Preamble

The future of life sciences lies at the crossroads of biology, medicine, physics, chemistry, mathematics, computer sciences and engineering. Whether to pave the way to personalized medicine, to meet today and tomorrow’s environmental challenges or to find new solutions to our planet’s energy needs, transdisciplinarity will be the key in academia, hospitals and industry alike. Geared towards this goal, the School of Life Sciences trains a new breed of scientist engineers whose combined skills in these various fields are set to address fundamental biological questions and to attack the major medical problems of our times with a truly integrative spirit. Researchers, in close to fifty groups, apply this philosophy to broad questions including cancer, diabetes, infectious diseases and mental or neurological disorders, pushing for holistic approaches that span a range of disciplines from functional genomics to high-tech bio-engineering, and from computer neurosciences to structural modeling.

A bachelor degree (Life Sciences and Technology), two masters degrees (Life Sciences and Technology; Bioengineering), and three Ph.D. programs (Biotechnology and Bioengineering; Neurosciences; Molecular and Systems Biosciences), constitute the educational arms of our school, hosting some six hundred students from all geographic and scientific horizons.

In 2010, our faculty further increased its team of ERC grant recipients to a total of 11 (8 seniors, 3 juniors), launched the “Synaptic basis of mental diseases” National Center of Competence in Research, saluted Jeff Hubbell’s entry in the US National Academy of Engineering, and was honored by the awarding of the Wenner Prize to Melody Swartz, of the INSERM Prize to Denis Duboule, and of the Bettencourt Prize to Bruno Lemaître. And our excitement is mounting, as we have started working with our new next-door colleagues from the nascent Nestlé Institute for Health Sciences. The challenges are high, but we are up to it!

Didier Trono, M.D.
Professor & Dean of the School of Life Sciences
Ecole Polytechnique Fédérale de Lausanne (Switzerland)
http://sv.epfl.ch
## Main Scientific Events

**April/May:** Launch of the National Center of Competence in Research (NCCR) “SYNAPSY”, the synaptic bases of mental diseases which will be directed by Prof. Pierre Magistretti (BMI). This NCCR targets an open dialogue between researchers in neuroscience and psychiatry through common projects; by creating a platform for cutting edge technology in brain imaging, genetics, and behavior studies. The center will explore the molecular and cellular origins of mental illness; in an intense collaboration between researchers and clinicians from the Lake Geneva region (EPFL, UNIL, UNIGE, and CHUV) as well as the University of Basel and the FMI-Friedrich Miescher Institute for Biomedical Research. [http://www.nccr-synapsy.ch/](http://www.nccr-synapsy.ch/)

**June 21-23:** International Conference on “Protein Kinases of Parasitic Protozoa”. Professor Christian Doerig and the Inserm-EPFL Joint Laboratory, a research Unit at the Global Health Institute, hosted 60 scientists from Europe, North America, Australia and India.

**July 5 to August 27th:** The 2010 International Summer Research Program for undergraduate students welcomed 25 high potential future researchers from all over the world. They joined the SV labs and learned cutting edge research techniques while investigating scientific questions relevant to today’s world.

**September 2-4:** The 2010 Life Sciences Symposium took place on the EPFL campus. This year it was dedicated to Bioengineering, under the motto “Engineering Life” and covered: biomolecular structure, single cell systems, multicellular systems, tissue and physiological systems, therapeutics and diagnostics.

The 2010 Debiopharm Life Sciences Award was awarded to Jean-Christophe Leroux, Professor of Pharmacology at the ETH-Zurich who is a young investigator in the field of Drug Deliver and Pharmaceutical Technology.

## Public-Oriented Events

**March 17:** Inauguration of the P3 Laboratory which specializes in the study of air-borne pathogens making the EPFL one of the top world centers for this type of research.

**March 7-13:** The SV labs welcomed 13 enthusiastic high school students from all corners of Switzerland under the framework of La Science Appelle le Jeunes! (Schweizer Jugend forscht!) These students experienced first-hand lab work and completed a mini-project.

March: The undergraduate (or Bachelor-Master) teaching section in Life Sciences and Technologies participated in the EPFL Prospective Students Days and welcomed more than 100 high school and “Lycées” students from the French speaking areas of Switzerland and France. The same event took place for Swiss Italian and Swiss German speaking high school students in December. More information: [http://ssv.epfl.ch/gymnasiens](http://ssv.epfl.ch/gymnasiens)

**May 29th to 30:** During the EPFL Open Doors, the SV welcomed a few hundred visitors (mostly families) who came to explore the Life Sciences up close. Ten different exhibits were available ranging from a robot salamander, a wheel chair controlled by human thoughts, to pondering the origins for life.
Honors-Awards-Announcements

February: Prof. Jeff Hubbell (BMI) was elected to the prestigious U.S. National Academy of Engineering (NAE). He has been honored for his contributions to the science, engineering, and technology of bioactive materials for the benefit of patients.

March: Prof. Nouchine Hadjikhani (BMI), is among one of the teams composed of five researchers who were awarded the Leenaards Prize 2010; they have been working on establishing a genetic model for the study of obesity, autism and schizophrenia.

March: Dr. Claudia Sala received the Swiss TB Award for her excellent research in understanding TB mechanisms.

