigations identified estrogen-dependent regulation of HIF-2 in breast cancer cell lines (Fuady et al. 2016). ■

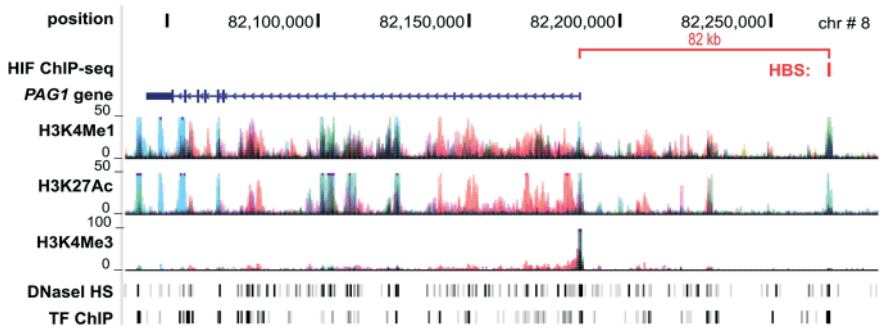

Fig.2 - Identification of a hypoxia response element 82 kb upstream of the PAG1 transcriptional start site. *UCSC Genome Browser output of the PAG1 genomic region, illustrating the location of the - 82 kb HRE. The ENCODE integrated regulation track containing H3K4Me1/3 marks, H3K27Ac marks, DNaseI hypersensitivity clusters and transcription factor ChIP-seq data are displayed (Schörg et al. 2015).*

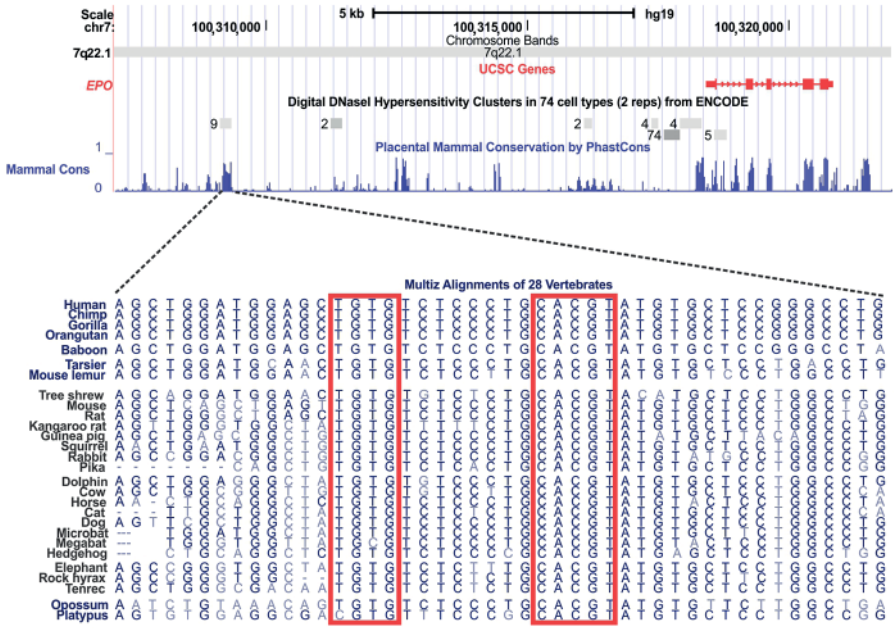

Fig.3 - A distal hypoxia response element is present in the 5' Epo regulatory region. *UCSC Genome Browser output of the Epo genomic and 5' upstream region. Shown are the ENCODE DNaseI hypersensitivity clusters and mammalian PhastCons conservation tracks with a closer view of the region in 28 vertebrates extracted using the MULTIZ whole-genome multiple alignment algorithm (Storti et al. 2014).*

Selected Publications

***Hoogewijs D**, Vogler M, Zwenger E, Krull S, Zieseniss A*
Oxygen dependent regulation of Aquaporin-3 expression. Hypoxia, 2016, 4, 91-97

*Fuady JH, Gutsche K, Santambrogio S, Varga Z, **Hoogewijs D**, Wenger RH*
Estrogen-dependent regulation of HIF-2α in invasive breast cancer cells. Oncotarget, 2016, 7, 31153-31165

*Schörg A, Santambrogio S, Platt J, Schödel J, Lindenmeyer MT, Cohen CD, Schrödter K, Mole DR, Wenger RH, **Hoogewijs D***
Destruction of a distal hypoxia response element abolishes *trans*-activation of the PAG1 gene mediated by HIF-independent chromatin looping. Nucleic Acids Res, 2015, 43, 5810-5823

*Christensen AB, Herman JL, Elphick MR, Kober KM, Janies D, Linchangco G, Semmens D, Bailly X, Vinogradov SN, **Hoogewijs D***
Phylogeny of echinoderm hemoglobins. PLoS ONE, 2015, 10: e0129668

*Wenger RH, Kurtcuoglu V, Scholz CC, Marti HH, **Hoogewijs D***
Frequently asked questions in hypoxia research. Hypoxia, 2015, 3, 35-43

Anna Lauber-Biason
Chair of Endocrinology

Experimental and translational endocrinology

INTRODUCTION

The development of the gonads is different from any other organ, as they possess the potential to differentiate into two functionally distinct organs, testes or ovaries. Sex development can be divided into two distinctive processes, «sex determination», which is the commitment of the undifferentiated gonad into either a testis or an ovary, a process that is genetically programmed in a critically timed manner and «sex differentiation», which takes place through factors produced by the gonads, once the developmental sex determination decision has been made
In humans, sex is determined by the constitution of the sex chromosomes, at the beginning of gestation (1st and 2nd week), embryos of both sexes differ only in their karyotype - males are XY and females are XX. Starting at the 3rd week of gestation, specific genes lead to the differentiation of the gonads, which in turn, produce hormones that induce anatomical and physiological differences. At 5 weeks of gestation the bipotential gonadal primordia, the genital ridges, are visible in humans.
At gestational weeks 6-7, the paramesonephric duct (Müllerian duct) develops adjacent to the mesonephric duct. If testes are to develop, they secrete testosterone; the mesonephric (Wolffian) duct enlarges and differentiates into epididymis, vas deferens and prostate. Anti-Müllerian hormone (AMH) or Müllerian inhibiting substance (MIS), a glycoprotein secreted from the Sertoli cells, results in the regression of the Müllerian ducts. If testes do not develop, the mesonephric duct does not grow and eventually degenerates, while the paramesonephric duct proliferates and the fallopian tube, uterus and the upper third of the vagina develop.
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 and from animal models. ***Fig.1*** summarises the function of such factors in humans.

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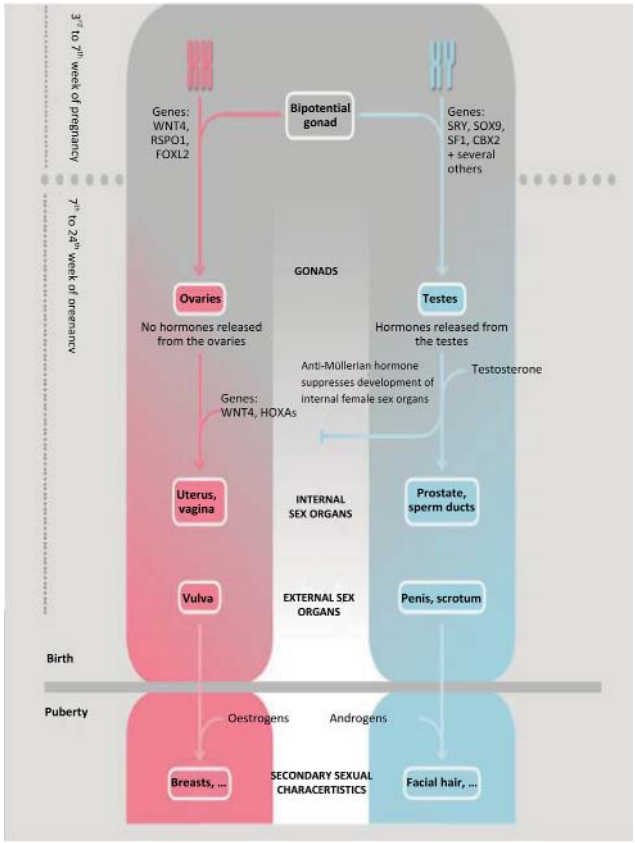

Fig.1 - Sex developmental pathways in humans

Disorders/differences of sex development (DSD)

DSD are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. DSD covers a wide spectrum of different phenotypes, with hypospadias being the most common defect with an average of 1 in 250-350 male births. In addition, 1 in 4,500 infants worldwide is born with ambiguous genitalia and DSD account for 7.5 % of all birth defects

Since the discovery of the sex-determining region Y gene (SRY) in 1990, there have been considerable advances in understanding the genetic factors involved in gonad differentiation. Nevertheless, it has been estimated that a molecular diagnosis is made in only approximately 20% of DSD cases and that up to 50% of 46,XY DSD patients can not be provided with an accurate diagnosis. Unpublished data from several research groups suggest the percentage of patients without a molecular diagnosis has decreased to approximately 70% for 46,XY gonadal dysgenesis and 10% for 46,XX testicular DSD, as more and more mutations are identified in known DSD genes (e.g., *SF1/NR5A1*). DSD represent a major medical challenge, due to the difficulty of clinical management of these complex conditions and their common sequelae of gonad cancer and infertility. The cause of these DSD conditions is most often the interruption of the complex network of gene regulation and gene expression, essential for proper development of testes or ovaries in the embryo.

Despite advances in understanding the genetic basis of human sexual determination and differentiation, in most subjects with DSD the underlying genetic cause is unknown. Whereas pathogenic mutations have been identified in DSD patients, the phenotype can be highly variable, even within families, suggesting that other factors, including genetic variants are influencing the expression of the phenotype. The identification of new genes involved in sex determination is therefore a goal of the utmost importance to the understanding of DSD and will allow for more accurate diagnosis and clinical management of these complex conditions.

Given the importance of gonadal determination for human sex development, our research has been focused on factors involved in gonadal development and the effect of their mutations in patients.

SELECTED RESEARCH RESULTS

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. Human CBX2 has two distinct isoforms (CBX2.1 and CBX2.2) that result from the different use of an alternative exon 4 and differ from each other in their C-termini. The function of the shorter isoform CBX2.2 is not well explored.

Targeted ablation of the polycomb M33, the mouse homolog human CBX2, causes 46, XY sex reversal in these animals.. Apart from their sterility, 50% of M33 knock-out Sry positive mice are phenotypically females (ovaries with follicles, uterus and normal external genitalia), placing M33 upstream of Sry in the murine sex development cascade(37). Similarly, our group made the discovery of a loss-of-function double heterozygote mutation state in a 46,XY girl with 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 CBX2.1. does not properly bind to and does not adequately regulate the expression of target genes essential for sex development, which we identified by means of DNA adenine methyltransferase and next generation sequencing in human testicular cells and analyzed the data with Pathway Studio and Gene Ontology Enrichment (such as SF1/NR5A1). Our data identified CBX2.1 as essential for normal human male gonadal development, suggested that it lies upstream of SRY in the human sex development cascade and identified a novel autosomal recessive cause of DSD. From a more mechanistic point of view, we demonstrated that CBX2 might have a role as transactivator distinct from its known function as chromatin-modifier.

We set to elucidate the role of CBX2.2, taking advantage of two distinct mutations in CBX2.2 identified with whole exome sequencing (***Fig.2***) in two unrelated 46,XY patients

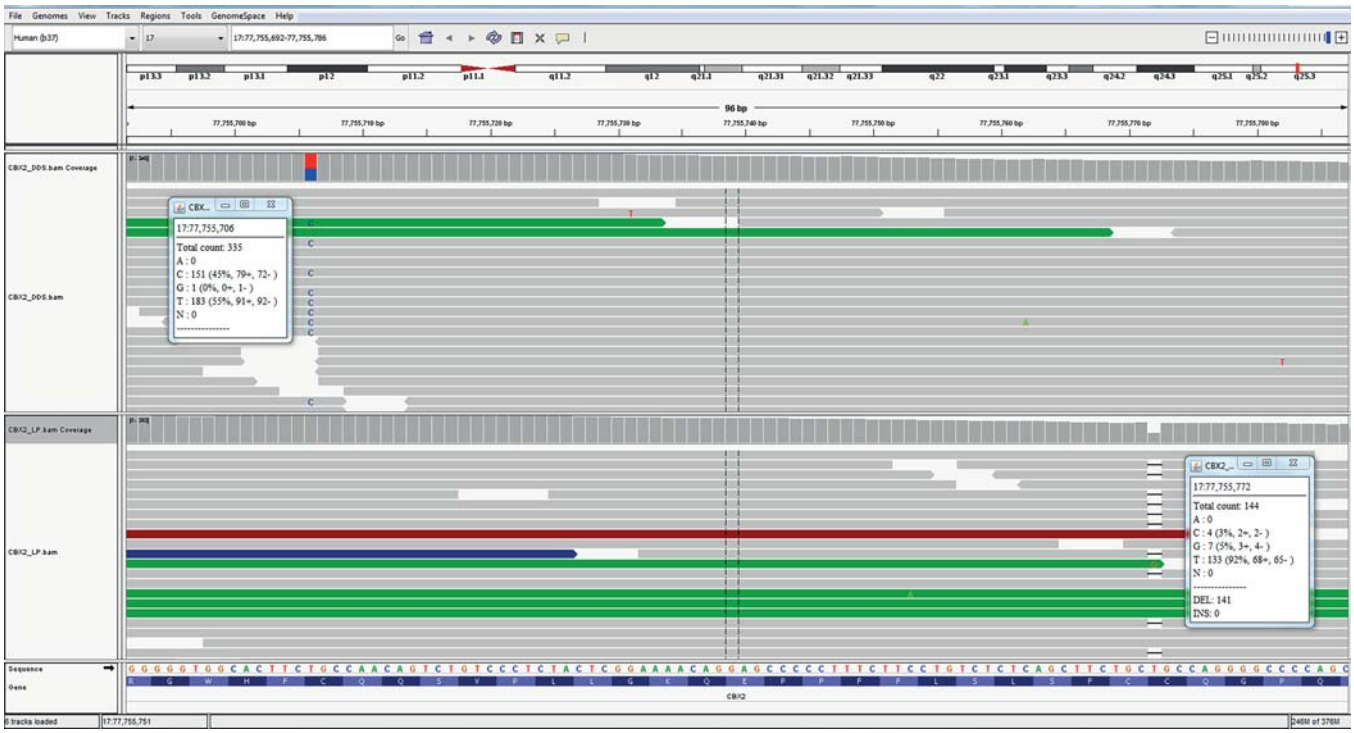

Fig.2A - Whole exome sequencing in one 46, XY DSD patient carrying a CBX2.2 mutation

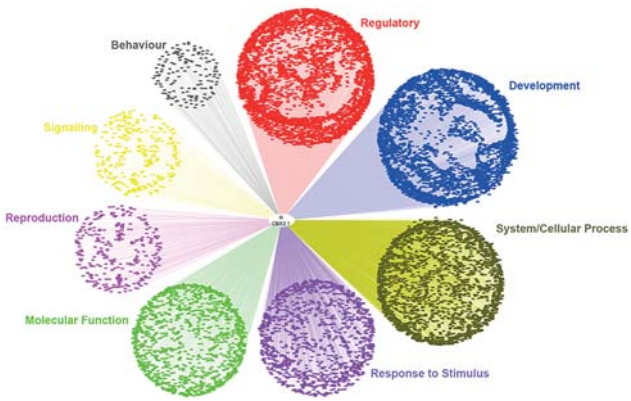

Fig.2B - Example of GO analysis of the targets of CBX2.2 (GO-enrichment: ToppCluster (FDR<0.01), Visualization: Cytoscape v3.3.0)

with female phenotype and dysgenetic testes, using DamID-Seq and RNA-seq as we did for isoform 1.

Differentiation of human induced pluripotent stem cells into functional Sertoli-like cells

Normal development of a male individual depends on the development of a functional testis. Sertoli cells (SC) are central players in the determination of the testis in its function as an endocrine (testosterone-secreting) and reproductive (germ cells-producing) organ. Thus, disorders of testicular function may have their origins in fetal or early life as a result of abnormal development or proliferation of Sertoli cells (SCs). Besides causing abnormalities of sex development, failure of Sertoli cells and inability to support spermatogenesis will result in reduced production of spermatozoa in adulthood. Reconstitution of SCs function might restore reproductive function in cases of congenital or acquired testicular insufficiency. One major hurdle in studying SCs function is that mature SCs are mitotically inactive, and primary immature SCs lose their unique characteristics during prolonged culturing. Therefore, finding an alternative source of these cells independent of donor testis cells is of utmost interest both for basic research and clinical applications.

Human induced-pluripotent stem cells (iPSCs) are developing as exciting cell sources for applications in regenerative medicine and drug discovery, primarily based on their extensive similarities to their human embryonic stem cell counterparts and shared properties of self-renewal and multilineage differentiation capabilities. iPSCs can be derived from somatic cells via ectopic expression of a number of transcription factors.

In our quest to develop an *in vitro* Sertoli cell model, we set to use iPSCs. To that end, we generated iPSCs from neonatal dermal fibroblasts (NDF) (***Fig.3***). ▸▸

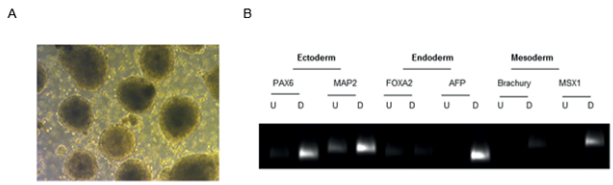

*Fig.3 - **Reprogramming of terminally differentiated skin fibroblasts into iPSC:** embryoid body formation and subsequent differentiation. (**A**) Embryoid bodies generated by allowing iPS cells to grow in ultra-low attachment plates. (**B**) The expression of different expression markers for the three germ layers detected by qRT-PCR analysis of embryoid bodies. U: undifferentiated. D: differentiated*

Molecular and functional characterizations confirmed the pluripotency of the colonies and their potential to differentiate into different germ layers. After developing and testing different differentiation protocols, we differentiated iPSCs into Sertoli-like cells (SLCs). In order to characterize the SLCs, we performed gene expression analysis which revealed that SLCs expressed Sertoli-cell markers such as SOX9, GATA4, FSHr, SF1 and AMH (***Fig.4***). Furthermore, ELISA analysis showed that SLCs secreted AMH into the cell culture medium, a hallmark of Sertoli cells.

Harnessing the power of iPSCs we were able to generate Sertoli-like cells that show genetic and functional similarity to human Sertoli cells. SLCs can be an alternative source of Sertoli cells which could be of paramount benefit for both basic research and clinical implications.

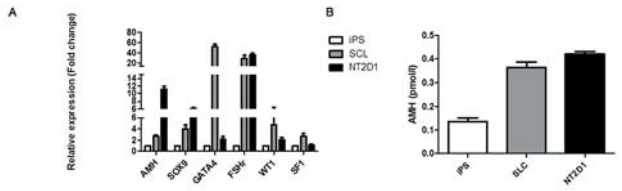

Fig.4 - Characterization of Sertoli-like cells. *(**A**) qRT-PCR analysis of the Sertoli-cell markers* AMH, SOX9, GATA4, FSHr, WT1 *and* SF1. *(**B**) Anti-müllerian hormone (AMH) levels were measured in cell culture medium using ELISA, values are presented in pmol/l. NT2D1-testicular cells were used as a positive control*

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 patients and their families, with clear benefit for the community. The recently published statement of Swiss National Advisory Board on Biomedical Ethics (NEK, http://www.bag.admin.ch/nek-cne/04229/04232/index.html?lang=de) further confirms the cultural relevance of this topic in our Country.

Taking advantage of the recently granted financial support by the SNF (Sinergia Grant) we plan to further extend our knowledge by applying whole exome sequencing to a larger cohort of DSD patients and study the role of the mutations in mice.

Also, our studies 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.

Other projects involve the characterization of a novel «alternative» androgenic pathway in humans in physiological and pathological conditions and the search for the mechanism of disease due SIRT1 mutation, chiefly related to its role in immunity and autoimmunity (e.g. diabetes). ■

Selected Publications

Eid W, Opitz L, ***Biason-Lauber A***
Genome-Wide Identification of CBX2 Targets: Insights in the Human Sex Development Network. Mol Endocrinol, 2015, 29, 247-257

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Cardiovascular and metabolic physiology

INTRODUCTION

Cardiovascular diseases are promoted by many risk factors. Our aims are to better understand the pathogenesis of some of the risks factors and how they impact on the cardiovascular system and on metabolic regulation.

In particular, our interests focus on the impact of meals (high in fat, sugar or salt) and drinks (sugary drinks, alcohol) in human studies with continuous cardiovascular and metabolic monitoring. We are particularly interested in the cardiovascular, cerebrovascular and metabolic effects of the ingestion of caffeinated soft drinks. An additional interest is related to weight cycling, and how it may impact fat distribution and cardiovascular function.

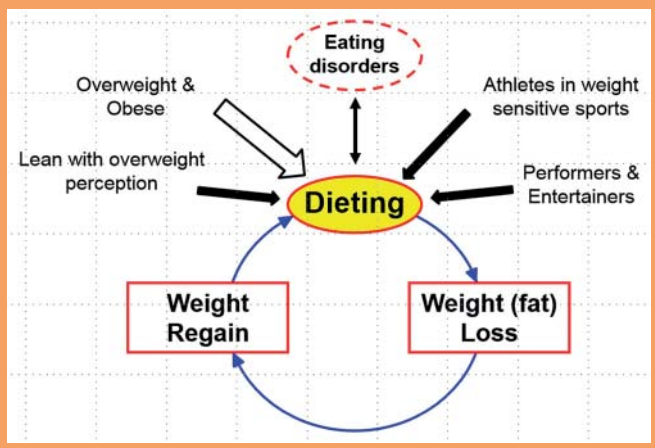

***Fig.1 - Typical population groups** that use dieting to lose weight and are at risk for weight cycling*

We also have a strong interest in the pathogenesis of postprandial and orthostatic hypotension with the concomitant intake of alcohol, particularly in elderly people, and we aim at finding countermeasures to prevent the hypotension. Finally, in a separate project funded by the NCCR, we aim to understand the mechanisms by which a primary reduction in renal function may alter lipid homeostasis and promote low-grade inflammation.

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Cardiovascular and cerebrovascular effects of energy drink consumption

We found that both T and B-lymphocyte trafficking to gut-Consumption of energy drinks is associated with an increased cardiovascular risk. In young healthy subjects, we could show that the ingestion of a single can (355 mL) of the energy drink Red Bull increased the workload of the heart and decreased cerebral blood flow velocity (CBFV). Interestingly, the decrease in CBFV was more pronounced in women than in men (***Fig.2***). Performing a mental arithmetic task imposed an additional cardiovascular load with higher absolute values of blood pressure and heart rate. Taken together, our data suggest that the acute ingestion of an energy drink leads to an unfavourable cardiovascular profile, which could affect adversely people suffering from hypertension, heart failure and cerebrovascular diseases.

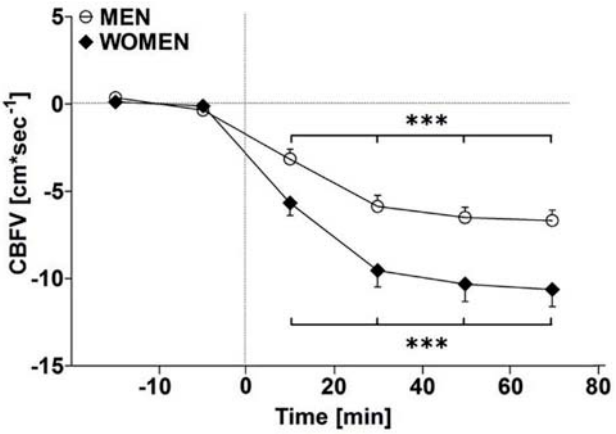


Fig.2 - Time course changes for cerebral blood flow velocity (CBFV) after ingestion of the energy drink Red Bull. *The energy drink led a greater decrease in CBFV in women (n=22) than in men (n=23).*

Mechanisms of postprandial hypotension and countermeasures to prevent it

An important consequence of ageing is the tendency for blood pressure to fall after eating a meal (postprandial hypotension), which could lead to dizziness and even syncope. In elderly individuals we could show that the prior ingestion of water before a breakfast would attenuate the decrease in blood pressure. We are currently studying, in a project funded by the SNF, the impact of concomitant alcohol intake during a festive meal.

Weight cycling: the repeated overshoot theory

Dieting and weight cycling are not limited to those who are obese or overweight, as many persons with normal body weight also attempt to lose weight. These include children and adolescents who perceive themselves as too fat, athletes in weight sensitive competitive sports and performers for whom a slim image is professionally an advantage. Our findings in experimental weight cycling have reinforced the notion that fluctuations (***Fig.3***) of cardiovascular risk variables (such as blood pressure, heart rate, sympathetic activity, blood glucose, lipids and insulin) with probable repeated overshoots above normal values during periods of weight regain, put an additional stress on the cardiovascular system.

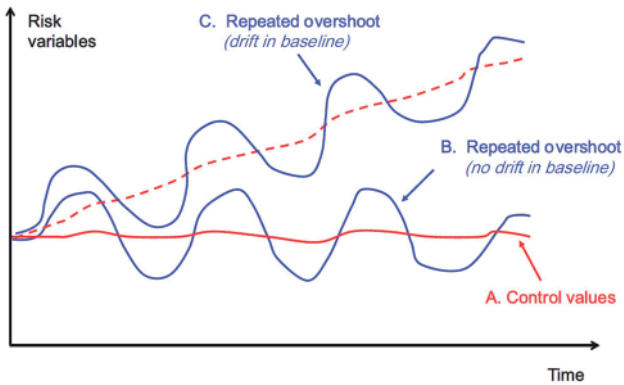


Fig.3 - Concept of repeated overshooting. *Weight cycling may lead to fluctuations of cardiovascular and renal risk variables, with repeated overshoots (B, C), even if the average values remain stable (A) or on a background of a baseline drift (C).*

Metabolic consequences of a primary decrease in renal function (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. To that purpose, we studied rats before and after UniNx, analyzing body composition, plasma and tissue levels of metabolic and inflammatory markers, several weeks after surgery.

Compared to sham-operated animals, UniNX resulted in decreased body fat due to increased lipolysis, related to mild fat sympathetic stimulation and to a low-grade inflammation with an increase of certain circulating cytokines of splenic origin.

Interestingly, the UniNX phenotype could be mimicked by unilateral renal denervation (uDNX), leading to the hypothesis that the unilateral removal of renal nerve afferents (such as after UniNx or uDNX) act on brain areas to stimulate the melanocortin 4 receptor (MC4R), which in turn may activate the sympathetic nervous system to promote lipolysis. ■

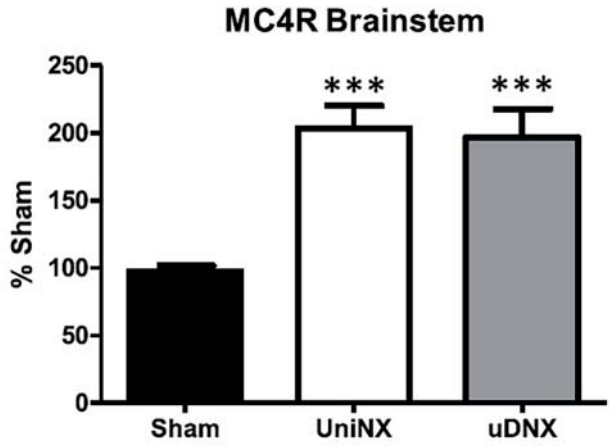


Fig.4 - Melanocortin 4 receptor (MC4R) mRNA levels in brainstem in Sham operated, UniNX, and uDNX rats. *Similar changes were seen in the hypothalamus.*

Selected Publications

Arsenijevic D, Cajot JF, Fellay B, Dulloo AG, Van Vliet BN, ***Montani JP***
Uninephrectomy-Induced Lipolysis and Low-Grade Inflammation Are Mimicked by Unilateral Renal Denervation. Frontiers in Physiology, 2016, 7:227

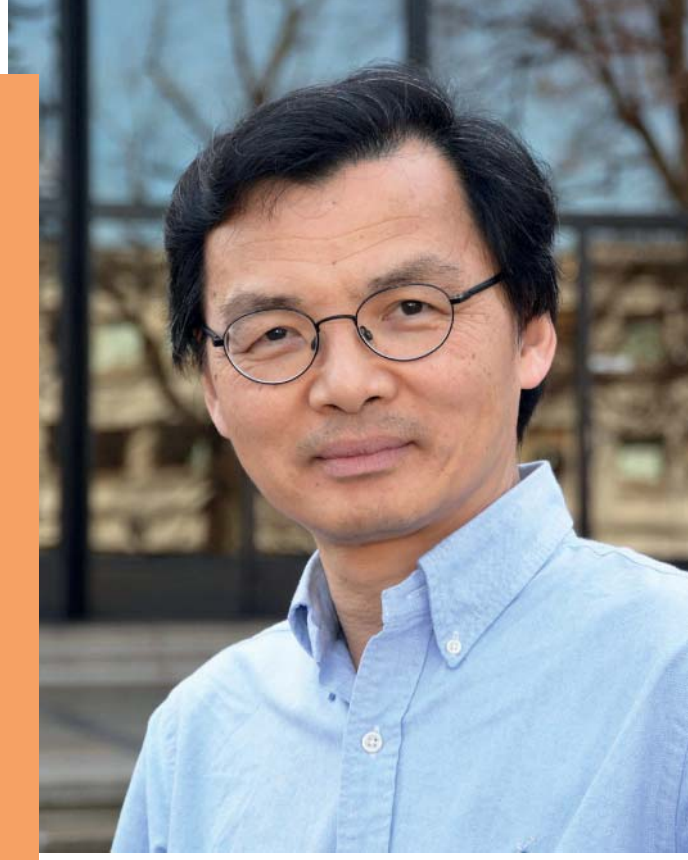
Grasser EK, Dulloo AG, ***Montani JP***
Cardiovascular and Cerebrovascular Effects in Response to Red Bull Consumption Combined with Mental Stress. American Journal of Cardiology, 2015K, 115(2):183-189

Montani JP*, Schutz Y, Dulloo AG*
Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk? Obesity Review, 2015, 16 Suppl 1:7-18

Arsenijevic D, ***Montani JP***
Uninephrectomy in rats on a fixed food intake potentiates both anorexia and circulating cytokine subsets in response to LPS. Frontiers in Immunology, 2015, 6:641

Zhihong Yang
Integrative Physiology

Cardiovascular and aging research



INTRODUCTION

Aging and age-associated diseases including cardiovascular disease, type-II diabetes, chronic kidney disease, and cancer represent the great challenge in our society, due to the global accelerating aging population. Our research work in 2015 and 2016 continues with investigating roles of the enzyme arginase-II (Arg-II) in aging-associated vascular dysfunctions and further explored the function of this enzyme in pathogenesis of vascular aging as well as obesity-associated liver and renal diseases.

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Role of p38 mitogen-activated protein kinase in vascular endothelial aging: interaction with arginase-II and S6K1 signaling pathway

p38 mitogen-activated protein kinase (p38) regulates cellular senescence and senescence-associated secretory phenotype (SASP), i.e., secretion of cytokines and/or chemokines. Previous work showed that augmented arginase-II (Arg-II) and S6K1 interact with each other to promote endothelial senescence through uncoupling of endothelial nitric oxide synthase (eNOS). In this study, we further demonstrated that eNOS-uncoupling, augmented expression/secretion of IL-6 and IL-8 in senescent human endothelial cells are mediated by a vicious interaction among Arg-II, p38mapk and S6K1. Silencing Arg-II or p38 or S6K1 in senescent cells recouples eNOS function and inhibits IL-6 and IL-8 secretion. Moreover, p38 activation and expression of IL-6 and KC (the murine IL-8 homologue) are increased in the heart and/or aortas of wild type (WT) old mice, which is abolished in mice with Arg-II gene deficiency (Arg-II$^{-/-}$). In addition, inhibition of p38 in the old WT mice recouples eNOS function and reduces IL-6 and KC expression in the aortas and heart. Thus, Arg-II, p38, and S6K1 form a positive circuit which regulates endothelial senescence and cardiovascular aging. The mechanisms are illustrated in ***Fig.1***.

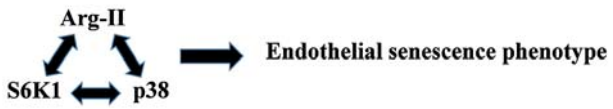

Fig.1 - A positive circuit among Arg-II, S6K1 and p38 in vascular endothelial senescence

Targeting arginase-II protects mice from high-fat-diet-induced hepatic steatosis through suppression of macrophage inflammation

Nonalcoholic fatty liver disease (NAFLD) associates with obesity and type 2 diabetes. Hypoactive AMP-activated protein kinase (AMPK), hyperactive mammalian target of rapamycin (mTOR) signaling, and macrophage-mediated inflammation are mechanistically linked to NAFLD. Studies investigating roles of arginase particularly the extrahepatic isoform arginase-II (Arg-II) in obesity-associated NAFLD showed contradictory results. Here we demonstrate that Arg-II$^{-/-}$ mice reveal decreased hepatic steatosis, macrophage infiltration, TNF-α and IL-6 as compared to the wild type (WT) littermates fed high fat diet (HFD). A higher AMPK activation (no difference in mTOR signaling), lower levels of lipogenic transcription factor SREBP-1c and activity/expression of lipogenic enzymes were observed in the Arg-II$^{-/-}$ mice liver. Moreover, release of TNF-α and IL-6 from bone marrow-derived macrophages (BMM) of Arg-II$^{-/-}$ mice is decreased as compared to WT-BMM. Conditioned medium from Arg-II$^{-/-}$-BMM exhibits weaker activity to facilitate triglyceride synthesis paralleled with lower expression of SREBP-1c and SCD-1 and higher AMPK activation in hepatocytes as compared to that from WT-BMM. These effects of BMM conditioned medium can be neutralized by neutralizing antibodies against TNF-α and IL-6. Thus, Arg-II-expressing macrophages facilitate diet-induced NAFLD through TNF-α and IL-6 in obesity (***Fig.2***). ▸▸

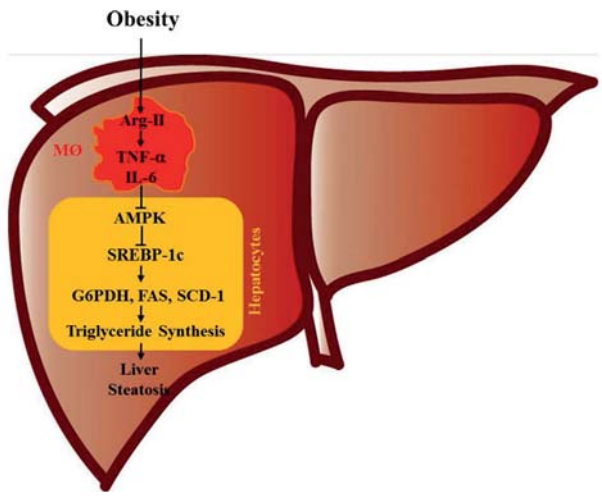

Fig.2 - Roles of hepatic infiltrating macrophages expressing Arg-II in development of obesity-associated fatty liver disease

Genetic Targeting of Arginase-II in mouse prevents renal oxidative stress and inflammation in diet-induced obesity

Using the same obesity animal model as above described, we demonstrate that Arg-II but not Arg-I is abundantly expressed in kidney and high fat diet (HFD) feeding causes frequent renal lipid accumulation, enhancement of renal reactive oxygen species (ROS) levels which could be attenuated by a NOS inhibitor, suggesting uncoupling of NOS in kidney. HFD feeding also significantly augmented renal Arg-II expression and activity. All the alterations in the kidney under HFD feeding were reduced in Arg-II$^{-/-}$ mice. Moreover, mesangial expansion and renal expression of vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in HFD-fed WT mouse are reduced in the HFD-fed Arg-II$^{-/-}$ mice, although there is no significant difference in body weight and renal weight/body weight ratio between the WT and Arg-II$^{-/-}$ mice. Thus, Arg-II expression/activity is enhanced in kidney of diet-induced obesity mice. Genetic targeting of Arg-II prevents renal damage associated with obesity, suggesting an important role of Arg-II in obesity-associated renal disease development. ■

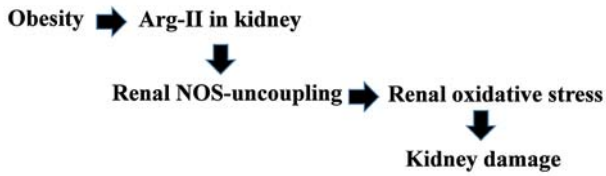

Fig.3 - Enhanced renal Arg-II mediates obesity-associated renal damage through oxidative stress resulting from NOS-uncoupling

Selected Publications

Wu Z, Yu Y, Liu C, Xiong Y, Montani JP, ***Yang Z****, Ming XF*
Role of p38 mitogen-activated protein kinase in vascular endothelial aging: Interaction with Arginase-II and S6K1 signaling pathway. Aging (Albany NY), 2015, 7(1):70-81, doi: 10.18632/aging.100722

Liu C, Rajapakse AG, Riedo E, Fellay B, Bernhard MC, Montani JP, ***Yang Z****, Ming XF*
Targeting arginase-II protects mice from high-fat-diet-induced hepatic steatosis through suppression of macrophage inflammation. Sci Rep, Feb 5, 2016, 6:20405, doi: 10.1038/srep20405

Huang J, Rajapakse A, Xiong Y, Montani JP, Verrey F, Ming XF, ***Yang Z***
Genetic Targeting of Arginase-II in Mouse Prevents Renal Oxidative Stress and Inflammation in Diet-Induced Obesity. Front. Physiol, 2016, 7:560, doi: 10.3389/fphys.2016.00560

Neurosciences is a research focus area of the University of Fribourg, with research groups active in this area present in the Departments of Biology and Medicine, as well as the Department of Psychology. Within the Department of Medicine, systems neuroscience is strongly represented, which modern state-of the art methods to study relations between neural ensemble activation patterns and behavior. Particular topics in this area include motor control and coordination, visual perception, memory and higher cognitive functions as well as more clinically oriented investigations to improve diagnostic and therapeutic methods. Research in systems neuroscience is complemented by work focusing on inhibitory neurotransmission using more molecular neuroscience approaches, as well as anatomical and functional characterization of particular neural circuit pathways. Intensification of scientific investigations and collaborative work within and beyond the University is expected to further enhance the visibility of the Department of Medicine.

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Control and perception of movement

Marco Celio
Brain circuits for positive emotions

Marco Merlo
Working memory and decision-making in healthy controls and psychotic patients

Gregor Rainer
Visual cognition laboratory

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Beat Schwaller
Calcium signaling in health and disease

Lucas Spierer
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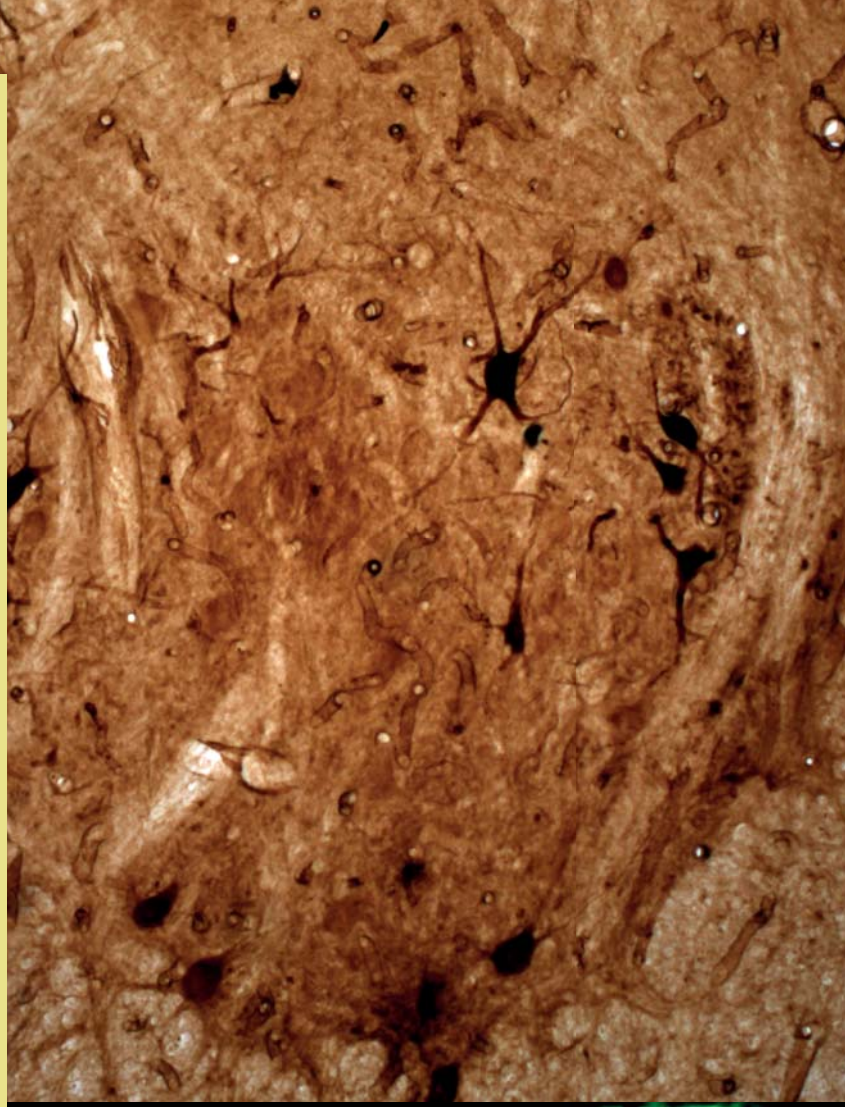
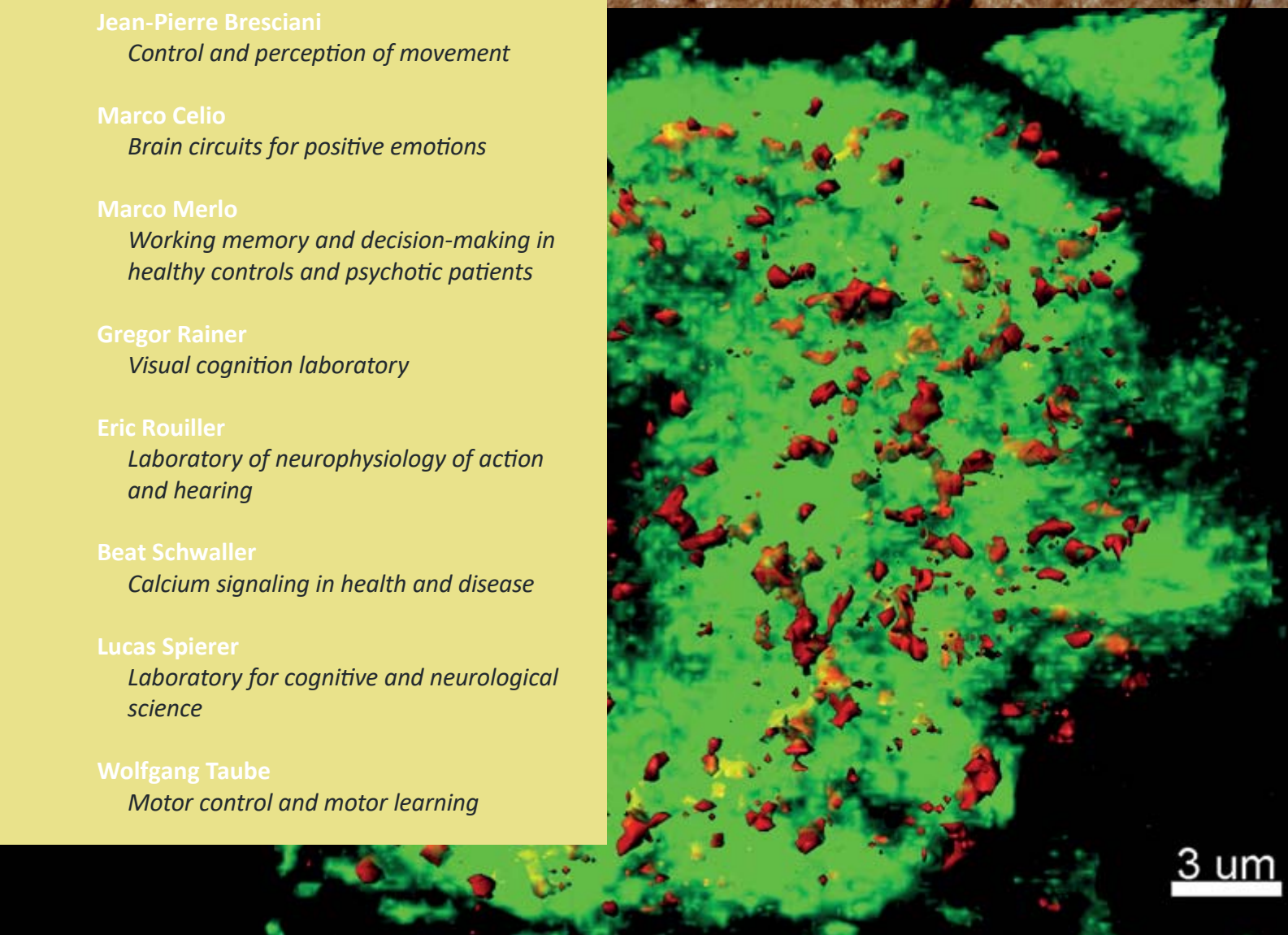
Wolfgang Taube
Motor control and motor learning





Jean-Marie Annoni
Chair of Neurology

Laboratory for cognitive and neurological science

INTRODUCTION

Extending a clinical collaboration with H-FR Fribourg - Cantonal Hospital

The laboratory has a mission of research and clinical development. Concerning the later point, two integrated neurological activities were possible through the collaboration between the H-FR (Neurology Unit, PD Dr Andrea Humm, Neuropsychology, Mrs Colombo) and the Department of Medicine of the University. A Memory Clinic and a Stroke Unit (certified in December 2015) have been developed in the H-FR and through the H-FR network, as a consequence of collaborative work between university and hospital.

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The healthy bilingual brain

Our research interest is the bilingual brain, as a model of environmental neural plasticity. In prior research programmes, we have shown that the brain processes may vary with language context and adapt to the orthographic depth of the used language. More precisely, a language's orthographic depth crucially modulates the engagement of non-lexical pathways, optimizing reading processing in the shallow versus deep language in terms of both eye movement strategies and neural network activation.
The current research takes advantage of the brain/language relationship that we could demonstrate and focuses now on neuromodulation. Particularly, we propose to test the hypothesis of preferential effect of executive functions on second language. We propose that such an impact is particularly present in non-native languages (L2), and we focus on the role of tDCS over the prefrontal cortex (as a key region in modulating cognitive control function): does left prefrontal activation improve access to the L2 lexicon in healthy bilingual speakers.

The clinical bilingual brain

In our clinical studies, we had between 2014 and 2016 three major focuses:

1) To identify the impact of stroke and dementia on the ability of the patients' first and second languages' resistance to neurological diseases (essentially neuro-degenerative disorders and strokes) and to develop predictors of language recovery of the first and second language.

2) To better understand the interconnection within the language-control network and the role of this network in the recovery of bilingual aphasia; we could show that connectivity between language and cognitive control areas is crucial in the recovery of languages.

3) To demonstrate clinically and electro-physiologically that only certain language therapies can transfer from one language to another bilingual aphasia. ■

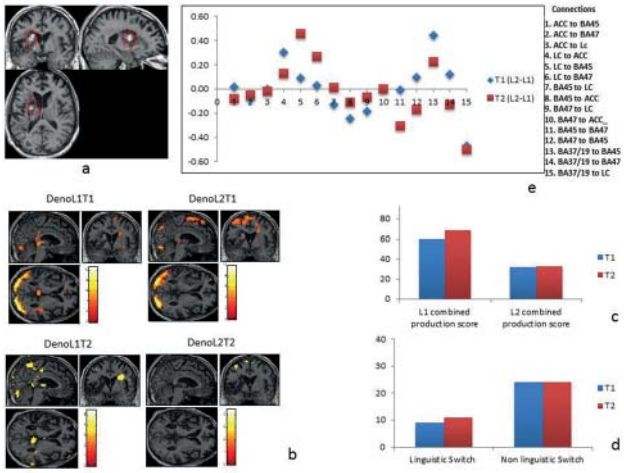

Fig.1 - Relationship between the extent of fat overshooting and the initial (pre-starvation) percentage body fat. *Data of one single subject with stroke;* ***a.*** *Ischemic stroke in left fronto-temporal area in the T1-weighted MRI image at T1;* ***b.*** *Pattern of brain activation in different conditions while picture naming, with an uncorrected p<0.001 for the main effects;* ***c.*** *Combined production scores in both languages across sessions;* ***d.*** *Linguistic and non-linguistic switching scores across sessions;* ***e.*** *Differences between L1 strength values and L2 strength values for each single connection across sessions*

Selected Publications

Accolla EA, Herrojo Ruiz M, Horn A, Schneider GH, Schmitz-Hübsch T, Draganski B, Kühn AA
Brain networks modulated by sub-thalamic nucleus deep brain stimulation. Brain, Sep 2016, 139(Pt 9):2503-15

Martory MD, Pegna AJ, Sheybani L, Métral M, Bernasconi Pertusio F, ***Annoni JM***
Assessment of Social Cognition and Theory of Mind: Initial Validation of the Geneva Social Cognition Scale. Eur Neurol, 2015, 74(5-6):288-95

Buetler KA, de León Rodríguez D, Laganaro M, Müri R, Nyffeler T, Spierer L, ***Annoni JM***
Balanced bilinguals favor lexical processing in their opaque language and conversion system in their shallow language. Brain Lang, Nov 2015, 150:166-76

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Control and perception of movement

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INTRODUCTION

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

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

1. Investigate how sensory information is integrated to perceive movement and implement efficient motor strategies

2. Analyze human movement and develop applications to improve human performance and learning.

Automatic measurement of fall risk indicators

Fall risk assessment is usually conducted in specialized centers using clinical tests. Most of the time, these tests are performed only after the occurrence of health problems potentially affecting gait and posture stability. Our aim is to define fall risk indicators that could routinely be used at home to automatically monitor the evolution of fall risk over time. For instance, we used the standard Timed Up and Go (TUG) test to classify thirty six individuals into two classes of fall risk, namely at-risk vs no-risk. Several parameters related to the gait pattern, and the sitting position included in the TUG test ▸ were automatically extracted using an ambient sensor (Microsoft Kinect sensor). We were able to correctly classify all individuals using machine learning algorithms relying on the combination of two parameters (see ***Fig.1***). The gait speed, the step length and the speed to sit down proved to be the most relevant parameters. Coupled to an ambient sensor installed at home to monitor the relevant parameters in daily activities, these algorithms could therefore be used to assess the evolution of fall risks, thereby improving fall prevention.