July: Prof. Carmen Sandi, was nominated as President of the European Brain and Behavior Society (EBBS), the oldest European neuroscientific society, and a founding member of The Federation of European Neuroscience Societies (FENS). The EBBS is a highly prestigious society committed to the study of the relationships between brain mechanisms and behavior.

November: Prof. Denis Duboule received a Dr Honoris Causa from the Ecole Normale Supérieure and also was awarded the prestigious Grand Prix International INSERM Prize. This award honors his research career and his important discovery of Hox genes, or “architect genes”, responsible for coordinating body patterning during embryonic life.

November: Prof. Melody Swartz received the 2010 Robert Wenner Prize for her research on the lymphatic system.

November: The EMBO (European Molecular Biology Organization) elected Prof. Douglas Hanahan and Prof. Freddy Radtke as new members for their proven excellence in research.

December: Prof. Bruno Lemaitre was awarded the Bettencourt Prize for Life Sciences in recognition of his outstanding research on modern immunobiology.

December: Congratulations to Prof. Didier Trono and Prof. Wulfram Gerstner for their European Research Council (ERC) Advanced Grants.

Click here for more information about awards and appointments.

To keep up to date with our events and news, please click SV General Media, Daily News, Upcoming Events, Photolibrary, and High School Days at EPFL.
Undergraduate Studies

The Life Sciences curriculum aims to educate a new generation of engineers who can master the technical and scientific skills needed for studying life processes and developing the biomedical technologies of tomorrow. This educational program, established under the direction of Prof. William F. Pralong, M. D., is unique in Switzerland and Europe.

Bachelor’s Program (3 years)
The first two years provide basic courses followed throughout the EPFL, such as analysis, linear algebra, physics, chemistry (general and organic), and numerical methods. Specific courses in Life Sciences begin with biochemistry, cellular, molecular biology, mass and energy balance, and biothermodynamics. In the first two years, life sciences courses make up less than 20% of the total academic load.

In the third year, engineering courses (signals and systems, electronic and electrical systems) and typical life sciences courses such as genetics and genomics, immunology, developmental biology, bio-computing, systems biology via the study of human physiology are integrated. Physiology practices also give the opportunity to integrate the engineering and biological knowledge acquired up to this point. During this year, the students also fine tune their training by choosing some of specific credits to better prepare themselves to one of the orientations offered in our masters’ programs. This includes a bachelor project either in bioengineering, in bio-computing, in biomedical technologies or in neurosciences and in molecular medicine.

Master’s Programs (2 years)
Master’s in Life Science and Technology includes several orientations. Among these are neurosciences, molecular medicine, and bio-computing. Each orientation is made up of 30 credits of optional courses selected under the supervision of a mentor.

Master’s in Bioengineering, is organized in collaboration with STI, provides classical courses in bioengineering; in addition students can chose different possible orientations through the choice of a minor such as biomedical technologies (STI), biotechnology(SB), or bio-computing (I&C). Each minor requires taking 30 specific credits chosen under the guidance of a mentor. The minors, as indicated, are organized within the different schools at EPFL.

Both degree programs share some common basic curriculum that aims to provide students with the knowledge of the modern technologies used in the life sciences such as imaging, bio-computing and optical systems applied to biology, etc. In addition, courses in management, economics, applied laws and ethics for the life sciences are offered. A large portion of the master’s program (60 credits) is dedicated to laboratory work and projects.

Graduate Studies

All three graduate programs comprise a combination of coursework, laboratory-based research, in-house seminars, and national or international conferences.

The Doctoral Program in Biotechnology and Bioengineering aims at providing doctoral students with the education necessary to be leaders in the fast-growing industrial and academic biotechnology and bioengineering sectors, i.e. a depth of knowledge and competence in their specific research area as well as a breadth of knowledge in biology, bioengineering and biotechnology. These program themes include: genomics and proteomics, biomolecular engineering and biomaterials, stem cell biotechnology, cell and process engineering, biochemical engineering, orthopaedic engineering, biomechanics, mechanobiology, cell biophysics, computational biology, biomedical imaging as well as molecular, cell and tissue engineering. ‘http://phd.epfl.ch/edbb’

The Doctoral Program in Neuroscience provides its students with training from the genetic to the behavioural level including molecular, cellular, cognitive, and computational neuroscience. Students enroll in the highly dynamic and interdisciplinary environment of the BMI-EPFL of the SV. The program is further strengthened by research and training opportunities in collaboration with the Universities of Lausanne and Geneva. http://phd.epfl.ch/edne’

The Doctoral Program in Molecular Life Sciences is a joint program between the Swiss Institute for Experimental Cancer Research (ISREC-EPFL) and the Global Health Institute (GHI-EPFL). The program provides training and research opportunities to highly motivated doctoral students in key areas of modern biology. Highly qualified applicants worldwide are chosen twice a year through a competitive selection procedure.
http://phd.epfl.ch/edms/en’
Core Facilities & Technology Platforms

In its goal to offer maximal support to its students and scientists in their training and research capabilities, EPFL and its School of Life Sciences have made a significant investment over the past years to establish state-of-the-art technology platforms and core facilities. These facilities are directed and managed by dedicated teams of highly trained and experienced staff and are run on a fee-for-service basis. They offer training, access to technology, assistance with experimental design and high level data analysis, and collaborations. The platforms are also involved in the School’s undergraduate and graduate teaching programs.