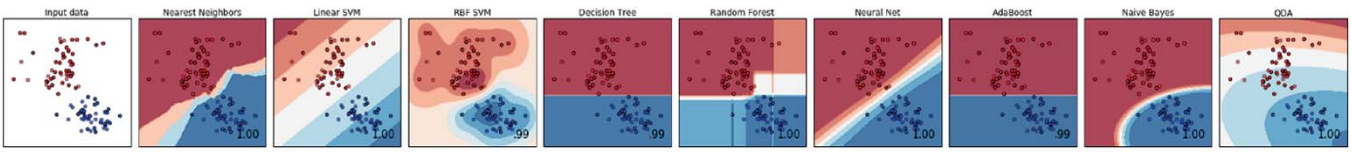

Fig.1 – Estimation of the risk of fall. *Different machine learning algorithms were used to classify the subjects into those who have a low (red) or a high risk of fall (blue). Here the classification relies on the combination of two parameters, namely «gait speed» and «speed to sit down», and it clearly «splits» the subjects into two distinct categories.*

A virtual reality simulator to assess and train penalty kicking skills

We developed and tested a virtual reality simulator allowing professionals to:

1. assess which players have the best sensorimotor skills to successfully take a penalty kick

2. train those skills to improve success rate

This simulator consists of a state-of-the-art virtual reality set-up integrating full-body motion-capture, avatar animation and psychophysics methods. In this simulator, the penalty taker is facing a 3-dimensional virtual goal, in a virtual stadium, with a 3-dimensional virtual goalkeeper. ▸ The movements of the virtual goalkeeper are human-like because its avatar is animated using motion-captured movements of a real goalkeeper. In addition, the virtual goalkeeper adaptively moves according to the movements of the penalty taker (human-avatar interaction, see ***Fig.2***). We successfully used this simulator to determine the average minimum time required to adjust and redirect penalty kick in players of different age categories, namely 10-12, 14-16 and young adults (18-30). More importantly, we devised a new training program that allowed us to successfully improve the performance of the players both in terms of threshold and scoring rate, and this for all age categories tested (see ***Fig.3***). ■

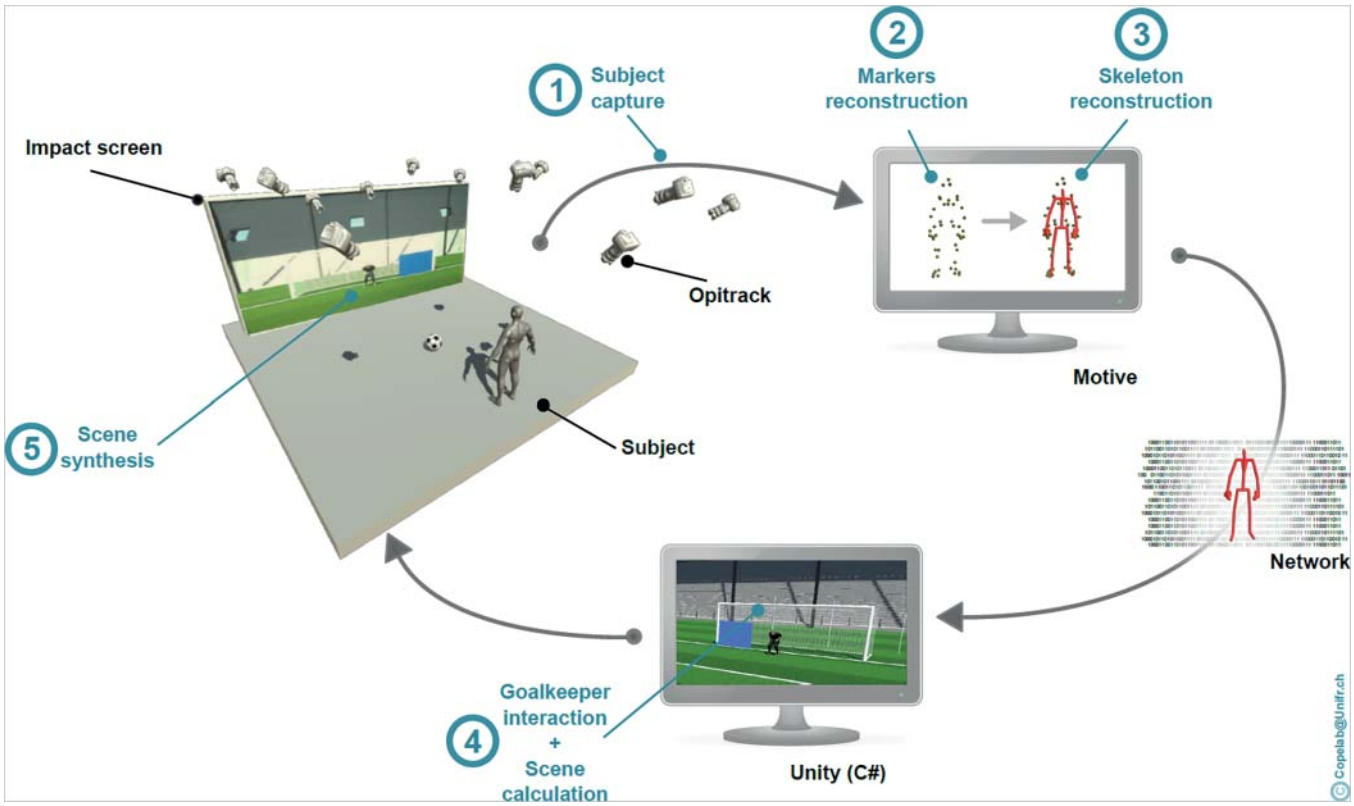

Fig.2 - Schematic representation of our simulator

Fig.3 - Performance improvement after training with the simulator. *On average, training resulted in a significantly lower threshold to successfully redirect the kick according to the movements of the virtual goalkeeper (indicated in ms in the orange area) and a significantly higher success rate.*

Selected Publications

Dubois A, ***Bresciani JP***
Person identification from gait analysis with a depth camera at home. Proceedings of the IEEE International Conference of the Engineering in Medicine and Biology Society, 2015, 4999-5002

Cian C, Gianocca V, Barraud PA, Guerraz M, ***Bresciani JP***
Bioceramic fabrics improve quiet standing posture and handstand stability in expert gymnasts. Gait & Posture, 2015, 42: 419-423

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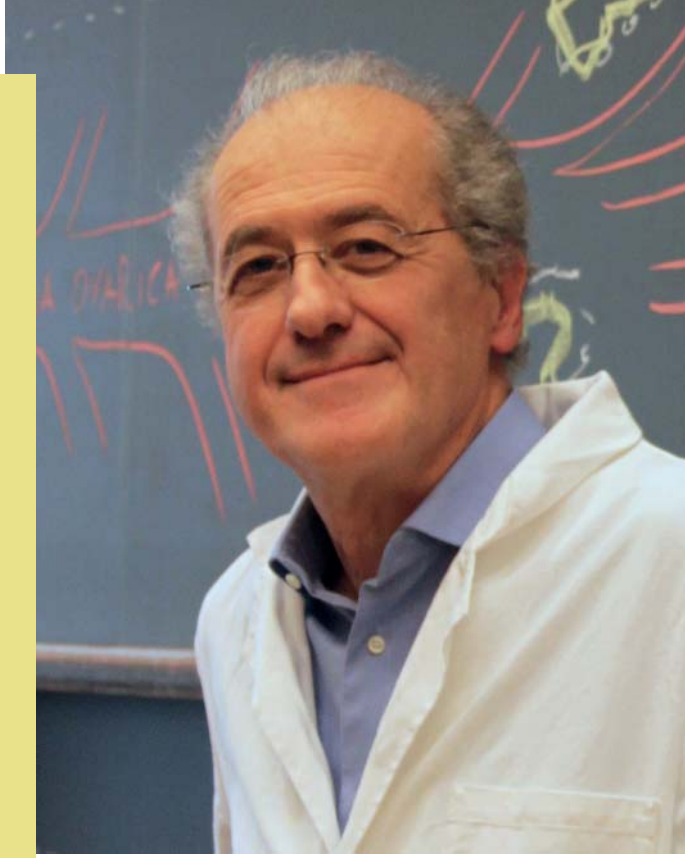
Brain circuits for positive emotions



INTRODUCTION

Calcium binding proteins of the EF-hand family (CaBPs) play a central role in all aspects of Ca^{2+} signaling, which include the control of Ca^{2+}-gating, modulation of the amplitude and the duration of Ca^{2+}-signals, and the transduction of Ca^{2+}-signals into biochemical responses. The involvement of the CaBPs in such a broad array of functions is rendered possible by the great diversity that they manifest in structure, cellular localization and functional activity.
During the past three decades, three members of the superfamily of EF-hand Ca^{2+}-binding proteins, namely, calbindin-D28k (Calb), calretinin (CalR) and parvalbumin (Parv), have been widely used as specific and robust markers for a discrete, often GABAergic neuronal population.
Our group exploits CaBPs for their utilization as cell markers in the brain. Parv-antibodies visualize an as yet unrecognized brain nucleus (parvafox) which may be involved in the expression of emotions. Studies in humans with magnetic resonance imaging confirm that the homologous region in humans is activated during laughter. Under pathologic conditions, Parv has been found to be expressed also in glial cells. During the reporting period, more than 100 «new» CaBPs have been found to occur in the brain and their utility as neuronal marker has been evaluated.

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Dr. Elise Wattendorf PhD

Connectivity studies of the parvafox-nucleus

Injections of Cre-dependent adenoviral constructs were targeted to the ventrolateral hypothalamus of *Foxb1/Cre* mice to specifically label and map the efferent connections of the *Foxb1*-expressing subpopulation of neurons (Bilella et al., 2016). High labelling densities were found in the dorsolateral and the upper lateral portion of the periaqueductal gray (PAG), the Su3-nucleus of the ventrolateral PAG (***Fig.1***) and the cuneiform nucleus. Intermediate densities of terminals were encountered in the retrofacial nucleus (cardiovascular control) and the retroambigual nucleus (vocalization control). Since the terminals were demonstrated to express the glutamate transporter VGlut2, the projections are presumed to be excitatory. The parvafox nucleus may contribute to the autonomic manifestations that accompany the expression of emotions (Alvarez-Bolado and Celio, 2016).

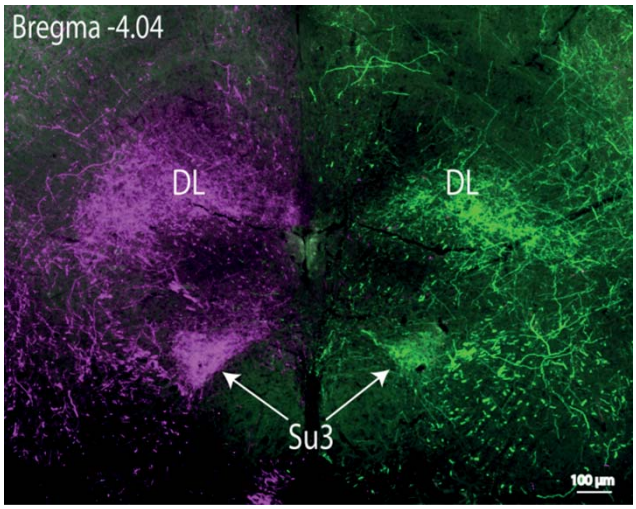

Fig.1 - Epifluorescent image of projections in the PAG after a bilateral injection of two different viral tracers, one bearing dTomato and the other EGFP in the parvafox nucleus. DL, dorsolateral periaqueductal gray; Su3, supraoculomotor nucleus

fMRI-studies in human laughter (in collaboration with Prof. Martin Lotze, Greifswald)

It has been postulated that the integrative monitoring of the bodily responses to environmental stimuli is crucial for the recognition and experience of emotions. Since emotional arousal is known to be closely coupled to functions of the anterior insula, we suspected laughter to be primarily associated with neuronal activity in this region. (***Fig.2***) An analysis of our imaging data appertaining to ticklish laughter, to inhibited ticklish laughter and to voluntary laughter revealed regional differences in the levels of neuronal activity in the posterior and mid-/anterior portions of the insula. Ticklish laughter was specifically associated with right ventral anterior insular activity, which was not detected under the other two conditions. Hence, apparently, only laughter that is evoked as an emotional response bears the signature of autonomic arousal in the insular cortex (Wattendorf et al., 2016).

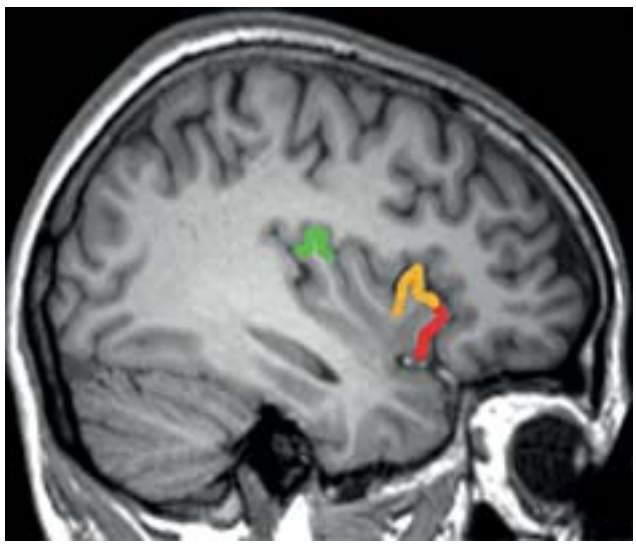

Fig.2 - Lateral view on the left insular cortex. *The primary interoceptive cortex in the posterior and anterior areas of the dorsal fundus of the insula (idfp and idfa) are marked in green, and the dorsal and ventral portions of the anterior insular cortex (daic, vaic) are labeled in yellow and red, respectively.*

The EF-family of calcium-binding proteins in the brain

The expression profiles of all members of the CaBP superfamily was mapped at the gene level by analysis of the *in-situ*-hybridization data in the Allen Mouse Brain Atlas (Girard et al., 2015). Potential new markers for specific neurons, as well as for certain brain nuclei, areas and layers, and also for specific functional systems were identified. Amongst the 249 putative members of the CaBPs, 135 were expressed in the brain. The expression profiles of four family-members, namely hippocalcin-like 4, neurocalcin-δ, tescalcin and plastin 3 were documented for the first time, at either the mRNA (*in-situ*-hybridization) or the protein (immunohistochemical) levels (***Fig.3***). Our analyses provide a comprehensive atlas of the gene-expression profiles of the entire CaBP superfamily in the murine brain. The assembled information could afford functional clues for further experimental pursuit.

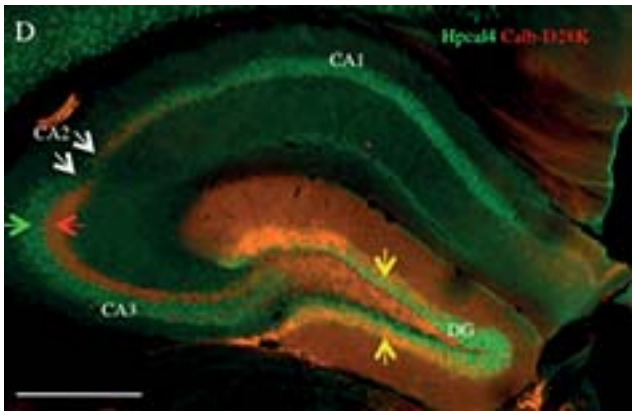

Fig.3 - Hpcal4, is co-expressed with Calb in granule cells of the dentate gyrus (yellow arrows). *Red arrow point to Calb-D28K immunoreactivity in neuronal projections from cell bodies localized in DG, while Hpcal4 antibody stains CA3 pyramidal cell bodies (green arrow). Scale bar is 500µm*

Parvalbumin-expression by ependymal cells

We described the *de-novo* expression of PV in ependymal cells of the lateral ventricle wall following *in-vivo* lesioning and brain slicing for the preparation of organotypic hippocampal slice cultures (OHSCs). In OHSCs, PV-expression begins shortly after the onset of culturing, and the number of ependymal cells implicated in this process increases with time. (***Fig.4***) Exposure of OHSCs to NF-KB-inhibitors and to antioxidants reduces PV-expression in ependymal cells, thereby implicating injury-induced inflammation in this process. Indeed, *in-vivo* stab injury enhances PV-expression in ependymal cells adjacent to the lesion. PV-KO mice manifest impaired wound-healing response to *in-vivo* injury, and reduced scratch-wound reparation capacity in OHSCs. Our data indicate that the injury-triggered up-regulation of PV-expression promotes the motility and adhesion of ependymal cells, thereby contributing to the re-establishment of a continuous ependymal layer (Szabolcsi et al., 2016). ■

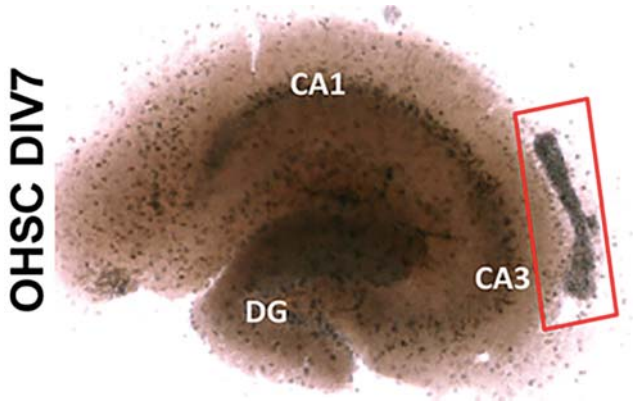

Fig.4 - Low magnification image of an OHSC at DIV7 indicating the hippocampal regions (b). *Red box highlights a typical ependymal cell aggregate derived from the lateral ventricle (LV) wall.*

Selected Publications

Alvarez-Bolado G, ***Celio MR***
The ventrolateral hypothalamic area and the parvafox nucleus: Role in the expression of (positive) emotions? The Journal of comparative neurology, 2016, 524(8):1616-1623

Bilella A, Alvarez-Bolado G, ***Celio MR***
The Foxb1-expressing neurons of the ventrolateral hypothalamic parvafox nucleus project to defensive circuits. J Comp Neurol, 2016, 524(15):2955-2981

Szabolcsi V, Babalian A, Bilella A, Chun X, ***Celio MR***
Brain wide projections to the parvafox nucleus of the ventrolateral hypothalamus, 2016

Wattendorf E, Westermann B, Lotze M, Fiedler K, ***Celio MR***
Insular cortex activity and the evocation of laughter. The Journal of comparative neurology, 2016, 524(8):1608-1615

Girard F, Venail J, Schwaller B, ***Celio MR***
The EF-hand Ca(2+)-binding protein super-family: a genome-wide analysis of gene expression patterns in the adult mouse brain. Neuroscience, 2015, *294:116-155*

Marco C.G. Merlo
Chair of Psychiatry and Psychotherapy

Working memory and decision-making in healthy controls and psychotic patients

INTRODUCTION

Modern psychiatry aims at an early detection of psychiatric disorders and emphasizes the importance of avoiding social disabilities. Patients who develop major psychiatric disorders show early cognitive and emotional dysfunctions during adolescence and young adulthood. Therefore, therapeutic interventions integrate pharmacological and psychotherapeutic interventions with real live coaching for education or employment («supported education/ employment model»). Up to date, research still needs a deeper knowledge of cognitive and emotional mechanisms («stress-coping model») in order to understand why these patients fail in their effort of being integrated in the community. Our research applies neurophysiological methods to measure attention, memory, emotional and decision-making functions in healthy subjects and psychiatric patients. All our projects have been accepted by the ethics committee. The last two years we focused on the following two studies:

1. Measuring auditory Event-related Potentials (ERPs) in psychosis patients to calculate a Time Index of Neural Network Variation (TINNV) to assess mental workload;

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

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Assessment of mental workload: A new electrophysiological method based on intra-block averaging of event-related potential (ERP) amplitudes

In the present work, we investigated mental workload using tasks varying in difficulty during an auditory oddball paradigm. For data analysis, we applied a novel method to compute ERPs by intra-block epoch averaging of the amplitudes of the P2, P3a and P3b components for the infrequent target stimuli. We obtained eight consecutive blocks of 5 epochs each, which allowed us to develop an electrophysiological parameter to measure mental workload (***Fig.1***). Statistical analysis revealed intra-block differences on the amplitudes of the ERPs of interest between the easy and the more constraining tasks, confirming that this method is sensitive to assess mental workload. In particular, these data clearly indicate that in a sequence of repetitive stimuli, the first few ones are treated with much more attention because of their psychological importance. Yet, with stimulus repetition, less attentional resources are engaged and can therefore be reallocated to supplementary processes required for tasks with a higher mental effort. Importantly, since a subject is his own control, the present method represents an electrophysiological parameter for individual measurement of mental workload and may therefore be applicable in clinical routine. These results have been published in *Neuropsychologia* 2016.

Utility of auditory ERPs as clinical tool in psychosis

Normal subjects and psychosis patients performed an auditory oddball task passively and with a strong memory task. P3a and P3b auditory ERPs were measured by applying the new averaging ERP method. As decision-making declines and attentional disturbances are present in psychosis patients, we expected to observe variations due to the task difficulty and the time course of the P3 components. With these variations, we hypothesized to discriminate psychosis patients from normal subjects.

In the ongoing study, we find that the method based on intra-block averaging of ERP amplitudes is a useful tool to further characterize the neurophysiological markers of psychosis. In the future such markers might help orientate the clinicians for diagnostic and even prognostic purposes.

Contribution of brain oscillations to study the perceptual organization and working memory in patients with first episode psychosis

It is well established in the literature that WM deficits represent one of the core features of schizophrenia. These cognitive impairments seem to be related to a defective activation of neural networks supported by frontal brain regions. The neural networks tend to undertake oscillating activities, and their activity is directly bound to the energy ▸▸

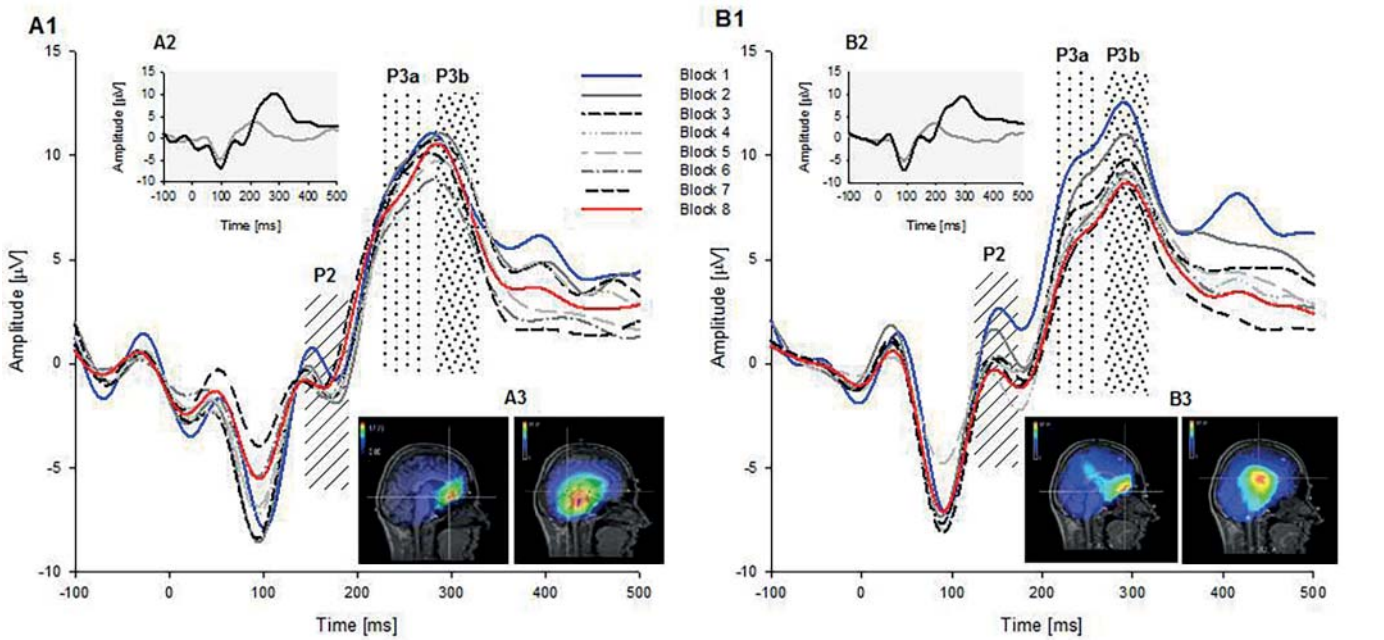


Fig.1 - Data show the cumulative averages of ERPs in 8 blocks of 5 epochs at central (C3, Cz and C4) electrode sites following infrequent target stimuli during the easy (A1) and more constraining (B1) task conditions.

Insets: Grand average ERP waveforms at central (C3, Cz and C4) electrode sites following frequent (grey line) and infrequent target (black line) stimuli during the easy (A2) and strong constraining (B2) task condition. Note the longer latency of the P3 component for the strong constraining, i.e. more demanding task.

Illustration of the source localization of the P3a and P3b components on a sagittal section (corresponding topography on the horizontal axis) using the swLORETA inverse solution performed for the easy (A3) and the strong constraining task condition (B3). Source localization revealed distinct activated regions for the P3a (A3a and B3a) and P3b (A3b and B3b) components, respectively.

consumption. Thus, it has been suggested that the decline of WM performances in FEP may be related to a deficit of the energy consumption in the participating neurons during neuronal oscillations. It is known that delta- and gamma-band oscillations supply the temporal bases for higher cognitive functions and they require an important amount of energy to work. We then explored whether subtle deficits of cortical activation were present in FEP in WM. With an adapted WM paradigm, we assessed frontal delta (1-4 Hz) and gamma (35-45 Hz) event-related oscillations (EROs) in 15 patients with FEP and 18 healthy controls. All subjects successfully performed an adapted 2-back WM task as well as an oddball detection and a passive fixation tasks.

We hypothesized to find abnormalities in delta and gamma oscillations that are related to the demands of the WM. Compared with controls, FEP patients displayed a lengthening of the first delta oscillation cycle for the working memory tasks only. Similarly, a synchronous firing of neuronal gamma oscillations between the four tasks was observed during the first delta oscillation cycle for controls but it was not the case for FEP patients (***Fig.2***). Together, these findings support the concept of a blunted electroencephalographic response in patients with FEP who recruit a maximal number of neural generators for simple attention conditions due to metabolic deficits.

Early disturbances of gamma band dynamics in first-episode psychosis

Earlier reports demonstrated a reduction of phase and dysfunctional long-range synchrony in gamma bands during various cognitive paradigms, highlighting a deficit in sensory processing in psychosis. Thus, the previous abnormal early gamma synchronization raises the question of the link between connectivity and temporality of distributed neural responses in order to form functional circuits in this population of psychiatric patients. We therefore examined temporal changes in gamma band dynamics in FEP to establish whether specific cognitive deficits may be caused by deficits of gamma synchrony at specific lag-times of the temporal evolution of these oscillations. To address this issue, we conducted an EEG activation study associated with lag-time and fractal dimension analysis of gamma oscillations in healthy controls and FEP patients who successfully performed a n-back working memory (WM) task plus an oddball detection and a passive fixation task.

We hypothesized to observed temporal synchronization abnormalities of gamma oscillations in the 1-20 ms time-range following stimulus onset in patients with FEP, and that such abnormalities promote the generation of the global binding deficit in psychosis. Multiple linear and logistic regression models were computed to explore the relationship between the cognitive status and gamma

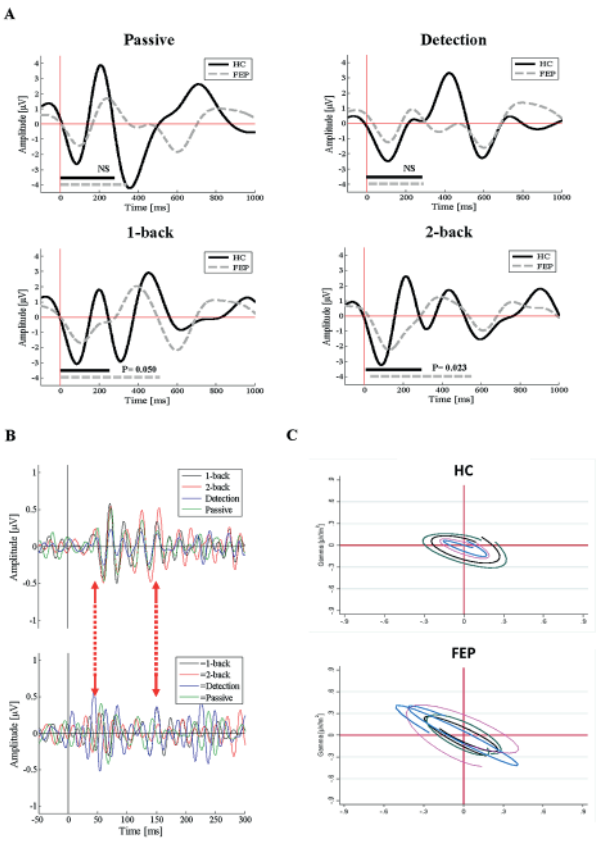
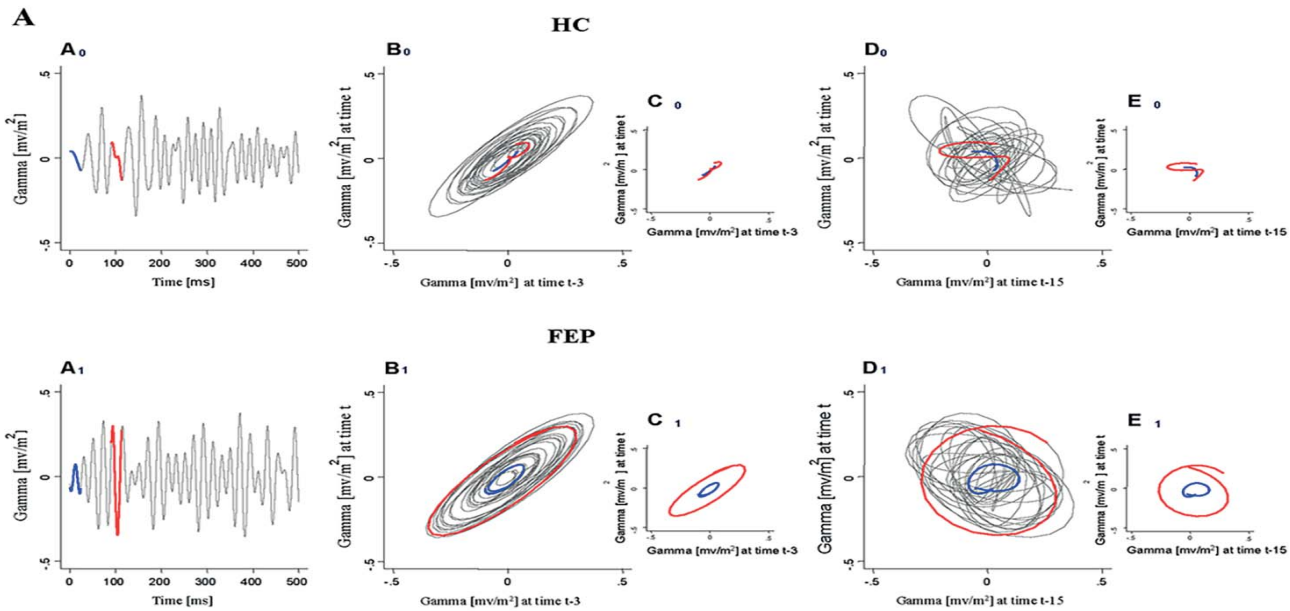


Fig.2 - A: Average frontal delta oscillations of both groups (HC: black line; FEP: grey dashed line) during tasks as a function of time. *Note the significant difference in the length of the first delta oscillation cycle in the patient group for the working memory tasks only.*
B: *Average frontal gamma oscillations of all tasks (1-back, 2-back, detection, passive) as a function of time for the control (top panel) and FEP (bottom panel) groups. A synchronous firing of neuronal gamma oscillations (the period of oscillation between conditions is superimposable) between the four tasks is observed in the 50-150 ms time interval after stimulus onset for controls (interval indicated by arrows) but it is not apparent in FEP patients. Note that the synchronous firing of gamma oscillations occurs in the first semi-period of oscillations in the delta band (red arrows).*
C: *In the phase diagram, a complete period of oscillation (A. blue line) is represented by a cycle around the zero of the* x, y *axes. The crossing between cycles indicates that the oscillations are not synchronous (in phase); amplitude differences between oscillations are represented by the distance to the zero of the* x, y *axes.*

oscillation changes over time. Based on the regression model results, phase diagrams were constructed and measures of phase diagram complexity were calculated using fractal dimension values. When adjusted for gamma values at lag -2 to -4 ms and at lag -15 to -16 ms, FEP patients displayed significantly higher average changes in gamma values than controls, independently of the nature of the task (***Fig.3***). The present results are consistent with the hypothesis of a discoordination of the activity of cortical generators engaged by the stimulus apparition in FEP patients, leading to a global cognitive binding deficit. Moreover, they provide evidence for the recruitment of supplementary cortical generators as compensating mechanisms of these deficits. ■



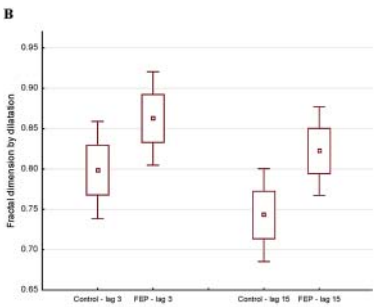


Fig.3 - A: Average frontal gamma according to the groups during the 2-back task as a function of time (A0, A1), and as a function of average frontal gamma at lag time -3 (phase diagrams B0C0 and B1C1) and -15 (phase diagrams D0E0 and D1E1). *The colored section represents the traces obtained during two limited time periods: blue (0 [ms]<t<24 [ms], C0C1) and red (275 [ms]<t<301 [ms], E0E1). They correspond to different loops of the ellipse in the control (B0D0) and the FEP (B1D1) group. For example, the red section corresponds to the envelope (external layer) of the ellipse in the FEP group, but to an inner loop in the control group. Note the difference of phase space diagrams between lags in both groups that indicates divergent trajectory of the attractor of a dynamic lag-dependent system.*

B: *Box plot of the fractal dimension of phase space (gamma power) for all electrode sites and task conditions at lag time -3 and time lag -15 according to the groups (control vs. FEP). Each dot corresponds to one subject. The mean value of each group is represented by the square in the plot. Note the increase of fractal dimension in patients compared to control subjects.*

Selected Publications

Missonnier P, Curtis L, Ventura J, Herrmann FR, ***Merlo MCG***
Early disturbances of gamma band dynamics in first-episode psychosis. Journal of Neural Transmission, 2017, in press.

Horat SK, Herrmann FR, Favre G, Terzis J, Debatisse D, ***Merlo MCG****, Missonnier P*
Assessment of mental workload: A new electrophysiological method based on intra-block averaging of ERP amplitudes. Neuropsychologia, 2016, 82:11–17

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. To this end, we have characterized neural responses in early visual cortex to complex grating stimuli, revealing the transformation of representation of visual stimuli at early stages of hierarchical visual processing. These findings advance our understanding of non-linear representation by neural systems and their transformation in reciprocally coupled brain structures. Investigating decision making in the frontal cortex, we have demonstrated a novel and interesting double dissociation between frontal lobe structures and two well-studied types of decision making. We show a very pronounced role of Cannabinoid modulation on these decision making processes, highlighting a potential novel and specific role for endogenous and exogenous Cannabinoid modulation. Based on these results, a review article has focused on linking our findings to available related literature in the area of pharmacology of decision making. A third project presented here relates eye position data during free object exploration to computer vision algorithms estimating saliency of different object parts. Our results show that real three-dimensional objects are much more visually explored than computer displayed images, and that exploration of the former stimulus category is better predicted by computer vision algorithms.

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Emergence of complex stimulus selectivity revealed using non-Cartesian gratings in tree shrew visual cortex

We examined spiking and visual evoked potential (VEP) activity in tree shrew V1 and V2 using Cartesian, hyperbolic, and polar gratings. Neural selectivity to structure of Cartesian gratings was higher than other grating classes in both visual areas. From V1 to V2, structure selectivity of spiking activity increased, whereas corresponding VEP values tended to decrease, suggesting that single-neuron coding of Cartesian grating attributes improved while the cortical columnar organization of these neurons became less precise from V1 to V2. We observed that neurons in V2 generally exhibited similar selectivity for polar and Cartesian gratings, suggesting that structure of polar-like stimuli might be encoded as early as in V2. This hypothesis is supported by the preference shift from V1 to V2 toward polar gratings of higher spatial frequency, consistent with the notion that V2 neurons encode visual scene borders and contours. Neural sensitivity to modulations of polarity of hyperbolic gratings was highest among all grating classes and closely related to the visual receptive field (RF) organization of ON- and OFF-dominated subregions. We show that spatial RF reconstructions depend strongly on grating class, suggesting that intracortical contributions to RF structure are strongest for Cartesian and polar gratings.

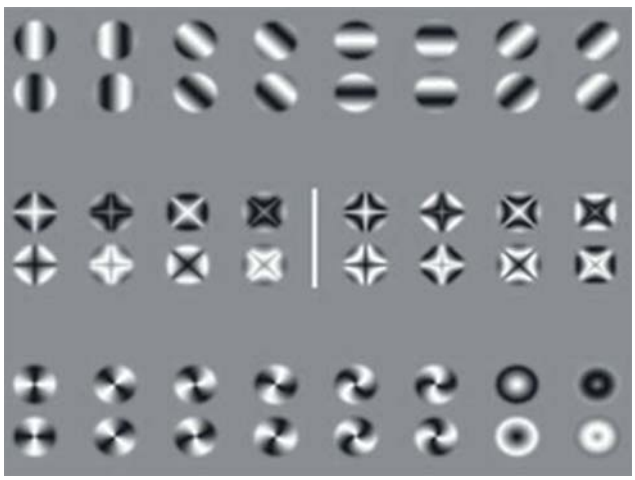

Fig.1 - Example visual stimuli used to study early visual cortex selectivity, composed of Cartesian (top row) and two types of non-Cartesian (middle row: hyperbolic and bottom row: polar) gratings.

Hyperbolic gratings tend to recruit least cortical elaboration such that the RF maps are similar to those generated by sparse noise, which most closely approximate feedforward inputs. Our findings complement previous literature in primates, rodents, and carnivores and highlight novel aspects of shape representation and coding occurring in mammalian early visual cortex.

Behavioral and immunohistochemical evidence for an involvement of Cannabinoid receptors in frontal cortex mechanisms of decision making

Despite the evidence for altered decision making in cannabis abusers, the role of the cannabinoid system in decision-making circuits has not been studied. Here, we examined the effects of cannabinoid modulation during cost-benefit decision making in the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), key brain areas involved in decision making. We trained different groups of rats in a delay-based and an effort-based form of cost-benefit T-maze decision-making task. During test days, the rats received local injections of either vehicle or ACEA, a cannabinoid type-1 receptor (CB1R) agonist in the ACC or OFC. We measured spontaneous locomotor activity following the same treatments and characterized CB1Rs localization on different neuronal populations within these regions using immunohistochemistry. We showed that CB1R activation in the ACC impaired decision making such that rats were less willing to invest physical effort to gain high reward. Similarly, CB1R activation in the OFC induced impulsive pattern of choice such that rats preferred small immediate rewards to large delayed rewards.

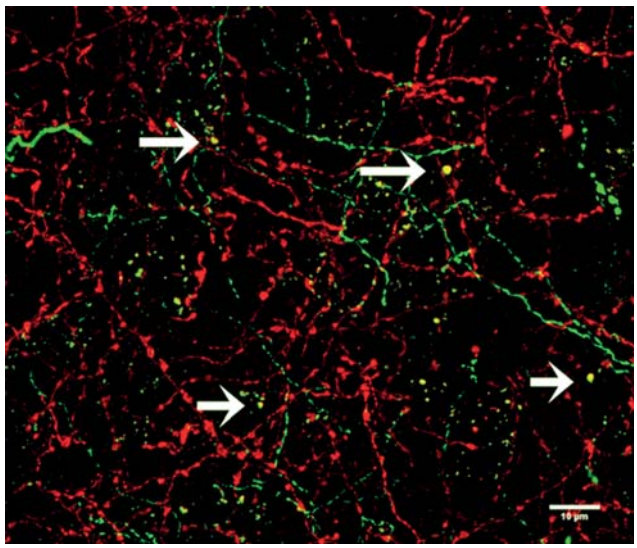

Fig.2 - The figure shows co-localization of Cannabinoid Receptor 1 with tyrosine-hydroxylase positive, putative Dopaminergic neurons (arrows) in the rat orbitofrontal cortex

Control tasks ensured that the effects were specific for differential cost-benefit tasks. Furthermore, we characterized widespread colocalizations of CB1Rs on GABAergic axonal ends but few colocalizations on glutamatergic, dopaminergic, and serotonergic neuronal ends. These results provide first direct evidence that the cannabinoid system plays a critical role in regulating ▸▸

cost-benefit decision making in the ACC and OFC and implicate cannabinoid modulation of synaptic ends of predominantly interneurons and to a lesser degree other neuronal populations in these two frontal regions.

Relating behavioral exploration of real objects using eye movements by macaque monkeys to computational vision computer algorithms

The question of whether animals perceive pictures as representation of real objects remains still unsolved. Object-picture perception is generally studied requiring animals to learn some information about real objects and transfer that knowledge to the pictorial domain, or vice versa.

Fig.3 - Gaze patterns and saliency estimation. *On the left, eye position (red circles) of fixations during free viewing of an object are shown. The center panel summarizes frequency of fixation for particular regions of a stimulus. The right panel demonstrates results of a computational image processing saliency algorithm.*

Here, we tackle the issue of object-picture perception from a different perspective, examining visual exploration behavior of two naïve macaque monkeys during free-viewing of objects and pictures of these objects on a computer monitor. Our main finding is that monkeys looked spontaneously longer at object rather than picture stimuli. However, we find striking similarities in temporal dynamics of gaze allocation within the time course of a single stimulus presentation, as well as in habituation rates within and across behavioral sessions. We also highlight differences between stimulus types in terms of spatial gaze patterns and looking strategies. Stimulus features that attract overt attention during spontaneous visual exploration are thus better predicted for object stimuli by a visual saliency model. Moreover, we provide evidence for a consistency in stimulus preference for objects and pictures, suggesting a correspondence of in how macaques perceive objects and their pictorial stimuli. Taken together, our data suggest that macaque monkeys exhibit evidence for correspondence between objects and pictures. This validates spontaneous visual exploration as a method for studying object-picture correspondence without a need for extensive behavioral training. We discuss the potential advantages of using object over picture stimuli in the context of studies on visual cognition.■

Selected Publications

Poirot J et al
Neural coding of image structure and contrast polarity of Cartesian, hyperbolic and polar gratings in the primary and secondary visual cortex of the tree shrew. J Neurophysiol, 2016, doi: 10.1152/jn.01000.2015

Khani A et al
Activation of cannabinoid system in anterior cingulate cortex and orbitofrontal cortex modulates cost-benefit decision making. Psycho-pharmacology, 2015, 232 (12): 2097-2112

Mustafar F et al
Enhanced visual exploration for real objects compared to pictures during free viewing in the macaque monkey. Behav Proc, 2015, 05/2015: 118

Eric M. Rouiller

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INTRODUCTION

The general theme of research in the laboratory is the plasticity of the central nervous system in relation to use (experience) or following injury/disease. The representation of body parts (e.g. cutaneous or muscular territories) in the sensorimotor cortex is not fixed even after development, but can be reorganized depending on somatosensory inputs (e.g. tactile stimuli) or on motor practice (e.g. playing an instrument). In the latter case, string instrument players show a greater cortical activity in response to touch than control subjects.

We addressed the question whether such plasticity is not limited to extraordinary activities (like music) but is also found in everyday activities like using the touchscreen phones requiring repetitive finger movements. In human subjects, using electroencephalography (EEG), we showed that tactile stimuli eliciting cortical activity was enhanced in frequent touchscreen phone users as compared to non-users.

Based on a non-human primate model (macaque monkeys), the benefit provided by autologous transplantation of adult neural progenitor cells was investigated in case of motor cortex lesion (confirming previous results from our laboratory) and also in case of Parkinson disease.

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The plastic changes of cortical activity in the sensorimotor cortex associated with the intense use of touchscreen phones were investigated in 37 human subjects (***Fig.1***) based on electroencephalography (EEG). A first group of subjects (n=26) used new technology touchscreen phones at an average rate of 100 minutes per day, typing with their thumbs in most of them (n=23), whereas three subjects used other fingers. A second group of subjects (n=11) still relied on old phone technology and were thus considered as «non-users» (of touchscreen), using their phone on average 20 minutes per day.

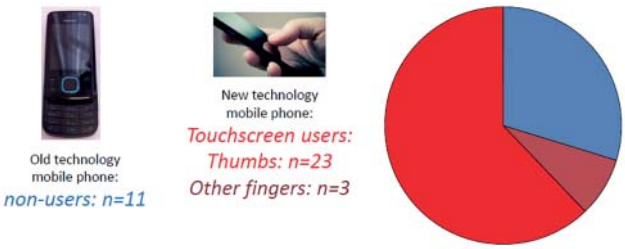

Fig.1 - Distribution of human subjects based on their utilisation of new generation touchscreen phones (in red) or of old technology mobile phone (in blue). *Note that, in the first group («touchscreen users»), three subjects used their touchscreen phone with other fingers than the thumbs. Derived from Gindrat et al., 2015*

Using EEG, the somatosensory evoked potentials (SSEPs) were recorded in all subjects in response to tactile stimuli (2 ms duration) delivered randomly to the tip of the thumb, index finger and middle finger, 1250 times at each of the three fingers. The average activity was significantly larger in the group of «touchscreen users» as compared to «non-users» (***Fig.2***). This was also true, but to a lesser extent though still significant, for the index finger, whereas there was no difference for the middle finger. In addition, in the group of «touchscreen users», the cortical potentials in response to tactile stimuli of the thumb and index finger were directly proportional to the amount of screen use during the 10 preceding days. In conclusion, the sensory processing of the hand in the cerebral cortex is continuously shaped based on the use of the smooth touchscreen and the corresponding repetitive movements.

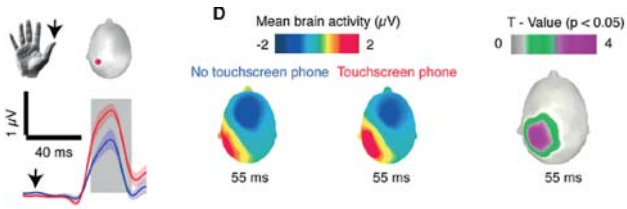

Fig.2 - Left: Group means of the SSEPs +- SEM (lighter shade) from the electrode with the highest positivity (red dot) in response to tactile stimulations delivered to the tip of the right thumb in each group of subjects (red curve is for «touchscreen phone users» and blue curve is for «non-users»). *The gray area indicates the time windows in which the 2 curves are significantly different. The arrow represents the onset of the tactile stimulus. Middle: Corresponding scalp voltage maps at 55ms after tactile stimulation onset for the same 2 groups. Right: Statistical comparison between the 2 groups showing in color the position of the electrodes with significant differences at 55 ms after stimulus onset, mainly above the contralateral somatosensory cortex. Derived from Gindrat et al., 2015*

In case of brain injury (stroke, head trauma) or degenerative nervous disease (Parkinson), the consequences often involve loss or serious impairment of motor control. Our laboratory has been involved in testing various therapeutic strategies to enhance functional recovery of motor control following such injury or disease, using a non-human primate model (macaques). Among various approaches, cellular therapy is a promising option. The autologous transplantation was chosen in order to avoid the difficulties of rejection by the immune system. The strategy was to perform a biopsy of an intact part of the pre-frontal cortex of the subject, extract and multiply adult neural progenitor cells to be re-implanted in the same monkey subjected to a motor cortex lesion (adjacent to the lesion) or to Parkinsonism (in the striatum). We have already shown in a pilot study with 2 monkeys, that such cellular therapy significantly improved functional recovery from motor cortex lesion (Keaser et al., 2011). In the last two years, these preliminary data were confirmed in two more monkeys, subjected to such autologous cellular therapy, paving the way to clinical trials.

A similar approach was tested in 4 parkinsonian monkeys, again in order to confirm previous results (Bloch et al., 2014), and to investigate some of the mechanisms involved in the functional recovery. First of all, it was shown that the biopsy in the prefrontal cortex to produce the autologous cells (***Fig.3***) did not induce undesired deleterious effects in motor performance. Second, as a result of the re-implantation of the autologous adult progenitor cells in the striatum, the monkeys exhibited a remarkable extent of functional recovery (more than expected by spontaneous recovery). Furthermore, the dopaminergic activity in the striatum, strongly reduced immediately after the MPTP exposure (to induce Parkinsonism), re-augmented after the cellular therapy.

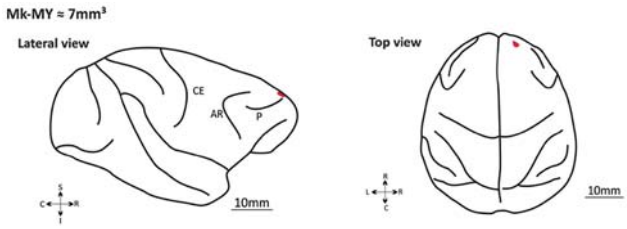

Fig.3 - Example of biopsy location performed in the intact prefrontal cortex of monkey Mk-MY. *The biopsied tissue is used for production of autologous neural adult progenitor cells, subsequently re-implanted in the striatum of this parkinsonian monkey. The volume of the biopsy is 7 mm³. Derived from Badoud et al., 2016*

Selected Publications

Badoud S, Borgognon S*, Cottet J*, Chatagny P, Moret V, Fregosi M, Kaeser M, Fortis E, Schmidlin E, Bloch J, Brunet JF,* ***Rouiller EM***
Effects of dorsolateral prefrontal cortex lesion on motor habit and performance assessed with manual grasping and control of force in macaque monkeys. Brain Struct Funct, Jul 9, 2016, (Epub ahead of print)
** Equal first authorship*

Gindrat AD, Chytiris M*, Balerna M*,* ***Rouiller EM****, Ghosh A*
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** Equal first authorship*

Beat Schwaller
Anatomy

Calcium signaling in health and disease

INTRODUCTION

Ca^{2+} signaling is of utmost importance for almost all aspects of biological processes. For this, cells are equipped with sophisticated machinery named the Ca^{2+} signaling toolkit that includes organelles such as the ER and mitochondria, as well as cytosolic Ca^{2+}-binding proteins including parvalbumin (PV) and calretinin (CR). In many cases intracellular Ca^{2+} signals occur in the form of Ca^{2+} oscillations; the elucidation and modeling of the processes implicated in these oscillations is one of the current research topics (***Topic 1***).
In cells expressing PV or CR, these proteins are considered as essential components of the Ca^{2+} toolkit. Based on our research projects, PV emerges as an important modulator of Ca^{2+} signals in a subpopulation of neurons, the so-called Pvalb neurons (***Topic 2***). Changes in their expression, i.e. mostly down-regulation, is strongly linked to autism spectrum disorders (ASD), as evidenced in $PV^{+/-}$ and $PV^{-/-}$ mice, as well as in other established mouse ASD models.
CR is a specific marker for malignant mesothelioma (MM), a tumor strongly associated with asbestos exposure. In recent projects, we investigated the putative role of CR in the development of mesothelioma using newly developed mouse cell lines *in vitro* and also *in vivo* approaches using transgenic mouse models, e.g. $CR^{-/-}$ mice (***Topic 3***).