In addition, scientists from our School of Life Sciences closely collaborate with other services in the Lemanic region, including the ‘Center for Biomedical Imaging’ (http://www.cibm.ch, http://www.cibm.ch/) and the ‘Lausanne Genomics Technologies Facility’ (http://unil.ch/dafm).

The following pages describe the Life Sciences-related core facilities and technology platforms currently available at the EPFL School of Life Sciences.
Introduction
Life science researchers at the EPFL frequently require an imaging resolution that is impossible to achieve with light microscopy. With the capability of seeing single molecules, electron microscopy (EM) can reveal the hidden structures that lie at the heart of the living world.

The BioEM Facility offers EPFL researchers the expertise and equipment to study tissues, cells and molecules with electron microscopy. This is provided by laboratories equipped with a variety of technologies for many of the different preparation methods, and electron microscopes, in the Interdisciplinary Centre of Electron Microscopy, with a range of imaging capabilities. As well as offering a service for research groups, the facility trains and teaches users in sample preparation methods, and the use of the microscopes.

During recent months the increasing needs in many aspects of EM has meant the acquisition of new microscopes. This includes a new high resolution cryo TEM for imaging samples frozen in their native state, for example; viruses, and proteins involved in neurodegenerative diseases. The Facility also continues to develop the new 3D imaging techniques of block face scanning electron microscopy (FIB-SEM), for imaging whole cells at an unprecedented resolution. For these advanced technologies the BioEM Facility is now well-placed within the swiss wide network of electron microscopy centres that comprises the ETH Zurich, University of Basel, and Friedrich Miescher Institute that make available the best possible electron imaging methods and expertise.

Selected Publications


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Services and Technologies
- Electron Microscopy
- Transmission electron microscopy, ambient and cryo temperatures
- Scanning electron microscopy
- Focussed ion beam and scanning electron microscopy
- Correlated light and electron microscopy
- Preparation techniques
- Resin embedding
- Semithin sectioning
- Ultrathin sectioning
- Serial sectioning
- Cryosectioning and immunolabelling
- Pre-embedding immuno labelling
- Negative staining

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**Introduction**

The Bioimaging and Optics platform (PT-BIOP) is located in the faculty of Life Science (SV) at the Ecole Polytechnique Fédérale de Lausanne (EPFL) and part of a network of core facilities at the institute. The general idea of the platform is to provide state of the art light microscopes and even more important expertise to solve challenging (biological) questions with modern light-microscopy. Currently a broad range of instruments ranging from simple wide-field imaging systems over standard point-scanning confocal microscopes up to a high-end 2-Photon-excitation microscope are available in the facility. Scientists who want to make use of the available equipment are trained by the PT-BIOP stuff so that they can use the instruments independently. Additionally there is a strong competence and necessary computer power to perform image processing. The idea is to link the image analysis with the image acquisition as early as possible as this guarantees optimal results. The microscopes and the image analysis capabilities can be used by scientists of the faculty and the EPFL but are also available to scientists coming from outside the EPFL.

**Services and Technologies**

- Wide-field transmission and fluorescent microscopes
- Life cell imaging microscopes
- Single and multiple-beam confocal microscopes
- 2P microscope
- High resolution and super resolution microscope (will be available in 2011)
- Image Processing tools (commercially available and/or custom built)

**Selected Publications**


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Introduction

The BSF enables research groups from EPFL and SystemsX.ch to access the infrastructure, expertise and collections of molecules required for performing High Throughput Screening (HTS) assays. Most of the incoming projects are related to Chemical Biology, Systems Biology or disease-oriented research in particular in the areas of Cancer, Neurobiology and Infectious Diseases. Our multidisciplinary laboratory provides scientists with adequate screening instrumentation, state-of-the-art technologies and methodological approaches for applications ranging from the probing of cellular pathways to the broad area of drug discovery research. These projects require access to a screening and compounds diversity infrastructure for pursuing a variety of objectives:

- The identification of bioactive compounds in cellular assays, both phenotypic and target-based assays as well as in biochemical in vitro target-based screens.
- The exploration of cellular pathways and biological systems using response modifiers and the identification/validation of pathways and targets

We perform our automated screens in 96 and 384 well plates for the following two main categories of assays: RNA interference (RNAi) cellular screens for probing gene function using collections of small interfering RNAs (siRNAs) targeting the human genome and the screening of chemicals for a variety of biochemical target-based and cellular assays using large, chemically diverse collections.

Services and Technologies

- Access to instrumentation dedicated to microplates and cell culture facilities
- Assay development and validation for HTS
- Assay automation and statistical validations
- Pilot screening
- Primary screening campaigns
- Hits confirmation
- Dose response assays
- Secondary screens
- Compound storage and management of collections
- Image processing for high content screening read-outs
- Data management using in house developed Laboratory Implementation Management System (LIMS)
- Cheminformatics

Selected Publications


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**Introduction**

The development of genetic tools for the manipulation of the mouse genome has led to the creation of numerous and sophisticated mouse models. The in-depth characterization of the phenotype of these mouse lines is crucial to decipher the roles of the gene of interest.