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Ca^{2+} oscillations serve as specific signals in physiological processes

Brief changes in the cytosolic and intra-organellar Ca^{2+} concentration often in the form of oscillations serve as specific signals for various physiological processes. In my lab we have investigated the mechanisms governing such oscillations with respect to several parameters and also in different cell types. Mathematical models were developed to simulate such oscillations and to make experimentally testable model-based predictions. In the initial model Ca^{2+} concentrations in 3 compartments and Ca^{2+} fluxes between them were considered: the cytosolic compartment (c_{cyt}), ER stores (c_{ER}) and the extracellular environment (c_{out}) (Pecze and Schwaller 2015). In mesothelial cells, serum administration-mediated re-entry in the cell cycle (G_0-G_1 transition) induces long-lasting Ca^{2+} oscillations with slowly decreasing frequencies that depend on plasmalemmal Ca^{2+} influx and the inositol trisphosphate concentration c_{InsP3}. Partial blocking of SERCA pumps modifies the oscillation frequency in both directions, i.e. increasing it in some cells and lowering it in others. The finding that oscillations also occur in mesothelial cells, if plasmalemmal Ca^{2+} is blocked prior to the induction of Ca^{2+} oscillations, indicated the involvement of an additional compartment: mitochondria (Pecze, Blum and Schwaller 2015) (***Fig.1***). Mitochondrial Ca^{2+} transport evidenced by measurements of c_{mito} is able to substitute for the plasmalemmal Ca^{2+} exchange function (***Fig.1C***). However, in conditions of physiological c_{out} (1-2 mM), mitochondria don't substantially contribute to Ca^{2+} oscillations. Cytosolic Ca^{2+} buffering by Ca^{2+}-binding proteins such as CR decreases the amplitude of cytosolic Ca^{2+} spikes during oscillations and diminishes the amount of Ca^{2+} ions taken up by mitochondria. We hypothesize that the increased CR expression in mesothelioma cells and certain colon cancer cells might be correlated with the increased resistance of these tumor cells to pro-apoptotic/pro-necrotic signals.

In sensory neurons and in breast and prostate cancer cells, agonist-induced Ca^{2+} influx via transient receptor potential vanilloid type 1 (TRPV1) ion channels also leads to Ca^{2+} oscillations (Pecze, Blum, Henzi and Schwaller 2016). Additionally, the TRPV1 agonist capsaicin (CAPS) generates intercellular Ca^{2+} waves in cultured breast and prostate cancer cells. Ca^{2+} oscillations and waves require the presence of extracellular Ca^{2+} ions and moreover concomitant phospholipase C activation, further documenting the crucial involvement of the inositol phospholipid pathway necessary to generate biologically relevant frequency-modulated Ca^{2+} signals. Strong activation of endogenous TRPV1 by CAPS results in overstimulation-based cytotoxicity in sensory neurons, a method currently used to ablate CAPS-sensitive neurons in patients with chronic neuropathic pain. However in breast and prostate cancer and derived cell lines also characterized by elevated TRPV1 levels compared to the healthy tissue, CAPS administration fails to induce overstimulation cytotoxicity *in vitro* (Pecze, Josvay, Blum, Petrovics, Vizler, Olah and Schwaller 2016). We attribute this to the still lower TRPV1 levels in cancer cells compared to sensory neurons, since ectopic TRPV1 expression renders these cells susceptible to the cytotoxic effect of CAPS evidenced by plateau-type Ca^{2+} signals, mitochondrial Ca^{2+} accumulation and Na^{+}- and Ca^{2+}-dependent membrane disorganization. Our results indicate that specific targeting of TRPV1 function remains a putative strategy for cancer treatment. ▸▸

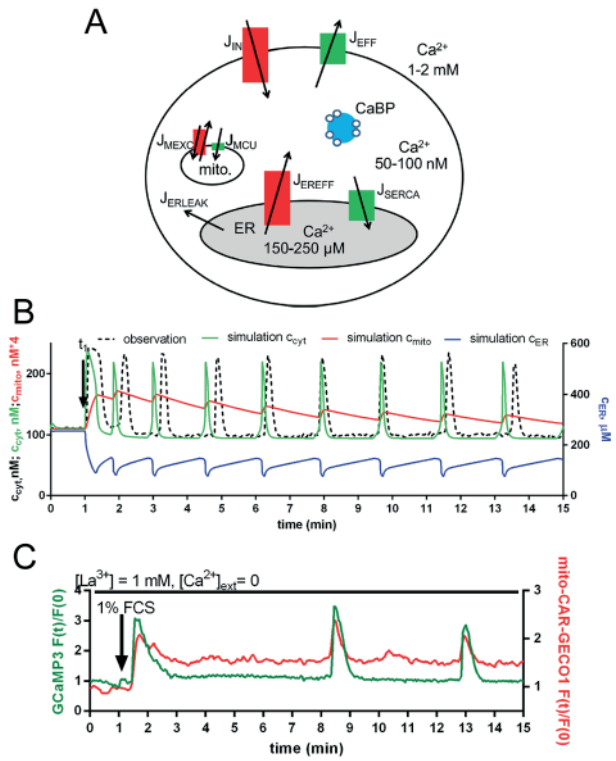

Fig.1 - Involvement of mitochondria in Ca^{2+} oscillations. ***A)*** *Model of cellular compartments and Ca^{2+} toolkit components implicated in Ca^{2+} oscillations in primary mesothelial cells (prMC). For details and abbreviations, see (Pecze, Blum and Schwaller 2015). The following components and compartments are considered: the extracellular milieu, the cytosolic compartment, ER stores, mitochondria and Ca^{2+} buffers. Arrows indicate Ca^{2+} fluxes between the components.* ***B)*** *Modeling of Ca^{2+} oscillations in c_{cyt}, c_{ER}, and c_{mito} in prMC. An experimental recording (black dashed line) in prMC showing low frequency oscillations was selected for the fitting. The changes in c_{mito} (red trace) consist of an initial rise after serum (FCS) administration followed by a slow return to basal levels. Each Ca^{2+} spike in c_{cyt} (green trace) results in a small hump in c_{mito} reaching its relative maximum with a small delay compared with the maximum in c_{cyt}.* ***C)*** *Addition of Lanthanum chloride (La^{3+} insulation) prior to serum administration renders Ca^{2+} oscillations independent of extracellular Ca^{2+} ions. Note that c_{mito} remains elevated during the entire period and that the frequency of Ca^{2+} oscillations is lower than in control conditions.*

The role of parvalbumin in autism spectrum disorders (ASD)

ASD covers a series of neurodevelopmental disorders characterized by deficits in social interaction and impaired communication, as well as in restricted and stereotyped behaviors. Although the etiology of ASD is far from being understood, disturbances at the level of synapses leading to alterations in the excitation/inhibition (E/I) balance emerge as a common theme. Within this framework, the subpopulation of neurons characterized by the expression of the Ca^{2+}-binding protein parvalbumin (PV) has gained particular attention; however, whether and how PV might be implicated in ASD had not been addressed before. Detailed analyses of PV knockout ($PV^{-/-}$) and heterozygous $PV^{+/-}$ mice revealed these mice to display behavioral phenotypes with relevance to all ASD core symptoms: abnormal reciprocal social interactions (***Fig.2A, 2B***), deficiencies in communication and repetitive and stereotyped patterns of behavior (Wohr, Orduz, Gregory, Moreno, Khan, Vorckel, Wolfer, Welzl, Gall, Schiffmann and Schwaller 2015). PV-reduced/depleted mice also show signs of ASD-associated comorbidities including reduced pain sensitivity and increased seizure susceptibility. The attenuated ASD-like phenotype evident in heterozygous mice indicates that already a decrease in PV levels is sufficient to elicit core ASD-like deficits. At the morphological level $PV^{-/-}$ mice show developmental neuroanatomical changes including transient cortical hypertrophy and cerebellar hypoplasia. Functionally, $PV^{-/-}$ mice display alterations of both inhibitory and excitatory synaptic transmission, likely resulting in changes in the E/I balance. Since a reduction of the PV-immunoreactive (PV^{+}) GABAergic interneuron subpopulation, the «Pvalb neurons» or a decrease in PV immunoreactivity was reported in several ASD mouse models including Shank mutant mice, with *SHANK* being one of the most important gene families mutated in human ASD, we assessed the presence of Pvalb neurons and PV protein expression levels in the ASD models $Shank1^{-/-}$, $Shank3B^{-/-}$ and in $PV^{+/-}$ mice (Filice, Vorckel, Sungur, Wohr and Schwaller 2016). Shank family members comprise a family of scaffolding proteins present in the postsynaptic compartment. The two possibilities, i.e. Pvalb neuron loss *vs.* decreased PV expression, have essentially opposing effects on the E/I balance, with decreased PV expression resulting in enhanced inhibition, but loss of the Pvalb neurons in reduced inhibition. Unbiased Stereology revealed no changes in Pvalb neuron numbers in the ASD-associated regions, i.e. medial prefrontal cortex, somatosensory cortex and striatum of $PV^{-/-}$, $PV^{+/-}$, $Shank1^{-/-}$ and $Shank3B^{-/-}$ mice (***Fig.2C***).

Pvalb neurons were identified by the marker Vicia Villosa Agglutinin (VVA), a lectin recognizing the specific extracellular matrix enwrapping *Pvalb* neurons. Thus, the reduced number of PV^{+} neurons in $PV^{+/-}$, $Shank1^{-/-}$ and $Shank3B^{-/-}$ mice is the result of decreased levels of *Pvalb* mRNA and PV protein. Our findings suggest that the PV system might represent a convergent downstream endpoint for some forms of ASD, with the E/I balance shifted towards enhanced inhibition. PV might emerge as a promising target for future pharmacological interventions and projects on this topic are ongoing.

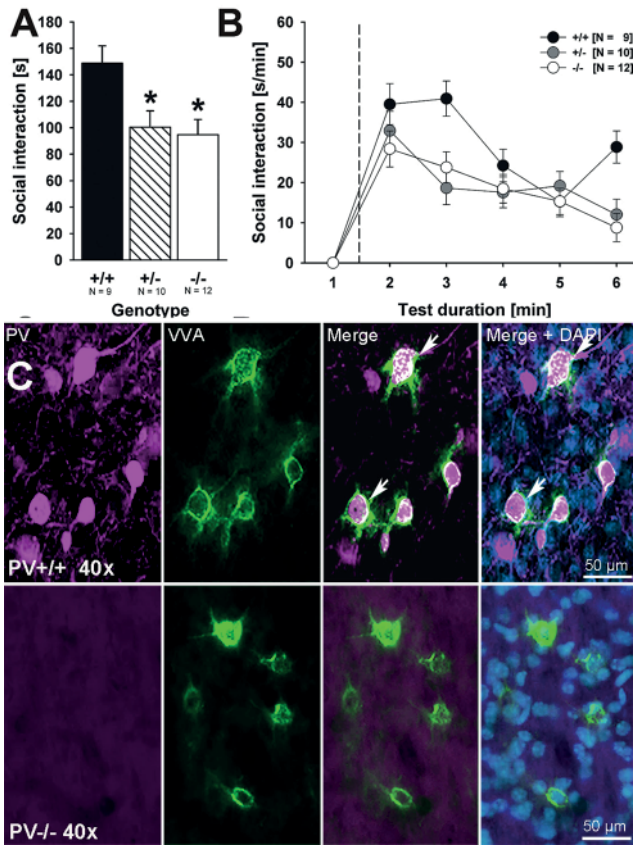

Fig.2 - A) Reduced social interaction in $PV^{-/-}$ and $PV^{+/-}$ heterozygous mice during reciprocal social interactions as juveniles. B) *Time course for the social interaction time displayed during each 1 min time bin across the 5 min social interaction period.* ***C)*** *Representative PV^{+} and VVA^{+} cells from PND25 mouse cortex. From left: single channel acquisition of PV^{+} (magenta), VVA^{+} (green) cells, merged images and additional counterstain with DAPI. Arrowheads indicate the $PV^{+}VVA^{+}$ double-positive neurons that are in focus (modified from Filice, Vorckel, Sungur, Wohr and Schwaller 2016)*

Immortalized mouse mesothelial cells and cells derived from mouse malignant mesothelioma (MM) serve as valuable models to investigate mesothelioma formation and the putative involvement of calretinin

Mesothelial cells covering the surface of the body's internal cavities (e.g. pleura, peritoneum) are susceptible to asbestos fiber-induced cytotoxicity and on longer time scales this leads to the formation of malignant mesothelioma (MM). MM is a highly aggressive tumor considered to be currently incurable. Cell culture models are extremely useful in the elaboration of mechanisms implicated in MM formation. However, mouse MM cell lines and also so-called «immortalized» mesothelial cells, the latter representing the pre-cancer stage of «reactive» mesothelial cells are still scarce. We generated SV40-immortalized cell lines derived from primary mesothelial cells (prMC) of wildtype and neurofibromatosis 2 (merlin) heterozygote ($Nf2^{+/-}$) mice, both on a C57Bl/6J background (Blum, Pecze, Felley-Bosco, Worthmuller-Rodriguez, Wu, Vrugt, de Perrot and Schwaller 2015). The use of syngeneic cells allows to perform experiments in mice with an uncompromised immune system. The tumor suppressor gene *NF2* is one of the most frequently mutated genes in human MM, but its precise function is still unknown. The immortalized cells can be propagated for more than 40 passages without any signs of morphological changes or a decrease in proliferation rate. These genotypically distinct cell lines likely relevant for MM mesothelioma formation are expected to serve as useful *in vitro* models. We additionally generated a novel murine mesothelioma cell line RN5 originating from an $Nf2^{+/-}$ mouse subjected to repeated asbestos exposure; RN5 cells are highly tumorigenic and are used in several ongoing studies. The role of CR was investigated, a protein that is currently used as a positive marker for identifying epithelioid MM and reactive mesothelium. With the aim of shedding light on CR's putative role in the early steps of MM generation, primary mesothelial cells from CR knockout ($CR^{-/-}$) and wildtype (WT) mice were compared with respect to morphology, marker proteins, proliferation, cell cycle parameters and mobility *in vitro* (Blum, Pecze, Felley-Bosco and Schwaller 2015). Although primary mouse mesothelial cells from both genotypes show a typical «cobblestone-like» morphology, cells from $CR^{-/-}$ mice cover all larger areas and have a decreased proliferation rate resulting from a prolongation of the G_1 phase of the cell cycle. $CR^{-/-}$-derived cells are also much slower to close a scratch in a confluent cell layer (2D-wound assay; ***Fig.3***). Lentivirus-mediated up-regulation of CR in mesothelial cells of both genotypes increases the proliferation rate and speeds up the scratch-closure time. A similar effect is also seen, if CR expression is targeted to the nucleus. Based on the fact that both WT and $CR^{-/-}$ primary mesothelial cells are negative for CR protein expression, we hypothesize that the differences in proliferation and mobility between WT and $CR^{-/-}$ mesothelial cells are the likely result from differences in their developmental trajectories. During embryonic development, CR is transiently expressed in lung embryonic mesenchyme and in the developing mesothelial cells of the parietal and the visceral walls.

Further projects aimed at better understanding the function of calretinin and its putative implication in signaling pathways in normal mesothelial cells may help understand its role during the processes that lead to mesothelioma formation. ■

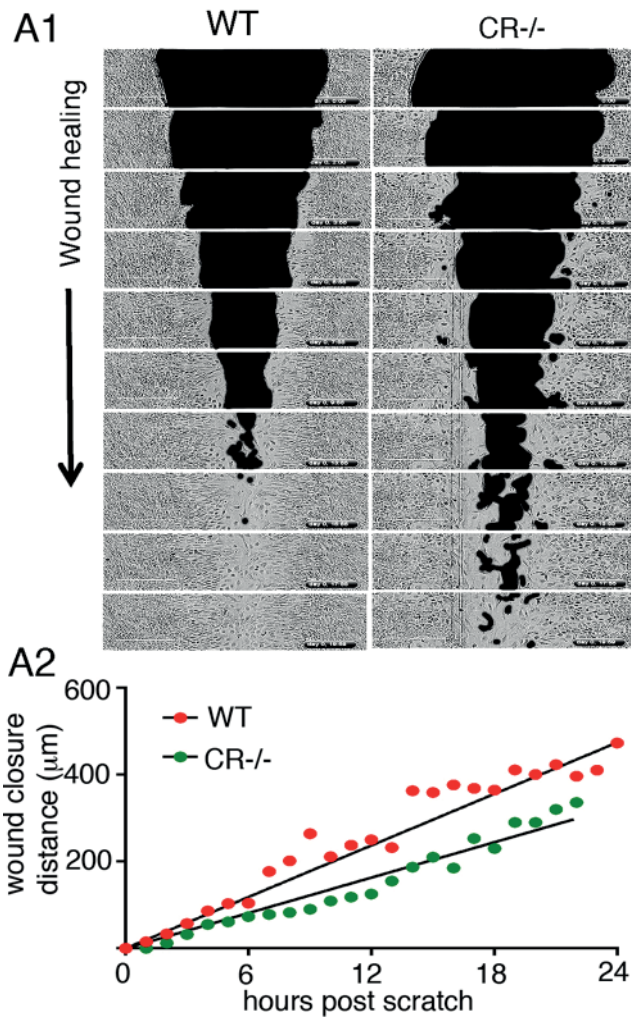

Fig.3 - A1) Time-lapse brightfield images were taken after a scratch (black area) was made at t=0 in a confluent layer (grey area) of prMC from WT and CR$^{-/-}$ mice. *Images were taken every 2 hours and «wound closure» was measured as the rate at which the scratched area (black) was repopulated with mesothelial cells (grey zone).* ***A2)*** *The wound closure distance as a function of time resulted in the rate of cell re-colonization («wound closure rate»: slope); modified from (Blum, Pecze, Felley-Bosco and Schwaller 2015)*

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Pecze L, Blum W, Henzi T, ***Schwaller B***
Endogenous TRPV1 stimulation leads to the activation of the inositol phospholipid pathway necessary for sustained Ca^{2+} oscillations. Biochim Biophys Acta- MCR, 2016, in press

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Reduction in parvalbumin expression not loss of the parvalbumin-expressing GABA interneuron subpopulation in genetic parvalbumin and shank mouse models of autism. Mol Brain, 2016, 9(1):10, Epub 2016/01/29

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Lack of parvalbumin in mice leads to behavioral deficits relevant to all human autism core symptoms and related neural morphofunctional abnormalities. Translational psychiatry, 2015, 5:e525, Epub 2015/03/11

Pecze L, ***Schwaller B***
Characterization and modeling of Ca^{2+} oscillations in mouse primary mesothelial cells. Biochimica et biophysica acta, 2015, 1853(3):632-45, Epub 2015/01/03

Pecze L, Blum W, ***Schwaller B***
Routes of Ca^{2+} Shuttling during Ca^{2+} Oscillations: Focus on the role of mitochondrial Ca^{2+} handling and cytosolic Ca^{2+} buffers. J Biol Chem, 2015, 290(47):28214-30, Epub 2015/09/24

Blum W, Pecze L, Felley-Bosco E, Worthmuller-Rodriguez J, Wu L, Vrugt B, de Perrot M, ***Schwaller B***
Establishment of immortalized murine mesothelial cells and a novel meso-thelioma cell line. In vitro cellular & developmental biology Animal, 2015, 51(7):714-21, Epub 2015/04/17

Blum W, Pecze L, Felley-Bosco E, ***Schwaller B***
Overexpression or absence of calretinin in mouse primary mesothelial cells inversely affects proliferation and cell migration. Respir Res, 2015, 16:153, Epub 2015/12/24

Lucas Spierer
Neurology

Laboratory for cognitive and neurological science

INTRODUCTION

Launching of a new platform for clinical and fundamental cognitive neuroscience research

The Non-Invasive Brain Stimulation and Imaging platform (NIBSI) has been launched beginning of 2015. The NIBSI is a platform for brain and cognition researchers, providing the equipment and expertise for conducting high-quality basic and clinical research.

The NIBSI Platform is directed by Dr Spierer and part of the Medicine Department of the Faculty of Science, University of Fribourg. The platform is open to collaborators from the University of Fribourg and to external users.

The NIBSI team supports researchers on all steps of their scientific projects, from the design and set-up of fundamental and clinical studies, to the preparation of protocols for ethics committees (incl. clinical trials), data acquisition, preprocessing and statistical analyses.

We provide access, support and training for the following neuroimaging, non-invasive brain stimulation and clinical methods:

- Transcranial magnetic stimulation (single-pulse TMS, Theta-burst stimulation…)
- Transcranial direct current stimulation (tDCS, tACS, tRNS…)
- Electrical Neuroimaging (EEG/ERP, incl. topographic, micro-states, distributed electrical source analyses…)
- Functional and Structural magnetic resonance imaging (MRI; incl. BOLD, DCM, DTI, VBM…)
- Voxel-based lesion-symptom mapping
- Eye-/head- tracking & Psychophysics

For more information please visit the platform's website: unifr.ch/med/nibsi

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Reshaping executive prefrontal anatomo-functional brain organization with cognitive interventions for impulse-control disorders remediation.

Training-based behavioral interventions to improve cognitive functions can help recovering from cognitive deficits or reaching supranormal performance levels. In the past years, we have developed a neurocognitive model of training-induced behavioral and brain plasticity in frontal executive functions in healthy populations.
This model not only enables generating predictions on the effects of specific training regimen and thus to conduct hypothesis-driven fundamental investigations of frontal executive plasticity, but also to develop neurophysiologically-informed rehabilitation protocols to prevent or help the recovery of executive function deficits in healthy aging and psychiatric/neurologic conditions.
We are now conducting a series of randomized controlled clinical trials to test the validity of these remediation strategies on healthy elderly, as well as on stroke and binge-type eating clinical populations.

Inhibitory control is a key aspect of executive functions referring to the ability to suppress ongoing cognitive or motor processes. For example, understanding speech in noisy environment requires inhibiting interfering sounds, and maintaining a healthy weight requires inhibiting impulses to eat palatable high-energy food.
Inhibitory control deficits are a direct consequence of normal aging and constitute a causal factor in emergence and maintenance of impulse control disorders including e.g. addiction, bulimia or ADHD. A normalisation of frontal executive functions with training-based behavioural interventions might thus help maintaining quality of life in aging and the rehabilitation of a wide range of brain-related disorders. Using neuroimaging and neurostimulation methods, we have identified the neural underpinnings of training-induced plasticity in inhibitory control and how interventions must be designed to target the cognitive mechanism and brain networks impaired in elderly and clinical populations.
Now that these interventions have been validated in healthy populations and their underlying mechanisms better understood, we are applying them to clinical populations. Two examples illustrate this translational approach: the remediation of inhibition deficits in healthy aging and in bulimia/hyperphagia.
Since executive functions are mostly supported by frontal areas and that neural deteriorations associated with aging manifest predominantly within prefrontal cortices, elderly typically show inhibition deficits. These impairments manifest as a slowing down of the neural communication between the subparts of the inhibition network and are initially compensated by the recruitment of additional functional resources within inferior frontal cortices. To improve inhibition performance and normalize the supporting functional brain organization in elderly, we have developed in young adults a training protocol that manages to increase the speed of fronto-striatal inhibition processes while reducing inferior frontal activity. In other words, we designed cognitive interventions inducing at both the behavioral and brain levels qualitatively similar but quantitatively opposite effects as aging on inhibitory control. Once applied to elderly, such interventions should thus restore a level of performance close to those of young adults and bring the associated functional brain organization back to a level corresponding to the pattern of younger individuals, a hypothesis we are currently testing.
The same approach is being applied to develop intervention for bulimia/hyperphagia. An over-reactivity to food cues and difficulties in stopping excessive eating are core deficits in binge-type eating disorders. To develop an intervention targeting these two processes, we have first investigated the interactions between the reward system and inhibitory control plasticity in healthy individuals. We found that repeated inhibition of motor responses to rewarding stimuli actually leads to their devaluation, to a decrease in the functional response of the fronto-orbital reward system and to an improvement of inhibitory control performance. These studies demonstrate that a single intervention could normalize the two key functions showing deficits in binge-type eating disorders. This approach is now being applied to clinical populations with binge-type eating disorders in association with the usual cognitive behavioral therapies. We expect that our training protocol will both reinforce the ability to resist the impulses to eat and reduce the perceived value of the stimuli eliciting the compulsive approach behaviors. ■

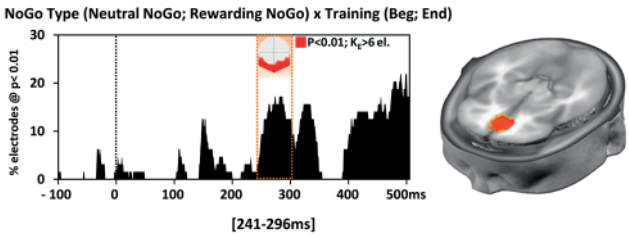

***Fig.1 - Stimulus devaluation induced by inhibitory control cognitive training**. Left: Time-wise, electrode-wise statistical analyses of the effect of inhibitory control training on the neutral vs rewarding stimuli (high-energy food). The training influenced differently the brain activity related to inhibiting responses to neutral and rewarding stimuli at early post-stimulus onset latency (ca. 250ms; 0=stimulus onset). Right: Statistical parametric mapping of distributed electrical source estimations revealed that the NoGo Type x Training interaction in the sensor space followed from a modulation within the fronto-orbital cortex, a key node of the reward system. At the behavioral level, these functional brain changes were accompanied with devaluations of the stimuli used as NoGo during the training.*

Hartmann et al., 2016

Selected Publications

*De Pretto M, Sallard E, **Spierer L***
State dependency of inhibitory control performance: an electrical neuroimaging study. European Journal of Neuroscience, 2016

*Hartmann L, De Pretto M, Sallard E, **Spierer L***
Modulation of reward responses with inhibitory control training. NeuroImage, 2016

*Chavan C, Mouthon M, Simonet M, Hoogewoud HM, Draganski B, van der Zwaag W, **Spierer L***
Sustained enhancements in inhibitory control depend primarily on the reinforcement of fronto-basal anatomical connectivity. Brain Structure and Function, 2015

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. The influence of ageing on motor control and motor learning
3. The influence of factors such as high-intensity training or interference on motor learning and memory consolidation
4. The influence of non-physical task execution (motor imagery or movement observation) on motor behavior and neural activation
5. The influence of augmented feedback and focus of attention on performance outcome and neural activation

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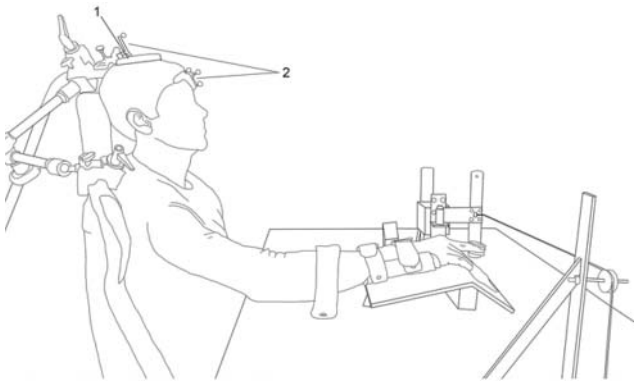
TECHNICIAN
Ranjith Sivagnanaselvam

How changing the focus of attention alters motor performance and neural processing

In recent years, studies on focus of attention have consistently demonstrated that an external focus (i.e., focus on the movement effect) enhances motor performance and learning relative to an internal focus (i.e., concentration on body movements) and a neutral focus of attention. For example, studies indicated benefits in balance, force production and fatiguing tasks. Although behavioral outcomes of using an external focus (EF) strategy are well investigated, the underlying neural mechanisms remain poorly understood. We therefore performed a series of studies to evaluate behavioral performance as well as neural activation while adopting an internal focus (IF) or EF of attention.

In one study, we aimed to clarify whether the focus of attention influences not only motor performance but also activity of the primary motor cortex (M1) when executing identical fatiguing tasks of the right index finger. In line with previous studies, we found that adopting an EF results in improved motor performance in the endurance task. Single-pulse transcranial magnetic stimulation (TMS) at intensities below the motor threshold (subTMS) and paired-pulse TMS inducing short-interval intracortical inhibition were applied to the primary motor cortex to measure and compare the excitability of inhibitory circuits within M1 during the two attentional focus conditions. The new finding of this study is that intracortical inhibition is modulated instantly depending on the attentional strategy adopted. More specifically, intracortical inhibition is enhanced as soon as participants use an EF. This (partly) explains on a neural level the increased motor efficiency of an EF compared to an IF.

In a second study, we evaluated surround inhibition (SI) in the motor system while adopting an IF or EF. SI is well known from sensory systems and is thought to help sharpen sensory perceptions. Concerning the motor system, SI could aid the selective execution of desired movements in humans and it is well known that impaired SI goes along with deteriorated motor execution. We therefore tested whether adopting an EF compared to an IF also affects the amount of SI. We could show that using an EF compared to an IF enhances motor performance/efficiency by increasing surround inhibition in the motor system.



Maximizing Performance: Augmented Feedback, Focus of Attention, and/or Reward?

Jump height can be improved in the short-term when providing augmented feedback (aF), which is defined as additional feedback from an external source. The mechanism underlying these immediate performance gains was speculated to rely predominantly on motivational factors such as an enhanced intrinsic motivation. In contrast to aF, monetary reward (RE) is dictated by external sources and, therefore, considered to act on extrinsic motivation. Furthermore, there are ways to instantly improve motor performance without influencing motivational factors. It was shown that an external focus of attention (EF), where the participant directs the attention to the effects of the movement, can increase movement efficiency and performance. In the present study, aF was combined with EF and/or RE to identify the most powerful instruction to instantaneously improve and maximize jump performance.

Participants were told to jump as high as possible in each single jump and to respect the additional instructions. Participant performed jumps in six different conditions: Neutral (NE), aF, RE, aF+EF, aF+RE and aF+EF+RE.

Participants showed the highest jump heights with aF+EF followed by aF+EF+RE and, as expected, the worst in the NE condition. The enhanced jump performance in aF+EF and aF+EF+RE indicates a positive impact of the EF approach. Furthermore, we could show that the muscular activation was reduced in the two conditions with EF. This finding of reduced muscular activity despite better performance is generally discussed as more efficient task execution as soon as participants focus externally. We assume that the largest performance gains in aF+EF resulting from additive benefits of two largely independent mechanisms: aF mainly acting on (intrinsic) motivation and EF improving movement efficiency. From a functional point of view, this finding is not only be important to maximize jump performance but may be transferred to many other sports disciplines as well. ▸▸

Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan

In everyday life, postural tasks, such as standing or walking, are rarely performed alone. More often, the postural tasks are performed concurrently with a second task. Walking and carrying a tray with glasses or while talking on the phone are examples for these so-called dual-task situations. These situations are rather unproblematic as long as the postural task is executed in an automatic way. However, in situations where postural control requires more central processing, attentional resources may be exceeded by the addition of an attention-demanding task. This may lead to interference between the two tasks, manifested in a decreased performance in one or both tasks. In the case of standing tasks or during walking this may, at worst, result in a fall. Due to changes in attentional demands of postural tasks as well as processing capacities across the lifespan, it might be assumed that dual-task costs are particularly pronounced in children and older adults. However, these changes in the ability of dual-tasking posture from childhood to old age have not yet been systematically reviewed. We therefore systematically searched online databases for studies comparing postural dual-task performance in different age groups. Seventy-nine studies met inclusion criteria. The results of our systematic review add to the evidence that older adults show age-related decreases in the performance of postural dual-tasks. In children, the limited literature available suggests a slight trend towards reduced performance compared with young adults, with the differences becoming smaller with age. Thus, processing of posture seems to be more cognitively controlled in children and older adults and thus require more of the limited attentional resources. More good-quality studies comparing dual-task ability in children, young, and, ideally, also older adults within the same paradigm are needed to draw unambiguous conclusions about lifespan development of dual-task performance in postural tasks.

Task-dependent changes of corticospinal excitability during observation and motor imagery of balance tasks

It is commonly agreed that non-physical task-execution and the physical execution of a motor task share overlapping neural activation. However, little is known about the potential to increase corticospinal excitability by mental simulation in lower leg muscles. Mental simulation of isolated, voluntary contractions of limb muscles increase corticospinal excitability but more automated tasks like walking seem to have no or only minor effects on motor-evoked potentials (MEPs) evoked by transcranial magnetic stimulation (MEP). This may be related to the way of performing the mental simulation or the task itself. Therefore, the present study aimed to clarify how corticospinal excitability is modulated by different ways of mentally simulating postural tasks. We compared the effects of motor imagery (MI), passive action observation (AO), and the combination of AO+MI on corticospinal excitability.

For this purpose, MEPs and H-reflexes were elicited during three different mental simulation conditions: AO+MI, MI, and AO. For each condition, two balance tasks were evaluated: (1) quiet upright stance (static) and (2) compensating a medio-lateral perturbation while standing on a free-swinging platform (dynamic). AO+MI resulted in the largest facilitation of MEPs followed by MI and passive AO.

MEP facilitation was significantly larger in the dynamic perturbation than in the static standing task. Interestingly, passive observation resulted in hardly any facilitation independent of the task. H-reflex amplitudes were not modulated as well as the background EMG.

The current results demonstrate that corticospinal excitability during mental simulation of balance tasks is influenced by both the type of mental simulation and the task difficulty. As H-reflexes and background EMG were not modulated, it may be argued that changes in excitability of the primary motor cortex were responsible for the MEP modulation. From a functional point of view, our findings suggest best training/rehabilitation effects when combining MI with AO during challenging postural tasks. ■

Selected Publications

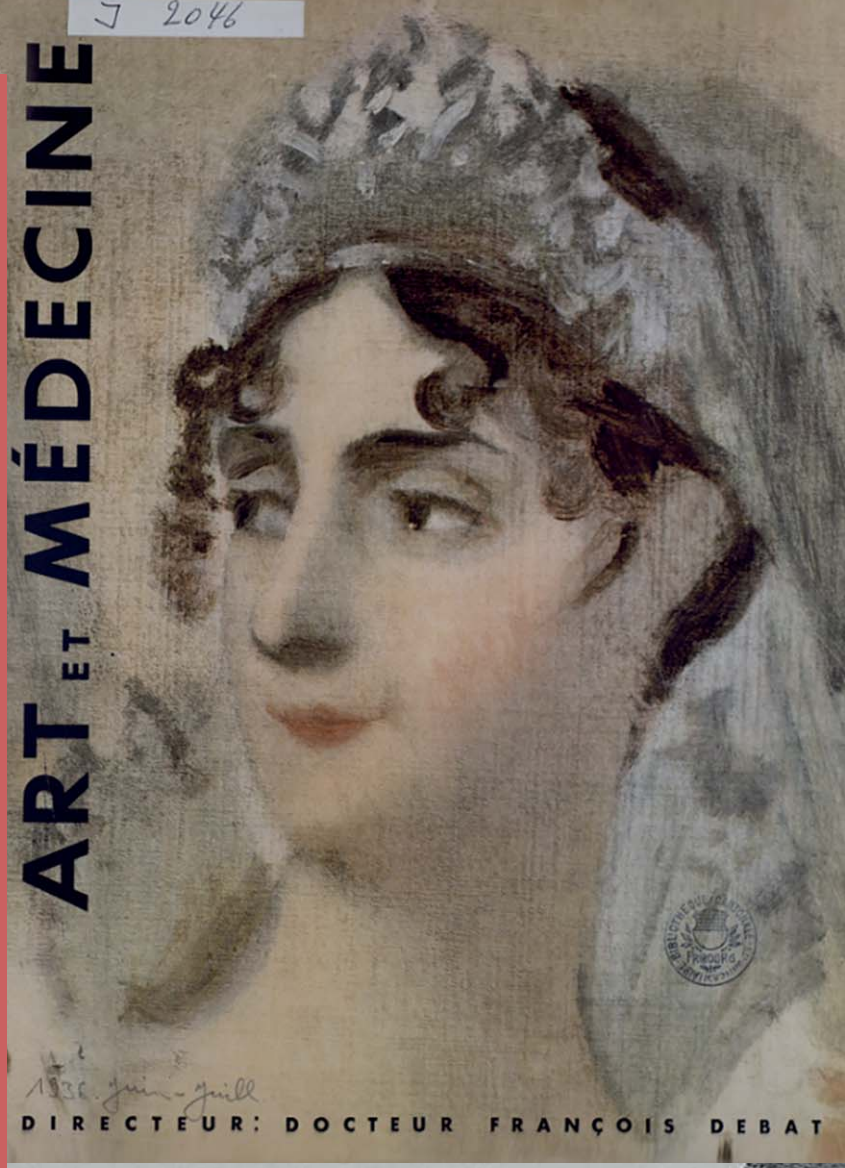
Ruffieux J, Keller M, Lauber B, ***Taube W***
Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports medicine (Auckland, NZ), 2015, 45(12): 1739-1758

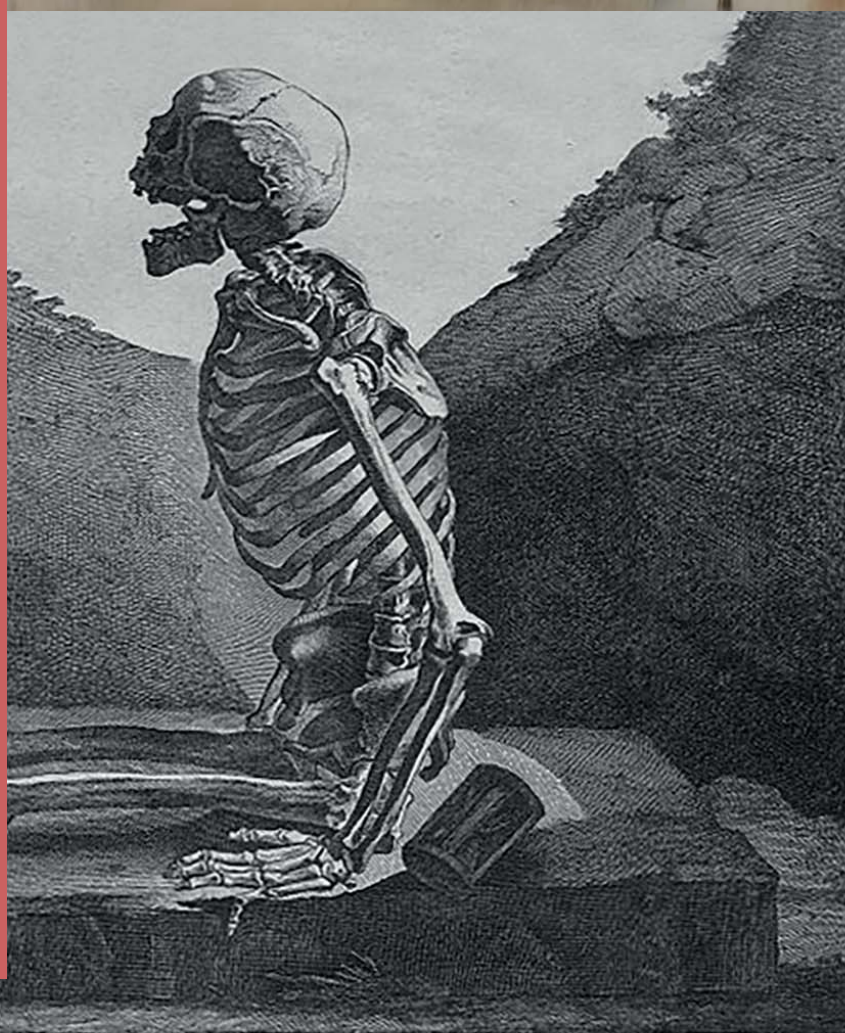
Mouthon A, Ruffieux J, Wälchli M, Keller M, ***Taube W***
Task-dependent changes of corticospinal excitability during observation and motor imagery of balance tasks. Neuroscience, 2015, 303: 535-543

Kuhn YA, Keller M, Ruffieux J, ***Taube W***
Adopting an external focus of attention alters intracortical inhibition within the primary motor cortex. Acta physiologica (Oxford, England), 2016, accepted online

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

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





Alexandre Wenger
Medicine, social sciences and the humanities

Alexandre Wenger
Chair of Medicine and Society

Medicine, social sciences and the humanities

INTRODUCTION

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

1. Reflect on the contemporary developments in healthcare
2. Foster interdisciplinary dialogue
3. Highlight the ethical, social, cultural, legal, economic or intellectual aspects of medical practice
4. Help students position themselves as future practitioners within a rather complex health system

GROUP LEADER
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SECRETARY
Margrit Walthert

ASSISTANT LECTURER
Julien Knebush, PhD

POSTDOCTORAL FELLOWS
Dr. Radu Suciu, PhD
Dr. Thomas Augais, FNS
Dr. Martina Diaz, FNS

DOCTORAL CANDIDATE
Bénédicte Prot

COMPUTER SPECIALIST
Adriano Perlini

Main Research Activities

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

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

Medicine and Society Teaching Program

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

UNI FR
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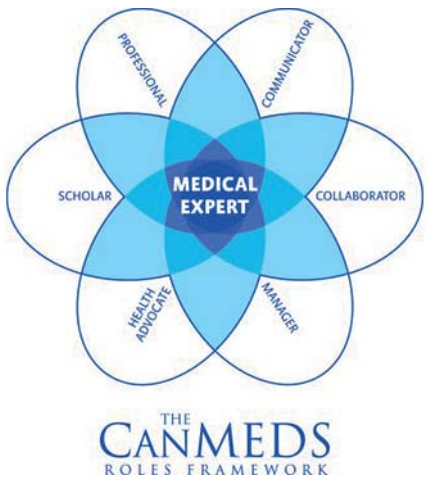
UNIVERSITÄT FREIBURG

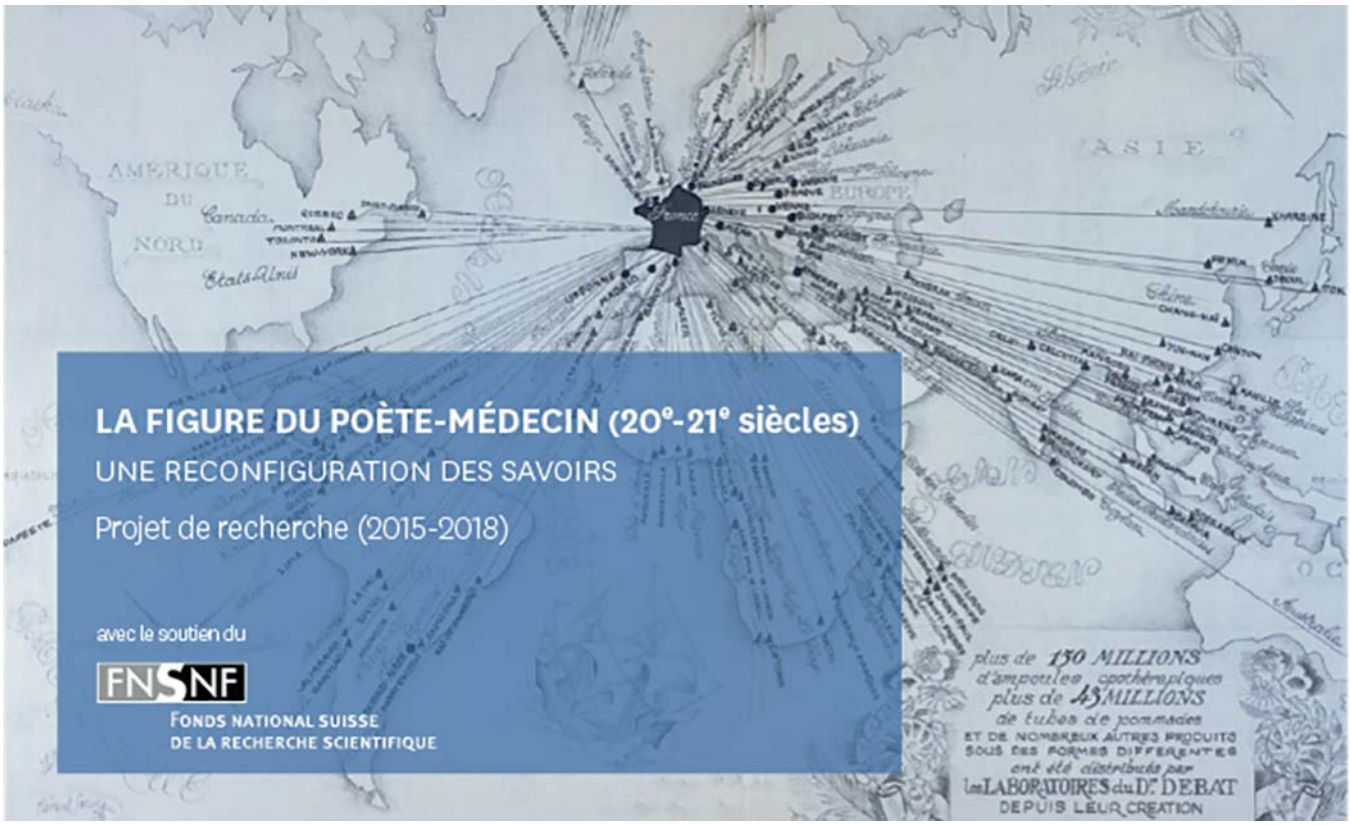
Fig.1 - Brochure of course offering Med & Soc

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, UniBS; Eve Rubli Truchard, CHUV; Markus Zimmermann-Acklin, UniFr)
- ***Public health*** (Philippe Chastonay, UniFR)
- ***History of Medicine*** (Hubert Steinke, UniBE)
- ***Literature, cinema and medicine*** (Alexander Wenger, UniFR; Julien Knebusch, UniFR)
- ***Medical Law*** (Jean-François Dumoulin, UniFR; Christiana Fountoulakis, UniFR; Alexis Overney UniFR; Franz Werro, UniFR)
- ***Medical Anthropology*** (Corina Salis-Gross, UniBE)
- ***Health Economics*** (Stéphane Guérard, UniZH)
- ***Health geography*** (Pascal Handschumacher, University of Strasbourg)
- ***Neuroscience and philosophy*** (Bernard Baertschi, UniGE)
- ***Medicine and the media*** (Patrick Nussbaum, RTS)
- ***Creative writing*** (Julien Knebusch, UniFR, Alexander Wenger, UniFR)

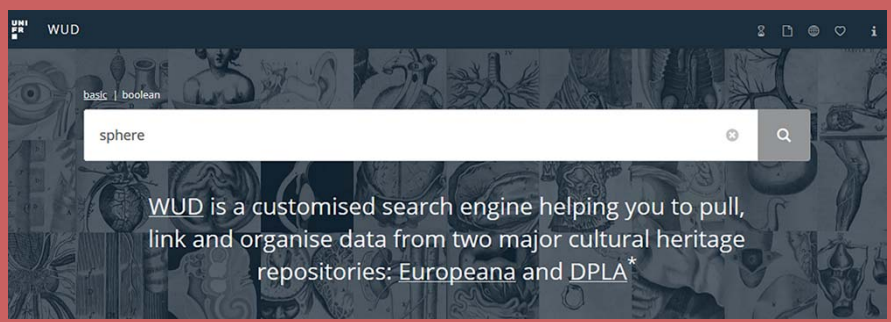
Every year, a seminar is organised as part of the program around a current or controversial subject related to medicine and society (e.g. DRGs, e-health, etc). The lectures and seminars prepare students to better understand their future roles within the medical community. In this respect, the Medicine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





Source: *www.unifr.ch/mh/research*

Online publication



WUD - A customised search engine helping to pull, link and organise data from two major cultural heritage repositories (Europeana and DPLA) is available at unifr.ch/mh/wud. The search engine has been developed as part of the research and outreach activities of the Medicine and Society chair. It helps researchers and students curate and link together collections of cultural artefacts related, but not limited to the field of Medical Humanities.