The clinical phenotyping unit of the Center of PhenoGenomics (CPG) is composed of highly interactive service platforms including clinical chemistry laboratory, metabolic and functional exploration platform, behavior and cognition exploration platform. The UDP provides a range of state-of-the-art equipment to enable cardio-metabolic, biochemical and behavioural exploration of mouse models.

We offer different types of support to the users of the platform, going from general support and training in protocols establishment to full completion of tests and analysis. We benefit for doing so from the scientific expertise of Prof. Johan Auwerx and Prof. Carmen Sandi, both experts in their respective fields of expertise, namely cardio-metabolism and neurobiology.

The UDP is part of the animal facility barrier unit, and encompasses a working area constituted of housing, testing and analysis rooms. The mouse models are housed in individual ventilated cages and maintained at a conventional sanitary status.

The UDP equipment has been chosen to ensure a high level of flexibility for the tests that can be performed. Additionally, most of experiments can be run by fully programmable and automated interfaces and thus the impact of experimental interventions by the researcher over the experimental period is reduced.

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We offer tests in the different scientific fields mentioned in the figure. A series of tests can be combined in a pipeline in order to answer questions related to a given topic such as neurodegenerative diseases or obesity or diabetes.
Flow Cytometry - FCCF

http://fccf.epfl.ch/

Introduction

Flow cytometry is a technology that simultaneously measures and then analyzes multiple physical characteristics of single particles, usually cells, as they flow in a fluid stream through a beam of light. Sorting allows us to capture and collect cells of interest for further analysis.

The FCCF mission is to provide comprehensive flow cytometric analysis and sorting including instrumentation, technical and professional assistance, training and consultation.

Services and Technologies

The Flow Cytometry Core Facility from EPFL is equipped with four self service cytometers. For cell sorting, the facility has two high-speed cell sorters from BD (BD FACSARia II SORP & FACSVantage SE). The Core Facility also operates an automated immunomagnetic bead cell separator from Miltenyi Biotec MACS® Technology.

The LSRII (Becton Dickinson) is a 5 lasers bench-top analyser capable of 18 colour, forward and side scatter analysis, equipped with a PC and DIVA digital acquisition software system.

The Accuri C6 is equipped with 2 lasers and 4 active detectors to allow maximum flexibility for easy experimental design. This machine is also equipped with a plate reader (CSampler).

The Cyan ADP (Beckman Coulter) is a 3-laser bench-top analyser capable of 9 colour, forward and side scatter analysis, equipped with a PC and Summit digital acquisition software system.

The AutoMACS Pro is a fully automated bench-top sorter that can be used to perform sterile bulk sorts. Designed for ultra high-speed positive selection as well as depletion, the AutoMACS Pro can isolate virtually any cell type.

The FACS Vantage DIVA (Becton Dickinson) is a 3-laser sorter capable of 8 colour, forward and side scatter analysis. It is equipped with DIVA digital acquisition software system.

The FACS Aria (Becton Dickinson) is a 5 laser high-speed sorter capable of 18 colour, forward and side scatter analysis. It is equipped with DIVA digital acquisition software system and ACDU.

Flow Cytometry Core Facility services

• Cell sorting
• User training on machines and software
• Help with acquisition and data analysis
• Advice on cell preparation
• Interpretation of results
• Help with manuscript preparation; i.e. figures, materials and methods

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Introduction

Histology involves the use of a set of techniques to examine the morphology, architecture and composition of tissues. The tissue samples are processed for the study of structures seen under the microscope, also called microscopic anatomy, as opposed to gross anatomy which involves structures that can be observed with the naked eye. The histology core facility is a competence pole which provides expertise in those analyses as well as routine work for researchers.

Services and Technologies

On one hand, the facility assists researchers in the setting up and optimizing of histological approaches specific for each scientific project. Members of the SV faculty can be trained on the available instruments like microtomes or cryostats and have then access to them for their own experiments. Furthermore a large panel of secondary antibodies are titrated and provided to the researchers by the service.

On the other hand technicians of the facility perform work for researchers:

- Tissue processing to frozen, paraffin or resin sections
- Histological stains like the standard Hematoxylin and eosin and routine stains like Masson’s trichrome or cresyl violet among others.
- Setup and optimization of immunohistochemistry and immunofluorescence protocols

Finally the laboratory has recently acquired two automates, which increase the facility work capacity and allow high throughput work:
- Sakura Prisma and G2-glas coverslipper for histological stains
- Discovery xT Ventana for Immunohistochemistry and in situ hybridization

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Histology - HCF
http://hcf.epfl.ch
Introduction
In the last 10 years mass spectrometry based protein analysis has become an invaluable tool in the arsenal of techniques offered to the biologist to study the proteome, the expressed and active part of the genome. The rapid evolution of the technique has been tightly bound to the continuous increase in performance of mass spectrometers. Today it is possible to get quantitative information about thousands of proteins in one experiment. Researchers can begin to think more globally, but there is still room for very detailed studies on single proteins especially those modified by post-translational modifications. The EPFL Proteomics Core Facility is a technological platform that has been created to address these needs and help researchers in using these techniques.