Third party funding to group leaders

Group Jean-Marie Annoni

Development of neuroimaging research and clinical skills in Lithuania (LSP15004): the programme «Research and development» within the frame work of the Lithuanian-Swiss cooperation programme

Group Carole Bourquin

Swiss National Science Foundation - 2 Individual research grants

Swiss National Science Foundation - ProDoc, research module

European Union Horizon 2020 and SEFRI, Marie Sklodowska-Curie Initial Training Network

IMMUTRAIN

NCCR Bioinspired Materials

Swiss doctoral Program SwissUniversities

Group Marco Celio

Swiss National Science Foundation
«Ein hypothalamischer Kern beeinflust die vegetativen Begleiterscheinungen der positiven Emotionen», 01.10.2015 - 31.09.2018

Group Abdul G. Dulloo

Swiss National Science Foundation, Individual Research Grant 2014 - 2017

Kristian Gerhard Jensen Grant, EPFL/ Lausanne - UniFR Collaboration

Group Luis Filgueira

PI L Filgueira
3R Research Foundation Switzerland
«Validation of a new in vitro microglia model», since 2014

PI M Walch
Project grant by the Swiss National Science foundation (SNSF)
«Characterization of cytotoxic lymphocyte responses against blood-stage human malaria», granted Oct 2016

Project grant by the Kurt and Senta Herrmann Foundation
«Characterization of innate cytotoxic lymphocyte responses against bacterial pathogens on the cellular and molecular level», since 2016

Project grant by the Gottfried and Julia Bangerter-Rhyner-Foundation
«Cytotoxic lymphocyte responses against blood-stage human malaria», since 2015

Project grant by the Research Fund of the University of Fribourg
«Killing blood-stage parasites with CTL effector molecules», since 2015

Project grant by the Research Pool of the University of Fribourg
«Inhibition of bacterial virulence by immune serine proteases», since 2014

Project grant by the Novartis Foundation for Medical-Biological Research
«Immune proteases as a novel bactericidal effector mechanism», since 2014

PI PY Mantel
Novartis Stiftung für medizinisch-biologische Forschung
«Modulation of neutrophil function by extracellular vesicles derived from red blood cells infected with Plasmodium falciparum», since 2015

Research Pool University Fribourg
«Modulation of neutrophil function by extracellular vesicles derived from red blood cells infected with Plasmodium falciparum», since 2015

Group Marie-Noëlle Giraud

KTI - Kommission für Technologie und Innovation, 2016 - 2018

3D-printed bioresorbable polymeric coronary scaffold (PriPoS) for duration: 2 years

PI (research partner): Giraud MN, Co-appliquant : Acrostak (implementation partner), Roseline Nussbaumer (research partner)

SystemsX.ch - Transition Post-doc Fellowship: Modelling Mechanobiology of the artery to drive the design of novel bioresorbable stents, PI: Gautham Yepuri, co-appliquant: Giraud MN, Sven Hirsch, 2015 - 2017

University of Fribourg - Pool of research, Bioresorbable coronary stents, PI: MN Giraud, 2015 - 2016

Group David Hoogewijs

NCCR Kidney.CH, 2015 - 2016

IFORES, 2015 - 2018

ELAN, 2016 - 2017

DFG, 2016 - 2019

Group Anna Lauber-Biason

Swiss National Science Foundation - Sinergia Grant

Swiss National Science Foundation - Individual research Grant

Swiss Society for Endocrinology and Diabetology Cohort Study Grant

Research Pool University of Fribourg

Group Marco Merlo

Swiss National Science Foundation - Individual research grant
Project: «Effects of Alcohol on mental workload: an ERPs study»

Group Jean-Pierre Montani

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

SNF-159512, Cardiovascular effects of acute alcohol consumption: interaction with festive meals, 01.11.2015 - 31.10.2017

Swiss Foundation for Alcohol Research, Cardiovascular interaction of acute alcohol consumption with soft drinks (alcopops), 01.10.2016 - 30.09.2017

Swiss Heart Foundation, Acute cardiovascular and energy expenditure response to the ingestion of tea (Yerba Mate): comparing hot versus cold tea, 01.01.2017 - 31.12.2017

SNF-152998 (G. Solinas), Investigating the Role of PI3Kgamma in Obesity and Insulin Resistance, 01.05.2014 - 30.04.2016

Group Patrice Nordmann

Seeded Grant, Colombia/Switzerland, PI: Nordmann P, 2016

INSERM research grant, PI: Nordmann P, 2016 - 2020

National Reference Center for Emerging Antibiotic Resistance, Nordmann P, 2016 - 2019

Group Gregor Rainer

ESF EURYI Program, 2008 - 2016

SNF Prodoc Program, 2012 - 2015

SNF Research grant, 2012 - 2017

EPFL-HU joint initiative, 2014 - 2015

Group Eric M. Rouiller

Co-investigator FNS Sinergia grant, with Prof. G. Courtine (EPFL PI), Prof. S. Lacour (EPFL co-), Dr J. Bloch (UniL co-), Prof. S. Micera (EPFL co-), 2015 - 2018

Co-investigator FNS grant, «An implanted neuroprosthesis based on peripheral intraneural electrodes to restore grasping functions (NeuGrasp)», Prof. S. Micera (EPFL, PI), 2016 - 2019

Group Curzio Rüegg

Main applicant:

SNF, Research grant, Mechanisms of therapeutic control and escape of breast cancer metastasis, 2015 - 2018

SNF ProDoc RM2 - Extention, Cell migration in tumorigenesis and metastasis, 2015 - 2016

SNF Sinergia Main applicant, Investigating the Role of Class-1 PI3K signaling in Obesity-Mediated Tumor Promotion: the interplay bet-ween fat metabolism, inflammatory cells and angiogenesis, 2015 - 2018

SNF R'Equip, Microchip-based flow cell sorting in biomedicine and material sciences, 2015 - 2016

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

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

3R foundation, Development of in vitro 3D multi-cellular culture models to study the role of heterotypic cellular interactions in colorectal cancer invasion, 2016 - 2017

FR - Research Pool, Monitoring the effects of radiotherapy on the frequency of blood circulating $CD11b^{+}$ ($cKit^{+}$) cells and their transcriptional profile in breast cancer patients, 2016

Co-Applicant:

SNF R'Equip, Main applicant Marie-Noëlle Giraud
«High frequency, high resolution Ultrasound imaging platform (Vevo 2100) for preclinical Imaging», 2015 - 2016

Exchange Fellowip from China*«Emodin prevent pancreatic cancer initiation through regulating Inflam-mation micro-environment»*, 2016 - 2017

Group Albert Santamaria-Martínez

Swiss National Science Foundation - Ambizione

Group Beat Schwaller

Novartis Foundation Grant #16C172
«The role of the calcium-binding parvalbumin in the etiology of autism spectrum disorders (ASD): in the search of convergent pathways in ASD using transgenic mouse models», obtained in December 2016, starting 01.01.2017

KTI-Grant 18778.1 PFLS-LS
«Herstellung von rekombinanten Antikörper gegen das Kalzium-bindende Protein Calretinin», 01.07.2016 - 30.08.2017

SNF Project Funding 310030_155952/1
«Parvalbumin deficiency – a common endpoint mouse model for Autism Spectrum Disorders?», 01.01.2015 - 31.12.2017

Forschungspool UniFR
«Beitrag zur Vorbereitung eines SNF-Forschungs-projekts und Förderung ausgezeichneter Nachwuchs-wissenschaftler» für Dr. Laszlo Pecze, 1.1.2016 - 1.3.2016

Group Wolfgang Taube

Swiss National Science Foundation
Wolfgang Taube (main applicant) with co-applicants Martin Keller, Marco Taubert and Bogdan Draganski: *«Neural adaptations in response to long-term balance learning in young and old: Behavioral, structural, functional and neurophysiological adaptations»*, 2016 - 2019

Swiss Federal Institute of Sport
Martin Keller (main applicant) and Wolfgang Taube (co-applicant): *«How to optimize service speed in tennis? Influence of augmented feedback, focus of attention, grunting and the visual perception»*, 2016

Swiss National Science Foundation
Craig Tokuno (main applicant) and Wolfgang Taube (co-applicant): *«Corti-cal control and adaptability of postural long-latency reflexes»*, 2015

Group Alexandre Wenger

Swiss National Science Foundation - Research project grant

Group Zhihong Yang

Swiss National Science Foundation, PI: Zhihong Yang, Individuel Research Grant

Chinese Scholarship Council, PI: Zhihong Yang

Swiss Heart Foundation, PI: Xiu-Fen Ming

NCCR-Kidney.CH, PIs: Zhihong Yang and Jean-Pierre Montani
Marie-CurieCo-Founding IKPP fellow-ship to Dr. Zhilong Ren, PI: Zhihong Yang

Publications

Group Carole Bourquin

Priebe M, Widmer J, Löwa NS, Abram SL, Mottas I, Woischnig AK, Brunetto PS, Khanna N, ***Bourquin C*****, Fromm KM**
Antimicrobial silver-filled silica nano-rattles with low immunotoxicity in dendritic cells. Nanomedicine, Aug 19, 2016, pii: S1549-9634(16)30110-1, doi: 10.1016/j.nano.2016.08.002 [Epub ahead of print]

Heidegger S, Gößl D, Schmidt A, Niedermayer S, Argyo C, Endres S, Bein T, ***Bourquin C***
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Piccand M, Bessa J, Schick E, Senn C, ***Bourquin C****, Richter WF*
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Anz D, Rapp M, Eiber S, Koelzer VH, Thaler R, Haubner S, Knott M, Nagel S, Golic M, Wiedemann GM, Bauernfeind F, Wurzenberger C, Hornung V, Scholz C, Mayr D, Rothenfusser S, Endres S, ***Bourquin C***
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Hotz C, Roetzer LC, Huber T, Sailer A, Oberson A, Treinies M, Heidegger S, Herbst T, Endres S, **Bourquin C**
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Mycoplasma hyorhinis-Contaminated Cell Lines Activate Primary Innate Immune Cells via a Protease-Sensitive Factor. PLOS ONE, Nov 13, 2015, 10(11):e0142523. (JIF 3.2)

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Selective bispecific T-cell recruiting antibody and anti-tumor activity of adoptive T-cell transfer. Journal of the National Cancer Institute, Print Jan 2015, 107:364, (JIF 15.2)

Group Abdul Dulloo

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Cardiovascular responses to sugary drinks in humans: galactose presents milder cardiac effects than glucose or fructose. European Journal of Nutrition, June 21, 2016 [Epub ahead of print]

Fares EJ, Charrière N, Montani JP, Schutz Y, ***Dulloo AG****, Miles-Chan JL*
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Hunma S, Ramuth H, Miles-Chan JL, Schutz Y, Montani J-P, Joonas N, ***Dulloo AG***
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How dieting makes the lean fatter: from a perspective of body composition autoregulation through adipostats and proteinstats awaiting discovery. Obesity Reviews, 2015, 16 (Suppl 1):25-35

Miles-Chan JL, ***Dulloo AG****, Schutz Y*
Fasting substrate oxidation at rest assessed by indirect calorimetry: is prior dietary macronutrient level and composition a confounder? International Journal of Obesity (Lond), 2015, 39:1114-7

Solinas G, Borén J, ***Dulloo AG***
De novo lipogenesis in metabolic homeostasis: More friend than foe? Molecular Metabolism, 2015, 4:367-77

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Adaptive Thermogenesis in Resistance to Obesity Therapies: Issues in Quantifying Thrifty Energy Expenditure Phenotypes in Humans. Current Obesity Reports, 2015, 4:230-40

Dulloo AG*, Montani JP*
Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: an overview. Obesity Reviews, 2015, 16 (Suppl 1):1-6

Group Marie-Noëlle Giraud

Jain M, Zellweger M, Frobert A, Valentin J, Van dem Berggh H, Wagnièers G, Cook S, ***Giraud MN***
Intra-arterial drug and light delivery for photodynamic therapy using Visudyne: implication for atherosclerotic plaque treatment. Front Physiol, 2016, 7:400

Valentin J, Frobert A, Aljabert G, Cook S, ***Giraud MN***
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Photodynamic therapy for the treatment of atherosclerotic plaque: lost in translation? Cardiovascular Therapeutics, 2016, ahead of publication

Giraud MN*, Borrego I*
Myocardial Tissue Engineering: a 5 year-update. Stem cells in Clinical Application vol3: Liver, Lung and heart regeneration. Editor: Phuc Van Pham, Springer, 2016, ISBN 978-3-319-46693-4

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Group Gregor Rainer

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Group Eric M. Rouiller

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* Equal first authorship

Group Curzio Rüegg

Rodriguez-Lorenzo L, Rafiee S, Reis C, Milosevic A, Moore TL, Balog S, Rothen-Rutishauser B, ***Rüegg C****, Petri-Fink A*
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*equal contribution

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Group Beat Schwaller

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Group Wolfgang Taube

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Group Alexandre Wenger

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«Pratiques de santé et ouverture au monde chez Valery Larbaud», Cahiers Valery Larbaud, under the direction of Françoise Lioure, Paris, Classiques Garnier, n° 52, May 2016

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«„Trois expériences éprises avant tout de la réalité“: Henri Maldiney, André du Bouchet, Pierre Tal Coat», À l'épreuve d'exister avec Henri Maldiney, under the direction of Chris Younès and Olivier Frérot, Paris, Hermann, 2016

Knebusch J
«A la recherche d'une humanité supérieure. Henri Cazalis/Jean Lahor: médecin thermal et poète», La Presse thermale et climatique, 153ème année, 2016

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Knebusch J
«Médecine, sciences de la vie et littérature en France et en Europe de la Révolution française à nos jours, sous la dir. de L. Dumasy-Queffélec et H. Spengler, 3 vol., Genève, Droz, 2014», Gesnerus. Swiss Journal of the History of Medecine and Sciences, n°1, 2016

Wenger A
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«Avant-Propos», Dix-Huitième Siècle 47, N° spécial «Raconter la maladie», 7-19, 2015

Wenger A
«Théophile de Bordeu. Histoire et fiction du grand homme», SVEC 2015:03 (n° spécial La Fabrique de la modernité scientifique: discours et récits du progrès sous l'Ancien régime, dir. par Frédéric Charbonneau), 199-218, 2015

Group Zhihong Yang

Yang Z*, Ming XF*
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Dissertations

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Meetings organised by department members

Group Abdul G. Dulloo

Mini-Symposium, Nov 2016, DepMed, UNIFR
Theme: Body Composition in Health and Disease

8th Fribourg Obesity Research Conference (FORC-2015), Sep 2015,
Theme: Nutrition, Movement and Sleep Behaviors: Their Interactions in Pathways to Obesity and Cardio-metabolic diseases

Group Marie-Noëlle Giraud

Cardiovascular and Metabolic Research Meeting 2016
5th Joint Meeting of the SSC working groups AGLA and CVBG, Jan 14-15, 2016

Cardiovascular and Metabolic Research Meeting 2015
4th Joint Meeting of the SSC working groups AGLA and CVBG, Jan 22-23, 2015

Group David Hoogewijs

XIXth International Conference on Oxygen Binding and Sensing Proteins (O2BIP), Hamburg, Germany. Session on hypoxia response and adaptation, Sep 11-14, 2016

Group Jean-Pierre Montani

8th Fribourg Obesity Research Conference (FORC-2015), Sep 2015
Theme: Nutrition, Movement and Sleep Behaviors: Their Interactions in Pathways to Obesity and Cardio-metabolic diseases

Group Eric M. Rouiller

«Non-human primates», Continuous education meeting LTK20E in animal experimentation, Fribourg, Switzerland, Sep 5, 2016 (with Dr. A. Zbinden and Prof. G. Rainer)

Group Curzio Rüegg

Vascular Remodelling in Biology and Medicine Small Artery Remodelling (SMARTER) Marie Curie Action Workshop, Nov 7-9, 2016, University of Fribourg, Switzerland. Chairs: Rüegg C, Xu Q

6th International conference on tumor-host interaction and Angiogenesis: basic mechanisms and therapeutic implications. Fondazione Stefano Franscini, ETHZ, Monte Verità, Ascona, Switzerland, May 17-20, 2015. Chairs: Rüegg C, Petrova T, Alitalo K

Group Alexandre Wenger

Augais Th, Diaz M, Knebusch J, ***Wenger A***
Workshop «Les réseaux médico-littéraires dans l'entre-deux-guerres: revues, institutions, lieux, figures», University of Fribourg, Nov 24-25, 2016

Vasset S, ***Wenger A***
Workshop Medicine & Media, Wellcome Library, London and Maison Française d'Oxford, Apr 7-8, 2016

Group Zhihong Yang

Annual Swiss Physiology Meeting, Sep 6, 2016, University of Fribourg

5th Joined AGLA & Cardiovascular and Metabolic Research Meeting, Jan 14-15, 2016, Fribourg
Arnold von Eckardstein (Zurich), Ernst Niggli (Berne), Stephan Cook (Fribourg), Marie-Noelle Giraud (Fribourg), Zhihong Yang (Fribourg)

4th Joined AGLA & Cardiovascular and Metabolic Research Meeting, Jan 22-23, 2015, Fribourg
Arnold von Eckardstein (Zurich), Ernst Niggli (Berne), Stephan Cook (Fribourg), Marie-Noelle Giraud (Fribourg), Zhihong Yang (Fribourg)

Lectures and seminars given by department members

Group Abdul G. Dulloo

Seminars of the Lausanne Integrative Metabolism and Nutrition Alliance (LIMNA); at EPFL, Dec 2016
Lecture: How dieting makes some fatter: from a perspective of adipostat(s) and proteinstat(s) awaiting discovery

11th Annual meeting of the Swiss Association for the Study of Obesity, Bern, Nov 2016
Lecture: Metabolic adaptations contributing to weight regain: Clinical significance and molecular mechanisms

Seminars of the Mauritius Medical Update Group, University of Mauritius, Oct 2016
Lecture: Beyond BMI: Phenotyping the Obesities

International Symposium on Energy Balance, University of Hohenheim, Stuttgart, Germany, Sep 2016
Theme: Regulation of Energy Balance: Classical Concepts and Novel Insights
Lecture: Novel Perspectives into Research on Energy Balance

13th International Congress on Obesity, Vancouver, Canada, May 2016
Talk: Energy expenditure phenotyping during low physical activity levels: validation using low power cycling exercise in sedentary humans

European Biotechnology Network & European Association for Study of Obesity (EBN-EASO) jointly-hosted Webinar, Jan 2016
Theme: «Beyond BMI: Improving obesity diagnosis for better prevention, diagnosis, stratification and treatment of patients with a high risk of co-morbidity»
Lecture: Body composition phenotypes in pathogenesis of cardiometabolic diseases

Seminars of University of Besançon, France, Nov 2015
Lecture: Does Dieting and weight cycling make people fatter?

Singapore Agency for Science, Technology and Research Conference, Singapore, Oct 2015
Public Lecture: Does Dieting and weight cycling make people fatter?

8th Fribourg Obesity Research Conference, Fribourg, Switzerland, Sep 10, 2015
Theme: Nutrition, Movement and Sleep Behaviors
Lecture: Movement-associated isometric thermogenesis: a neglected variable in energy expenditure and obesity predisposition

22nd European Congress on Obesity (ECO), Prague, May 6-9, 2015
Symposium Debate: Central or Peripheral Regulation in Obesity and Insulin Sensitivity
Lecture: The need to focus on Central regulations

Group David Hoogewijs

«Androglobin, a novel oxygen-binding protein expressed in the hypoxic testis, is essential for spermatogenesis», Hypoxia 2016, Nantes, France, Oct 2016

«Comparative oxygen physiology», National Museum of National History, Department of Regulations, Development and Molecular Diversity, Paris, France, host G. Levi, Sep 2016

«Androglobin, the fifth mammalian globin type is essential for spermatogenesis», XIXth International Conference on Oxygen Binding and Sensing Proteins (O2BIP), Hamburg, Germany, Sep 2016

«The globin superfamily: from bacteria to mammals», Clinic for Anesthesiology, University of Duisburg-Essen, Germany, host M. Hartmann, May 2016

«Distal hypoxia response elements mediate HIF regulated gene expression» MPN&MPNr-EuroNet Eleventh Meeting: Diagnostic of sporadic and hereditary myeloproliferative diseases Poznan, Poland, Apr 2016

«Diversity of globins: beyond hemoglobin and myoglobin», Institute of Physiology, University of Fribourg, Switzerland, host F. Müller, Feb 2016

«Novel oxygen-binding globins», Institute of Physiology, University of Göttingen, Germany, host B. Schwappach, Jan 2016

«Destruction of a distal hypoxia response element abolishes transactivation of the PAG1 gene mediated by HIF-independent chromatin looping», 10th International Lübeck Conference on the Pathophysiology and Pharmacology of Erythropoietin and other Hemopoietic Growth Factors, Lübeck, Germany, June 2015

Group Anna Lauber-Biason

«Abweichende Geschlechtsentwicklung». Pharmazeutische Gesellschaft Zürich, CH, Dec 8, 2016

«Stress, Happiness und Hormone». LabMed, Bern, CH, Nov 19, 2016

«Steroids and rare (endocrine) diseases». SGED/SSED Jahresversammlung, Bern, CH, Nov 17-18, 2016

«Das Polycystische Ovarial-Syndrom (PCOS): Klinik, Genetik und Epigenetik». Fortbildung für Ärzte und med. Fachpersonal, labormedizinisches Zentrum Dr. Risch, Liebefeld (BE), CH, Nov 3, 2016

«Transition from pediatric to adult care». COST DSDnet training School, Bologna, IT, Oct 6-8, 2016

«Puberty induction and HRT in girls». COST DSDnet training School, Bologna, IT, Oct 6-8, 2016

«Biologie der Geschlechts-Entwicklung». Swiss Society for Endocrinology/Diabetology Continuous Medical Education, Biel (BE), CH Apr 21, 2016

«Das Adrenogenitale Syndrom: vom Neugeborenenscreening zur Diagnose». Schweiz. Informationswoche für Labor und Medizin, Horgen (ZH), CH, Apr 19, 2016

«Steroid profile in the diagnosis of endocrine diseases: many strength and some weaknesses». Winter Symposium of the Israel Endocrinology Society. Tel Aviv, Israel, Jan 29, 2016

«Why girls will be girls: WNT4 and its partners in human ovarian development». Winter Symposium of the Israel Endocrinology Society. Tel Aviv, Israel, Jan 29, 2016

«Why boys will be boys and girls will be girls: human sex development and its defects». 7th Vertebrate Sex Determination Symposium, Kona (HI), USA, Apr 13-15, 2015

«La sindrome dell'ovaio policistico nel terzo millennio: clinica, genetica ed epigenetica». Seminario di formazione in endocrinologia/ginecologia (Associazione Ginecologi Canton Ticino), Hotel Dante, Lugano, Mar 26, 2015

Group Marco Merlo

Marco Merlo

«La désorganisation schizophrénique: Aspects cliniques» 13e Congress de l'Encephale, Jan 2015

«Atypische Antipsychotika» 10. Wiler Mittagssymposium. Wil, Mar 2015

«Analyse des pratiques de réhabilitation, quel avenir?» Update in psychiatry. Neuchâtel, June 2016

«Psychiatrie au futur: Soins et prévention dans la psychose» 35èmes Journées de la Société de l'Information Psychiatrique, Bruxelles, Sep 2016

Gregoire Favre

«Schizophrénie et neurosciences: de la recherche à la clinique». Lesson (2h) in Marster Psychology, Institute of Psychology, UNIL, Nov 2015

Group Jean-Pierre Montani

«Markers of renal function and evolution with age», Health Sciences eTraining Foundation, Bern symposium, Oct 13, 2016

«Intégrité scientifique: principes/fraude/conflits d'intérêt», Formation d'investigateur Clinique, CHUV-UNIL, Sep 5, 2016

«A Guytonian view of sodium homeostasis, sodium sensitivity and blood pressure control», OMRON Corporation, Kyoto, May 20, 2016

«Salt and Health», Cycle of three conferences to the Museum of Natural History, Fribourg:
(1) «Sel et maladies cardiovasculaires», Dec 10, 2015
(2) «Sel et maladies associées» Feb 18, 2016
(3) «Salz und Gesundheit», Feb 25, 2016

«Hypertension, sodium transport and Guyton's Hypothesis», Nephrology Symposium, Inselspital Bern, Sep 22, 2015

«Nutrition, Movement & Sleep Behaviors», Introduction to Fribourg Obesity Research Conference (FORC-2015), Fribourg, Sep 10, 2015

Group Patrice Nordmann

Patrice Nordmann

RICAI (36ème Réunion de Chimiothéparie Anti-Infectieuse), Paris/FR, Dec 13-14, 2016, «Emerging Resistance to polymyxins in Enterobacteriaceae»

BacTouBac, Toulouse/FR, Dec 6-7, 2016, «Emerging Antibiotic Resistance»

TTA goes Nordic - Turning the Tide of Antimicrobial Resistance, Oslo/NO, Nov 28, 2016, «Emerging Antibiotic Resistance in 2016»

45th Annual Meeting of the Japanese Society for Bacterial Drug Resistance, Hiroshima/JP, Oct 21-22, 2016, «Emerging resistance to polymyxins in Enterobacteriaceae»

17th World Vaccine Congress 2016,Barcelona/E, Oct 10-12, 2016, «Epidemiology: how big is the problem of AMR?»

ATCIP 2016 (Antimicrobial Therapy in Immunocompromised and Critically Ill Patients), Lugano/CH, Sep 29-30, 2016, «Novel Antibacterial Agents»

26th ECCMID (Europea Conference of Clinical Microbiology and Infectious Diseases), Amsterdam/NL, Apr 9-12, 2016, «Emerging antibiotic resistance and their detection»

8th International Congress of Laboratory and Clinical Medicine & 1st National Congress of Basic Medical Sciences, Tehran/IR, Feb 6-7, 2016, «Detection of emerging antibiotic resistance»

27th Annual Meeting of Japanese Society for Clinical Microbiology, Sendai/JP, Jan 28-29, 2016, «Worldwide emergence of antibotic resistance»

IBis-Institut of Biomedicine of Sevilla, Sevilla/SP, Jan 19, 2016, Workshop: «Global spread of carbapenemase-producing Gram negative bacilli: a major challenge for the treatment and infection control», «Emergence of carbapenemase producers: here is the storm»

43rd International SRLF Congress (French Intensive Care Society), Paris/FR, Jan 16, 2015, «Résistances Emergentes 2015 en Réanimation»

25th ECCMID-European Congress of Clinical Microbiology and Infectious Diseases, Apr 28-30, 2015, Copenhagen/DK «Rapid Diagnostic of Emerging Antibiotic Resistance»

JNI Journées Nationales d'Infectiologie Nancy/FR, June 6, 2015, «Epidemiologie des résistances emergentes»

5th Edition World HAI Resistance Forum, Veyrier-du-Lac/FR, June 14-16, 2015, «Rapid diagnostic techniques for antibiotic resistance»

American Society for Microbiology (ASM) Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC), San Diego CA / USA, Sep 15-17, 2015, Lecture for the Research Award: ASM's premier award honoring outstanding accomplishment in antimicrobial research, «Wordwide spread of antibiotic resistance»

ESCMID Post-Graduate Education Course, Verona/IT, Sep 22-23, 2015, «Carbapenemases in Enterobacteriaceae: challenges and preparedness»

XIII National Congress for Microbiology Antalya/TK, Nov 21, 2015, «Emerging Antibiotic Resistance»

RICAI 2015, 35ème Réunion interdisciplinaire de chimiothérapie anti-infectieuse, Paris/FR, Dec 14-15, 2015, «Novel techniques for diagnostic of antibiotic resistance»

Laurent Poirel

40th Annual Conference of Indian Association of Medical Microbiologists, Chandigarh/IND, Nov 25-27, 2016, «Carbapenemases in the world: which and where are the threats?»