Services and Technologies
The PCF-PTP laboratory is currently equipped with sample preparation and fractionation devices (HPLC, FPLC, PI), 2 ion traps, 1 Orbitrap and 2 QQQ LC-ESI-MS/MS and 1 MALDI-TOF/TOF instruments. The bioinformatics analysis pipeline includes Mascot, Phenyx, Xtandem! and SEQUEST servers for matching MS data with protein sequence databases and data post-treatment tools like Maxquant, Perseus, Proteome Discoverer and Scaffold for protein identification validation and pipelining of quantitative studies.

The PCF-PTP has implemented several complementary workflows for protein analysis and offers an increasing palette of services...
- Protein/Peptide Molecular Weight Measurements by Mass Spectrometry.
- Mass Spectrometry based Protein/Peptide Identification from Gel or Solution.
- Protein Relative Quantification by SILAC or Label-free Quantitative Analysis on collaborative basis.
- Protein separation by FPLC and HPLC.

We contribute also to collaborative based services requiring heavy involvement of both parties such as:  
- Accurate protein quantification by SRM-MRM.
- Localization and eventually quantification of PTM’s other than phosphorylation.
- Lipid mixtures profiling.

Our platform entertains tight collaboration with other proteomics facilities (UNIL-PAF, UNIGE-PCF, UNIBE) within a network called Repp-SO and with computer science and bioinformatics research centers (Vital-IT, SIB, etc.).

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Introduction
The Protein Crystallography Core Facility provides instrumentation and expertise at every stage of the structure determination process for non-crystallography groups who are interested in solving the structures of their favorite macromolecule. Expertise and advice include consultation on protein purification, crystallization, and crystal optimization, as well as assistance with X-ray crystal screening, data collection, data processing and structure determination and analysis.

X-ray crystallography is the primary method for determining three-dimensional structures of biological macromolecules, and is therefore an essential tool, which should be available to a broad range of researchers. Presently, it is possible for a non-crystallographer to access this technology thanks to automation and a variety of commercially available kits as well as to the more user friendly and intuitive programs that have been developed in recent years. With personalized advice, training, and follow-up, users are in the optimal environment to manage their crystallization screens, and to solve, refine and analyze the structures of their favorite proteins.

Services and Technologies
The Protein Crystallography Core Facility provides the EPFL community with:
- Advice on larger-scale protein expression and purification, if required.
- Set-up of crystallization screens using commercial and facility-made conditions.
- Optimization of crystals.
- Data collection of quality crystals at facility x-ray source and synchrotrons.
- Data processing using popular packages such as XDS and Mosflm.
- Structure determination using molecular replacement, MAD and SAD techniques.
- Structure refinement, fitting and analysis using ccp4i and Phenix software.
- Deposition of structures in the protein database.
- Preparation of images for publication using PyMol software.

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**Introduction**

The objective of the PECF is to provide recombinant proteins, rapidly and at low cost, to EPFL researchers. Both cultivated mammalian cells and E. coli are used as production hosts. One of our main activities is recombinant protein production by transient transfection of Chinese hamster ovary (CHO) or human embryo kidney (HEK293) cells in suspension at volumetric scales from 5 mL to 15 L. With this technology, we are also capable of producing virus vectors for gene delivery such as adeno associated virus. We also produce proteins from existing recombinant cell lines developed by our clients. This may involve adapting the cell line to serum-free suspension culture. In this case, cultures at volumetric scales up to 15 L are used. Similarly, we produce monoclonal antibodies by the scale-up of hybridoma cell lines. When using E. coli as a host for production, the scales of operation range from 1 – 20 L. For all the types of production mentioned here, the PECF has both instrumented and non-instrumented bioreactors available for use. After production, we also provide some services in protein recovery. This mainly concerns the recovery by affinity chromatography of proteins secreted from mammalian cells (antibodies and Fc- and his-tagged proteins) and GST- and his-tagged proteins produced in E. coli.

**Services and Technologies**

- Large-scale transient transfection for recombinant protein in mammalian cells
- Scale-up of existing cell lines for recombinant protein production
- Scale-up of existing hybridoma cell lines for monoclonal antibody production
- Recombinant protein production in E. coli
- Affinity protein purification

**Selected Publications**


Introduction

Genetic manipulation of rodents through the generation of transgenic animals is a procedure of paramount importance for biomedical research, either to address fundamental questions or to develop preclinical models of human diseases.

We offer a centralized resource and state-of-the-art technology for the generation of transgenic animals. We can perform direct pronuclear injection of DNA in the mouse oocyte, which has been the standard method of transgenesis for more than three decades.

As an attractive alternative, we are one of the very few platforms that provide a fast and efficient way to generate transgenic animals through the use of lentiviral vectors. Lentivector-mediated transgenesis is relatively easy to perform and leads to high percentages of provirus-positive animals. Moreover, a wide variety of lentiviral vectors have been developed that can all be used in transgenic animals, thus allowing for a broad range of genetic manipulations including externally controllable expression and knockdown, the latter offering an economically advantageous alternative to stable knockout.

In addition to this primary service, we also offer general support in both vector design and lentiviral vector production and titration, as our expertise in lentiviral vectors has become of general interest for many other applications than transgenesis.

An important variable that affects the results of mouse studies is the sanitary status of the animals. Taking advantage of our expertise in embryo manipulation, we also propose the rederivation of mouse transgenic lines as a routine service. This procedure allows cleaning and hosting of a wide range of mouse lines in the SPF area of the EPFL animal house.

Services and Technologies

Pronuclear injection: plasmids and BACs.

Classic transgenesis technique, consisting of direct injection of naked DNA into the pronucleus of fertilized mouse oocyte.

Lentiviral vector mediated transgenesis.

Injection of high titer lentiviral vectors beneath the zona pellucida of a fertilized mouse oocyte.

Vectorology

Know how in the choice/engineering of vectors (lentiviral and retroviral vectors / expression vectors AAV...).

Access to a plasmid database that comprises now more than 500 plasmids with annotated map.

Lentiviral vectors production/titration

Training in the laboratory: production/titration of own stock of lentiviral vectors.

Possibility to obtain aliquot of standard lentiviral vector to perform feasibility test (if new target cells or technique).

Rederivation of established mouse lines by embryo transfer.

In progress:

-Sperm and embryo freezing.
-ES mediated transgenesis.

Selected Publications


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Introduction
The Bioinformatics and Biostatistics Core Facility (BBCF) provides the EPFL and Lemanic institutions with extensive support in bioinformatics and biostatistics, from designing experiments to interpreting and visualizing complex data. Its main competences are in management and analysis of genomic data, mathematical modeling and statistical analysis of quantitative biological data.

The facility works in close relationship with the Geneva and Lausanne Genomics platforms and complements their respective bioinformatics team with additional support for the analysis of large or complex data sets, for the development of data management pipelines for new high-throughput technologies (e.g. high-density arrays, high-throughput sequencers) and for the statistical planning in complex experimental designs. It also helps researchers in the areas of mining public databases, designing and setting up local databases, inferring mathematical models from experimental data and running simulations to validate a model. The facility acts as a point of contact between the experimental biologists and the research groups in bioinformatics and in basic sciences. It also makes the junction between the EPFL life science community and the various resources maintained by the Swiss Institute of Bioinformatics, and in particular the Vital-IT high performance computing center.

Services and Technologies
- Analysis of high-throughput sequencing data, in particular for applications to ChIP-seq, RNA-seq, 4C-seq & whole genome re-sequencing.
- Development of software for the management and statistical analysis of Genomics Data.
- Analysis of quantitative biological data with complex experimental design.

Selected Publications


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BMI - Brain Mind Institute

The mission of the Brain Mind Institute is to understand the fundamental principles of brain function in health and disease, by using and developing unique experimental, theoretical, technological and computational approaches. The scientific challenge addressed by the BMI consists of connecting different levels of analysis of brain activity, such that cognitive functions can be understood as a manifestation of specific brain processes; specific brain processes as emerging from the collective activity of thousands of cells and synapses; synaptic and neuronal activity in turn as emerging properties of the biophysical and molecular mechanisms of cellular compartments.

Understanding information processing in the brain and its higher emerging properties is arguably one of the major challenges in the life sciences. Research at the BMI focuses on three main areas: i) Molecular neurobiology and mechanisms of neurodegeneration ii) Molecular and cellular mechanisms of synapse and microcircuit function up to the behavioural level and including metabolic aspects; iii) Sensory perception and cognition in humans. In all areas, the BMI strives to integrate knowledge gained by multidisciplinary approaches and across different disciplines and research laboratories. Finally, underlying all levels of analysis, research at BMI is characterized by a sustained interest in pathological processes.

In order to achieve these scientific goals, the Brain Mind Institute benefits from a unique academic environment:

- An institute organized as a network of independent laboratories reflecting complementary technological approaches; each laboratory collaborates with several others within the institute in addition to cross-disciplinary interactions on campus.
- A campus that stands out as a premier technological university in engineering, computer science and basic sciences.
- An intimate collaboration with the Blue Brain Project which stands out as one of the most challenging neuroscience simulation and data basing projects worldwide.
- A proximity to and joint affiliations of our faculty with top university hospitals in Lausanne and Geneva in particular for projects related to cognition and neurodegenerative diseases.
- A new initiative in neuropsychotics to which the BMI is strongly committed that will further the collaboration with engineering sciences by a host of inspiring common projects.

A feature of the Brain Mind Institute is that several faculty members have strong expertise in physics or mathematics; this holds not only for theoretical but also for experimental neuroscience. In this way, the Brain Mind Institute reflects the mission of the School of Life Science: to provide a life science curriculum with a strong emphasis on quantitative approaches. As far as teaching is concerned, the BMI Faculty is committed to provide a comprehensive and formal training in neuroscience from the undergraduate to the graduate levels. [http://bmi.epfl.ch]
Patrick Aebischer was trained as an MD (1980) and a Neuroscientist (1983) at the University of Geneva and Fribourg in Switzerland. From 1984 to 1992, he worked as a Faculty member at Brown University in Providence (Rhode Island, USA). In 1991, he became the chairman of the Section of Artificial Organs, Biomaterials and Cellular Technology of the Division of Biology and Medicine of Brown University. In the fall of 1992, he returned to Switzerland as a Professor and Director of the Surgical Research Division and Gene Therapy Center at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne. In 1999, Patrick Aebischer was nominated President of the Swiss Federal Institute of Technology in Lausanne (EPFL) by the Swiss Federal Council. He took office on March 17th, 2000. He is the founder of 3 biotechnology companies.