8th International Meeting on Biotechnology «BIOSPAIN 2016» Bilbao/SP, Sep 30, 2016, «Innovations for the diagnosis and treatment of multidrug resistant bacetrial infections» «Rapid biochemical and culture-based techniques for detecting multidrug resistance in Gram negatives»

Kuwait Institute for Medical Specialization (KIMS) Annual Meeting Kuwait City, Kuwait, Mar 6-8, 2016, «Carbapenemase in the world: which and where are the threats?», «Antibiotic resistance in food, animals and people», «The future diagnostics of antimicrobial resistance (culture and non-culture techniques)», «What every laboratory should be doing for detection of carbapenem-resistant Enterobacteriaceae?»

26th European Congress of Clinical Microbiology and Infectious Diseases Amsterdam/NL, Apr 9-12, 2016 «Genotypic and phenotypic detection of colistin resistance in Gram-negative bacilli»

ESCMID European Congress of Clinical Microbiology and Infectious Diseases Summer School. Seville/SP, July 2-7, 2016 «Phenotypic and genotypic methods for detection of carbapenemases»

1st Antibiotic Resistance Conference, Caiparica/PT, Jan 20, 2015, «Carbapenemase-producing Enterobacteriaceae; European epide-miology and detection techniques»

Royal Society of Medicine Symposium «Antibacterial resistance: the bigger picture», London/GB Mar 5, 2015, «Superbugs and genes uprising: who are the enemies? How can we combat them?»

American Society of Microbiology General Meeting, New Orleans, USA, May 10, 2015, «The biology and epidemiology of carbapenemase-producing bacteria: what we know and what we don't know»

International Acinetobacter Meeting, Athens/GR, June 10, 2015, «New insights into dissemination and detection of antibiotic resistance»

Panamerican Infectious Diseases Meeting, Quito/EQ, July 17, 2015, «Mechanisms of Resistance to Colistin»

European Society for Microbiology and Infectious Diseases (ESCMID) Summer School, Istanbul/TK, July 4-8, 2015, «Conventional vs newly developed techniques for identification of resistance»

ESCMID Post-Graduate Education Course, «Carbapenemases in Enterobacteriaceae: challenges and preparedness», Verona/IT, Sep 22-23, 2015, «Multiple genetic vectors as a source of spread of carbapenemase producers»

South Pacific Congress, «Value of Medical Laboratory Science», Auckland/NZ, Oct 28, 2015, «Emerging antibiotic Resistance in a world of globalization»

Association for Molecular Pathology (AMP) 2015 Annual Meeting, Austin/USA, Oct 13, 2015, «Carbapenemases; detection and epidemiology»

Brazilian Congress of Microbiology 2015, Florianopolis/BR, Oct 2015, «Genetic context of Carbapenemases»

35ème Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuses, Paris/FR, Dec 14-15, 2015, «Diagnostics actuels et épidémiologie de la résistance aux polymyxines»

Group Eric M. Rouiller

«Neurosciences: Le cerveau révèle ses secrets, opportunité pour une meilleure qualité de vie. KeyNote lecture and Moderator: Repousser les limites du savoir», Rouiller EM. BioAlps Networking Day 2016, Campus Biotech - Genève - Switzerland, Nov 2, 2016

«Non-human primates: Swiss context, importance, history and perspectives» Rouiller EM. Training Course in animal experimentation LTK20E, Fribourg Switzerland, Sep 5, 2016

«Main et Cerveau chez les primates non-humains et chez l'homme», Rouiller EM. La mano e l'uomo - Symposio Eccles, Monte-Verità, Ascona, Switzerland, Oct 3, 2015

«Post-lesional cortical plasticity», Rouiller EM. The Brain and Gliomas - When the connections are crucial, Brescia Italy, Sep 24, 2015

«Non-Human primates (NHP) models in neuroscience», Rouiller EM. ABS Animal Science Day 2015, Bern Switzerland, Sep 11, 2015

Group Curzio Rüegg

Adolphe Merkel Institute, Invited Lecture, University of Fribourg, Fribourg, Switzerland, Nov 29, 2016

Friedrich Miescher Institute FMI, Invited Lecture, Basel Breast Consortium Tandem Seminar Series, Basel, Sep 6, 2016

Deutsches Krebsforschungszentrum (DKFZ), Invited Seminar, Heidelberg, Germany, July 5, 2016

Institut für Tumorbiologie, Invited Seminar, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, 2016

Inserm Unit U1029, Invited Seminar, University of Bordeaux, Bordeaux, France, May 20, 2016

Breast Cancer Translational Res Lab - BCTL, Invited Seminar, Institut Jules Bordet, Brussels, Belgium, May 9, 2016

BRIC, Biotech Research and Innovation Center, Invited Lecture, University of Copenhagen, Copenhagen, Denmark, Mar 30, 2016

Laboratory Experimental Surgical Oncology, Section Surgical Oncology, Invited Seminar. Department of Surgery, Erasmus MC, Erasmus University, Rotterdam, The Netherlands, Jan 28, 2016

Josephine Nefkens Oncology Lecture, Erasmus MC, Erasmus University, Rotterdam, The Netherlands, Jan 27, 2016

Invited Seminar, University of Berne, Institute of Pathology, Berne, Switzerland, Nov 10, 2015

6th International conference on tumor-host interaction and Angiogenesis, Invited Lecture. Monte Verità, Ascona, Switzerland, May 17-20, 2015

Annual meeting of Swiss Gynecology Department Heads, Invited Lecture, Bern, Switzerland, May 6, 2015

Introductory lecture. 1st NCCR bio-inspired materials, annual visit, Fribourg, Switzerland, Apr 27-28, 2015

INSERM workshop on «Methodologies and Experimental Strategies in Angiogenesis Research», Invited Lecture, Bordeaux, France, Apr 8-10, 2015

German Society for Matrix Biology, Invited Lecture, Muenster, Germany, Mar 12-14, 2015

SCOPES workshop, Invited Lecture, University of Kragujevac, Serbia, Feb 2-3, 2015

Group Alexandre Wenger

Alexandre Wenger

«The Knick», cycle The Historians, season 1: cycle de conférences de la Maison de l'Histoire, UniGe, (with Rieder Ph), Dec 13, 2016

«Les Medical Humanities», Colloque de médecine générale, CHUV / Medical School Univeristy of Lausanne, Dec 13, 2016

«Prophylaxe von venerischen Krankheiten: Geschichte, Kino, Literatur / Prophylaxie des maladies vénériennes: histoire, cinéma, littérature», conference of the Swiss Society of Dermatology and Venerology, HUG, Aug 26, 2016

«Les intuitions scientifiques de Mary Shelley», round table (org. Fondation Brocher), Fondation Martin Bodmer, Cologny, May 18, 2016

«Medical Humanities: Mapping the Landscape», Centre for Medical Humanities, University of Zurich, Apr 5, 2016

«Le médecin doit-il porter la barbe?», Rencontre des Medalumi, University of Fribourg, Nov 13, 2015

«Enseigner les Medical Humanities: buts, enjeux et défis», workshop Teaching Medical Humanities, University of Fribourg, (with Knebusch J), Sep 18, 2015

«Faire écrire les étudiants en médecine: une nécessité!», Congrès du CoSHSEM, Lyon, (with Knebusch J), June 24-26, 2015

«Les défis de l'enseignement des SHS en médecine», Table ronde inaugurale, Congrès du CoSHSEM, Lyon, June 24-26, 2015

«WUD: A new search engine in the Medical Humanities», (with A. Perlini) Salon Digital Humanities, University of Geneva, May 15, 2015

«Comment l'esprit vient aux filles… et comment les garçons le perdent. Maladie d'amour, médecine et fiction romanesque (18e s.)», International Symposium The Life of the Mind: Literature, Aesthetics, and the «sciences de l'homme» 1700-1900, The University of Wisconsin-Madison, Apr 16-18, 2015

«Littérature et sciences: un défi méthodologique?», École doctorale CUSO, University of Neuchâtel, Mar 12, 2015

Julien Knebusch

«Introduction», study day Les réseaux médico-littéraires dans l'entre-deux-guerres, University of Fribourg / Swiss National Science Foundation, Nov 24-25, 2016

«Paul Morand et la „surexcitation cosmopolite"», conference Santé et bien-être à l'épreuve de la littérature, VIIIème Rendez-vous de la Critique, Faculty of Letters, University of Porto, Oct 3-4, 2016

«A la recherche d'une humanité supérieure. Henri Cazalis/Jean Lahor: médecin thermal et poète», study day «Que faire de la littérature thermale ?», Société française de médecine thermale et Université Paris 7 Diderot, Châtel- Guyon, May 10, 2016

«Mondor et Valéry : vers une poétique de la chirurgie», with Thomas Augais, conference Médecins écrivains en France et dans les cultures francophones, Universität des Saarlandes, Saarbrücken, Jan 28-30, 2016

«Enseigner les medical humanities: exemple d'un cours sur le thermalisme du 19è s. au début du 20è s.», Teaching Medical Humanities, annual meeting of the Swiss Society of the History of Medicine and Sciences, University of Fribourg, Sep 18, 2015

«Présentation du cluster „Médecine et société": l'exemple d'une recherche sur l'histoire du thermalisme au 19è – début 20è siècle», retreat of the University of Fribourg Department of Medicine, Schwarzsee FR, June 30, 2015

«Larbaud curiste. Pratiques de santé et ouverture au monde», exposition Larbaud curiste, Fonds patrimonial Valery Larbaud, Médiathèque de Vichy, Apr 27, 2015

Julien Knebusch, Alexandre Wenger

«The Image of the Poet-Physician», Medicine and Media, Wellcome Library London & Maison Française d'Oxford, Apr 7-8, 2016

«Faire écrire les étudiants en médecine: une nécessité!», with Prof. A. Wenger, conference of Collège des Enseignants de Sciences Humaines et Sociales en Médecin et Santé, Faculté de Médecin de Lyon Est, June 24-26, 2015

Martina Diaz, Alexandre Wenger

«La revue Art et médecine: vers une géographie des réseaux de poètes-médecinsw dans les années 1930», conference Médecins écrivains en France et dans les cultures francophones, Universität des Saarlandes, Saarbrücken, Jan 28-30, 2016

Benedicte Prot

«Le nu et la retenue, les sens et l'indécence. Représentations du corps féminin et du corps du médecin dans les débats sur le rôle de l'accoucheur», study day Le corps social au XVIIIe siècle. Regards sur le corps et discours social dans l'Europe des Lumières, University of Geneva, Sep 23, 2016

«L'anatomie sensuelle de la Vénus de Médicis au XVIIIe siècle», 57th Annual Conference of the Society for French Studies, University of Glasgow, Jun 27-29, 2016

«La nudité entre littérature et médecine au XVIIIe siècle (Le Camus, Sade, Diderot)», Journée internationale des jeunes chercheurs. Aux frontières des disciplines. Recherche et interdisciplinarité: quelles pratiques pour quels enjeux?, Université de Lorraine, Nancy, Jun 17, 2016

«Médecins et moralistes face aux „abus des nudités de gorge" au XVIIIe siècle», ADEFFI PG Symposium, Queen's University Belfast, Mar 7, 2015

Group Zhihong Yang

L-arginine metabolism and arginase in health and disease. Seminar series: «Current topics in Pharmacology and Theranostics», Institute of Pharmacology, Inselspital, University of Bern, Switzerland, Dec 7, 2016

Arginase in vascular aging and disease. 2016 SmArteR Workshop (organized by Dr. Curzio Rüegg and Qingbo Xu), University of Fribourg, Switzerland, Nov 7-9, 2016

Targeting Arginase in Age-associated Cardiovascular and Metabolic Diseases. University Bern, DKF, Switzerland, Nov 9, 2015

Further achievements

Group Carole Bourquin

Nomination as Full Professor, University of Geneva

Group Marie-Noëlle Giraud

Ines Borrego, PhD student Second **best poster presentation** Cardiovascular and metabolic Research meeting Jan 2016

Marie-Noelle Giraud, **prize for Business Concept** from the CTI/EPFL/HEG-FR Entrepreneurship - Fall Edition 2016 in Fribourg (together with other collaborators from the faculty of Science, Renata Andrade Bitar (Department of Medicine), Meike Ramon (Department of Psychology), Frederik Neuhaus (Department of Chemistry) and Christoph Fasnacht (HEG-FR)

Broadcast: Radio suisse romande: CQFD, «La régénération des cellules du cœur après un infarctus»

Group Anna Lauber-Biason

Networking
Swiss Representation and active participation in international consortia, e.g. COST Action DSDnet of the European Community (http://www.dsdnet.eu/general-information-in-english.html) and Study Sessions (e.g. IFCAH). Several Collaborations with colleagues inland and abroad (see also publication list)

Public relations and communication
Significant contribution in communicating advances in DSD research and understanding to the community (most recent Horizons, https://issuu.com/snsf/docs/horizons_107-en-issue?e=1883535/31585077; Tages Anzeiger 02.03.2016, page 58)

Group Jean-Pierre Montani

Scientific Committee of the Marcel Benoist Prize (renewal 2015-2019 by the Federal Council)

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

Interviews for the broadcasts of the Télévision Suisse Romande
(1) A Bon Entendeur, Manuelle Pernoud, Oct 4, 2016
(2) 36.9, Isabelle Moncada, Nov 23, 2016

Group Patrice Nordmann

Creation of Research Unit/Structure
Foreign INSERM Unit (Institut National de la Santé et de la Recherche Médicale, France), University of Fribourg; *Emerging Antibiotic Resistance in Gram negatives*, June 2016

National Reference Center for Emerging Antibiotic Resistance (*Nationales Referenzlaboratorium zur Früherkennung neuer Antibiotika-resistenzen und Resistenzmechanismen*), University of Fribourg, Office Fédéral de la Santé Publique, Berne, Dec 2016

Awards
Thomson Reuters Award 2016, Top 1% most cited researchers, any scientific field (Nordmann P and Poirel L), (3,100 researchers selected worldwide, 78 selected for Switzerland)

Industrial development
Test for determining suscepibility to resistance to polymyxins in *Enterobacteriaceae*, «*Rapid Polymyxin NP test*», European market by Nov 15, 2016 (ELItech Ltd.)

Public outreach activities
INSERM communication, Paris. Brèves. Mis au point du test de diagnostic rapide de la résistance aux polymyxines, Dec 7, 2016

18.11.2016, Le Figaro Santé, Print media: «Antibiotiques - la hausse de la consommation inquiète»

02.10.2016, Le Matin Dimanche, Print media: «Superbactéries - La menace silencieus»

22.09.2016, Radio Vatican, «Le recours excessif aux antibiotiques inquiète le Saint-Siège et la communauté scientifique»

03.09.2016, La Gruyère, Print media: «L'ère des infections mortelles»

03.07.2016, Mise au point, Emission télévisuelle RTS: «Alerte à la résistance aux antibiotiques»

27.06.2016, CQFD, Emission radio RTS: «Des super-bactéries qui résistent à tous les antibiotiques»

15.05.2016, Swiss Lab Med. «L'inexorable développement de la résistance aux antibiotiques»

18.03.2016, Beobachter, Print media: «Killer-Keime - Das Ende der modernen Medizin»

19.01.2016, La Liberté, Print media: «Découverte inquiétante à Fribourg»

15.10.2015, CQFD, Emission radio RTS: «Résistances aux antibiotiques en Suisse»

15.02.2015,La Gruyère, Print media; «Résistances Emergentes aux antibiotiques»

Group Eric M. Rouiller

Partnership for Non-Human Primate Research platform at UniFr with EPFL and Centre Wyss (Campus Biotech, Geneva) as an extension of the Swiss Primate Competence center for Research (SPCCR: www.unifr.ch/spccr/)

Group Curzio Rüegg

Felix Burda **Finalist Award** 2015, Berlin, for the development of a blood-based test for the early detection of colorectal cancer

Re-election as member of the Scientific Committee of the Swiss Cancer League for the period 2016-2018

Re-election as member of the Scientific Evaluation Committee of the Advanced Postdoc. Mobility in Biology and medicine of the Swiss National Science Foundation

Re-election as member of the Scientific Committee of the Ligue Fribozurgeoise contre le Cancer

Article in Universitas Oct 2015, «Une thérapie en or»

University News, May 2015, «Cancer du colon: folie à deux»

Scientific Report Swiss Cancer League, 2015, Featured research domain «Tumour microenvironment and metastasis»

36.9. Our lab participated to the 10th year anniversary from the 36.9 emission on new therapy against cancer with a **fully report** and **interview**. Link: http://www.rts.ch/emissions/36-9/7389197-nouvelles-therapies-contre-le-cancer.html

Group Wolfgang Taube

Audrey Mouthon

1st place «Young Investigator Award», Swiss Society of Sport Science, Lausanne, Switzerland

Yves-Alain Kuhn

5th place «Young Investigator Award», European College of Sport Science, Vienna, Austria

Martin Keller

1st place «Young Investigator Award», European College of Sport Science, Malmö, Sweden

«Prix Vigener 2015»: **best PhD thesis** in the Faculty of Science

Group Alexandre Wenger

Alexander Wenger

«Le retour de la syphilis» – RTS1, invité du jour du jour du 12:45, Dec 6, 2016

«Manger végan : une industrie ?» – RTS 1, **broadcast** A Bon Entendeur, Nov 15, 2016

«Le Végétarisme» – Invité du jour, RTS La Première, **broadcast** de société Tribu, Sep 30, 2016

«200 ans après, Frankenstein interpelle toujours la science» – RTS, **broadcast** sciences et santé CQFD, June 8, 2016

«Pourquoi devient-ont végétarien ?» – **interview** in Universitas, pp. 10-12, June 4, 2016

«Frankenstein toujours d'actualité?» – RTS 2, **broadcast** Babylone, May 24, 2016

«Un **Prix d'écriture** pour les étudiants en médecine», Bulletin des médecins suisses, 2016, 97 (42), 1440-1442

«**Auszeichnung** für die Studierenden der Medizin: Ein Preis für den Besten Bericht», Schweizerische Ärztezeitung, 2016, 97 (42) 1440-1442

«Quoi d'neuf, docteur ?» – **interview** Universitas, Oct 2015

Julien Knebusch

«Des belles-lettres à la bonne médecine. Entretien avec Emmanuel Venet, psychiatre et écrivain», Alma & Georges, Oct 2016

«Poésie et société», Radio Primitive, **broadcast** «De l'encre sur les ondes», Nov 10, 2015

«Le thermalisme, entre médecine et société», Radio Télévision Suisse, **broadcast** «Tribu» de Laurent Caspary, June 10, 2015

Group Zhihong Yang

Mr. Yuyan XIONG (PhD) received the Young Investigator **Fellowship** of 2015 Eur Athero Society (EAS) (EAS 2015 Fellowship)

Yi YU (PhD student) received the Young Investigator **Fellowship** of 2016 Eur Athero Society (EAS) (EAS 2016 Fellowship)

Zhihong Yang, **Vice-president** of Swiss Physiology Society from 2015

Zhihong Yang, **Promotion** to Full Professor of Integrative Physiology, Nov 1, 2016

«Der Geist sitzt im Herzen», **Interview** by Zürich Heart House, 2015

«Autophagie: Saubermachen in der Zelle», Universität Fribourg **Communication**, 2015
http://www.unifr.ch/news/de/14187/

«Vascular investigations – Age and Arginase», **Interview** by International Innovation, 2015, issue 184: page 37-39

External experts/panels for grant evaluation

Zhihong Yang, External thesis advisor of PhD-Doctoral thesis (Mss. Srividya Velagapudi, University of Zürich 2015/2016)

Zhihong Yang, External expert for recruitment of «Assistant Professor-ship in Vascular Biology» at Faculty of Medicine, University of Zürich, Switzerland

Zhihong Yang, External expert for Deutsche Forschungsgemeinschaft (DFG), Germany

Zhihong Yang, External expert for European Science Foundation

Zhihong Yang, External expert for Diabetes UK Research Foundation

Zhihong Yang, External expert for The Wellcome trust/ DBT

Xiu-Fen Ming, International panel expert for reviewing & hearing participation of a K1-Application: ASCage-C for The Austrian Research Promotion Agency (FFG)

Xiu-Fen Ming, External expert for reviewing of a research proposal of Funding scheme SONATA BIS for the executive government agency of National Science Centre Poland

Acknow-ledgments

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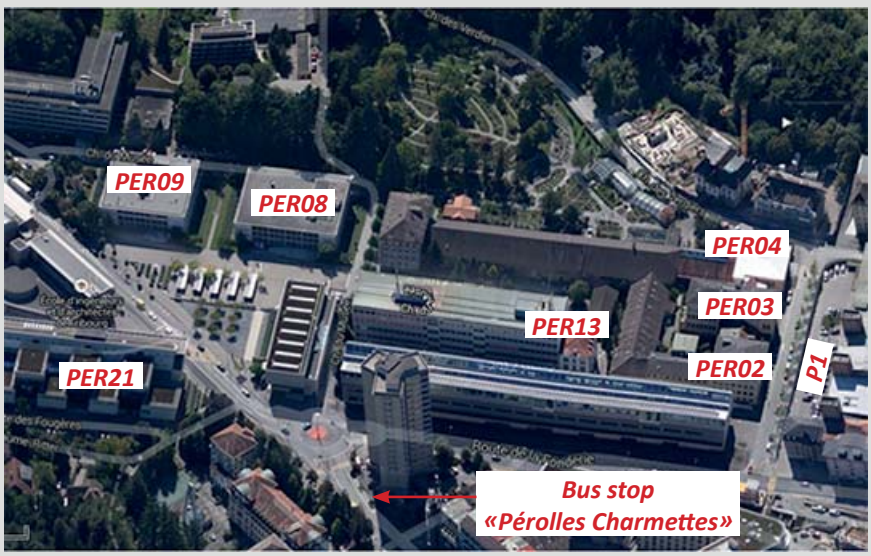
Visiting the Department of Medicine at UNIFR

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 along «Rue Albert Gockel» (P1) or behind the «College of Engineering and Architecture of Fribourg» (P2) - 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 permits available for visitors.



PER13
- Department of Medicine

PER02
- Anatomy
- Pathology

PER03
- Anatomy
- Medical Humanities

PER04
- Microbiology

PER09
- Cardiology
- Endocrinology
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- Pharmacology
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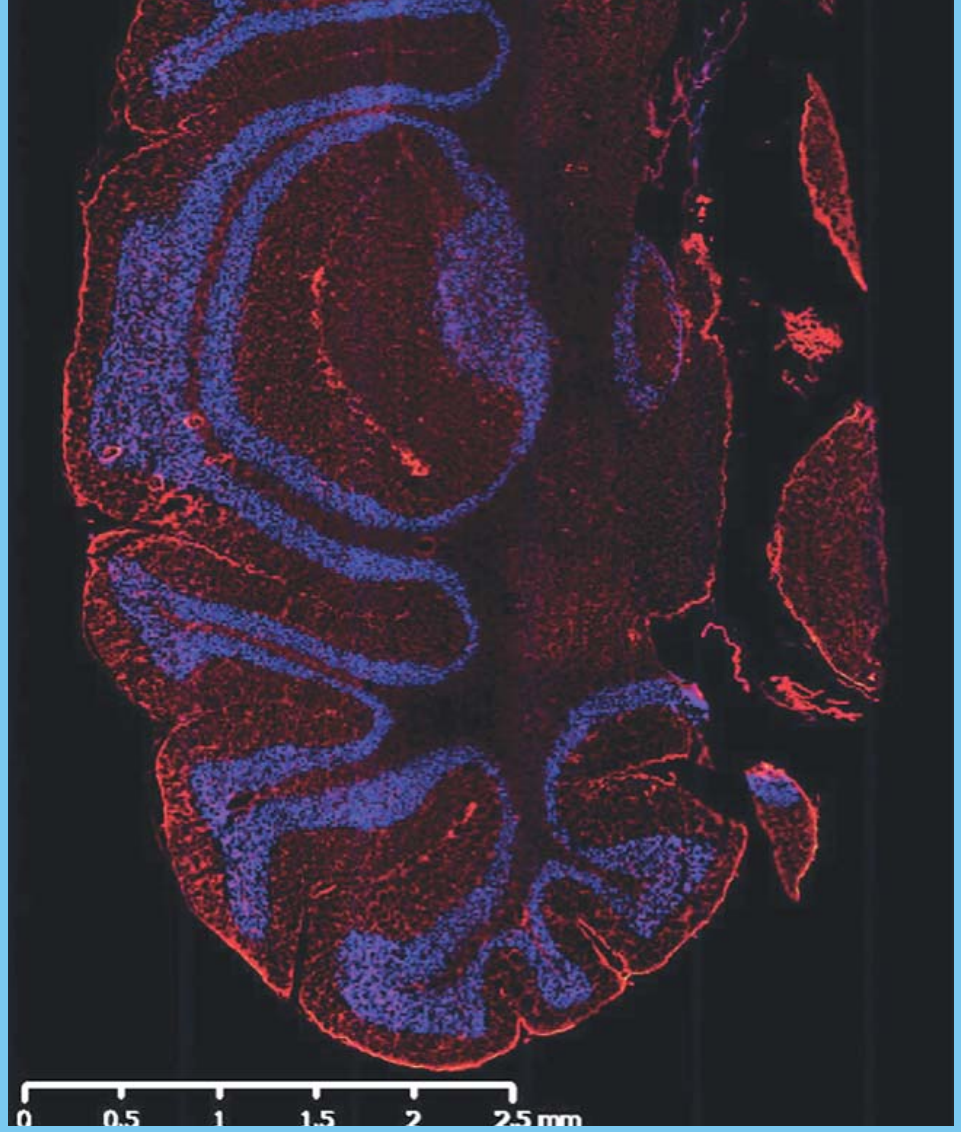
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