Introduction
Recently developed viral vectors show unprecedented efficacy to deliver genetic information to the central nervous system and correct the molecular defects leading to devastating conditions including fatal neuromuscular diseases. In addition, the use of viral vectors to introduce pathogenic genes in adult neurons can generate useful rodent models to decipher the molecular mechanisms leading to complex disorders such as Parkinson’s and Alzheimer’s diseases.

Keywords
Disease modelling, gene therapy, animal models, Parkinson’s disease, Amyotrophic lateral sclerosis, Alzheimer’s disease, viral vectors, lentivirus, adeno-associated virus, cell encapsulation

Results Obtained in 2010
Adeno-associated viral particles (AAV) have a remarkable capacity to broadly diffuse in the central nervous system and deliver genetic information to non-dividing cells, such as neurons and astrocytes. Based on this promising technology, our lab has developed gene therapies strategies against neuromuscular disorders such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). Harnessing the ability of AAV vectors to be retrogradely transported along axonal processes, we have generated specific vectors and explored routes of administration to transduce motor neurons across the entire spinal cord. In particular, the injection of AAV vectors encoding the SMN1 protein in the ventricular cavity leads to a dramatic extension of lifespan in a mouse model for SMA, highlighting the potential of these vectors in translational research. We are currently investigating a similar approach to correct genetic defects in the challenging SOD1 mouse model for ALS.

Viral gene delivery systems have been further developed to establish novel animal models replicating the neurodegeneration and functional impairments characteristic of Parkinson’s (PD) and Alzheimer’s diseases (AD). These models are based on the local delivery of genes implicated in autosomal dominant familial forms of the disease, such as alpha-synuclein, LRRK2, APP and tau. Notably, we have further developed a symptomatic rat model based on the AAV-mediated expression of human alpha-synuclein, a protein implicated in genetic and sporadic forms of PD. Similarly, we found that the expression of the G2019S mutated form of LRRK2 in dopaminergic neurons of the substantia nigra using an adeno viral vector leads to specific neurodegeneration and therefore provides a novel model for this prevalent form of PD.

We are currently focusing our research on existing model systems for PD and AD to explore innovative therapeutic approaches that aim at preventing neuronal degeneration. In this context, we are currently developing bioactive cellular implants for the chronic delivery of recombinant antibodies. This approach may possibly find application for passive immunization against the pathogenic proteins implicated in neurodegenerative disorders.
Selected publications


Towne, C., B.L. Schneider, D. Kieran, DE Redmond Jr, P. Aebischer, Efficient transduction of non-human primate motor neurons after intramuscular delivery of recombinant AAV serotype 6, Gene Ther., 17:141-6, 2010


Towne, C., M. Pertin, AT Beggah, P. Aebischer, I Decosterd, Recombinant adeno-associated virus serotype 6 (rAAV2/6)-mediated gene transfer to nociceptive neurons through different routes of delivery, Mol Pain, 8:52, 2009


Introduction
We focus our investigations on the functional and neural mechanisms of body perception, corporeal awareness and self-consciousness. Projects rely on the investigation of healthy subjects as well as neurological patients (who suffer from selective neurocognitive deficits and illusions) by combining psychophysical and cognitive paradigms with state of the art neuroimaging technique such as intracranial EEG, surface EEG, fMRI and Virtual Reality. Our interdisciplinary expertise – bridging cognitive neurology, experimental epileptology intracranial, electrophysiology experimental psychology and neuroimaging – has recently been extended to engineering-based approaches to the cognitive building of a virtual reality (VR) neuroimaging platform with a portable 256 channel EEG system (VR-EEG). This VR-EE platform allows us to carry out cognitive experiments in highly realistic ecologically valid environments that close the perception-action loop while the participant’s brain activity (and soon also of brain damaged neurological patients) is continually monitored.

Next to studying the neural mechanisms of bodily self-consciousness experimentally, we expect this novel technological amalgam to also become a key research technique in the larger field of the cognitive neurosciences as well as the adjacent fields of virtual reality, presence research, brain-computer interfaces, and neurorehabilitation.

Results Obtained in 2010
The major achievement in 2010 was the recording of three full empirical brain imaging studies in healthy subjects and patients with bilateral vestibular loss. The studies were carried out using our in-house 3D human centrifuge including an on board 192-channel EEG and evoked potential recording system. The findings revealed the sequential activations and oscillatory patterns (especially so called alpha oscillations) of the cortical vestibular system.

A major collaborative study was published that fully immersed human subjects using high-level virtual reality technology while applying techniques from cognitive science (Slater et al., 2010). The work was carried in collaboration with University College London and University of Barcelona and based on previous cognitive science work from LNCO. We are currently carrying out a follow-up study where we also record electrical brain signals in fully immersed human subjects.

With several publications in major neuroscience and biology journals, we extended our investigation of the cognitive and neurobiological mechanisms of body perception, bodily self-consciousness, and subjectivity using brain imaging techniques such as fMRI, high-density EEG, virtual reality and robotics.

Keywords
Multisensory perception, bodily awareness, self-consciousness, intracranial human electrophysiology, neuroimaging, fMRI, EEG, neuropsychology, cognitive neurology, epilepsy, optical body tracking, virtual reality, neuroscience robotics, vestibular system, mental imagery.
Selected Publications


Team Members

Post-Doctoral:
Jane Aspell
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Brain activity in temporo-parietal cortex during a manipulation of bodily self-consciousness (from Tadi et al., 2009).
Introduction
The Laboratory of Molecular and Cellular Biology of Alzheimer’s Disease is focusing on better understanding the molecular, cellular and biochemical mechanisms of γ-secretase and Alzheimer’s disease. Our laboratory is also implicated in the design and development of new therapeutic strategies to slow down the pathogenesis of Alzheimer’s disease.

Keywords
Molecular and Cellular Biology of Alzheimer’s disease, γ-Secretase, Amyloid-beta peptides (Aβ), intramembrane-cleaving proteases, therapeutic targets.

Results Obtained in 2010
Processing Of The Synaptic Cell-Adhesion Molecule Neurexin-3B By Alzheimer’s Disease A- And γ-Secretases.
Neurexins (NRXNs) and Neuroligins (NLGNs) are synaptic cell adhesion molecules having essential roles in the assembly and maturation of synapses into fully functional units. Despite extensive investigations, the mechanisms by which NRXNs modulate the properties of synapses remain largely unknown. We found that the α-secretase metalloprotease TACE/ADAM17 and γ-secretase can sequentially process neurexin-3β (NRXN3β), leading to the formation of two final products: a ~80 kDa N-terminal extracellular domain (sNRXN3β) and ~12 kDa C-terminal intracellular domain (NRXN3β-ICD), with both of them being potentially implicated in the regulation of NRXNs and NLGNs functions at the synapses, or in yet unidentified signal transduction pathways. Importantly, we found that this processing is altered by several PS1 mutations in the catalytic subunit of the γ-secretase that cause early-onset familial Alzheimer’s disease.

Novel γ-secretase inhibitors uncover a common nucleotide-binding site in JAK3, SIRT2 and PS1.
In this study, we discovered new inhibitors of γ-secretase that we used as chemical tools to better understand the catalytic and substrate-binding sites of the enzyme. First, we identified 2-hydroxy naphthyl derivatives as new γ-secretase inhibitors. In evaluating target protein determinants of inhibition, we identified a common GXG signature nucleotide-binding site (NBS) shared by the γ-secretase subunit presenilin-1 C-terminal fragment (PS1-CTF), SIRT2, and Janus kinase 3 (JAK3). Next, we took advantage of the known crystal structure of JAK3 and its NBS to model for the first time the NBS of the PS1-CTF. Collectively, our results suggest that the flexible PS1-CTF 381LGLG384 loop is a substrate-docking site of γ-secretase capable of recognizing specifically different substrates and support a model in which the side chain residue L381 is implicated in the binding/processing of APP-C99 while the residue L383 is preferentially implicated in the binding/processing of the Notch-based substrate.

Gene expression profiling in cells with enhanced gamma-secretase activity.
Processing by γ-secretase of many type-I membrane protein substrates triggers signaling cascades by releasing intracellular domains which, following nuclear translocation, modulate the transcription of genes regulating a diverse array of cellular and biological processes. We analyzed by cDNA microarray the cellular transcriptomes of mammalian cells with enhanced and inhibited γ-secretase activity - this revealed several affected clusters of molecular functions, several key players of the three Wnt pathways to be transcriptionally altered in response to enhanced γ-secretase, and more specifically 21 genes that hold significant potential for a better understanding of the biology of γ-secretase and its roles in Alzheimer’s disease pathology.
Selected Publications


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Alzheimer’s disease cerebral amyloid-beta deposits (green) surrounded by microglia (red) in plaque-bearing mice
**Introduction**

The Laboratory of Computational Neuroscience uses theoretical methods from mathematics, computer science, and physics to understand brain function. Questions addressed are: What is the code used by neurons in the brain? How can changes of synapses lead to learning?

**Keywords**

Modeling, Hebbian Learning, Spike-Timing Dependent Plasticity, Simulation, Spiking Neuron models

**Results Obtained in 2010**

We have been active in three different, but connected areas:

**Single-Neuron Modeling:**
We have shown that the electrical behaviour of neurons under somatic current or conductance injection can be well described by simplified neuron models with only one or two equations. The parameters of these neuron models can be directly extracted from experimental data. Our work has answered in this context two questions: first, what is the best simplified neuron model – the answer is exponential integrate-and fire model combined with adaptation and/or refractoriness (Badel et al 2008). Second, is there a way to quantify the heterogeneity of neurons – the answer is yes, since model parameters can be estimated reliably and on a neuron-by-neuron data from a few seconds of electrophysiological data (Badel et al. 2008c). The mathematical properties of such neuron models have been analysed (Naud et al 2008). To compare our approach with other approaches, we have organized an international competition – and indeed the simplified neuron models from our and one other lab were the winners (Jolivet et al. 2008, 2008b). The work on single-neuron modeling involves collaborations with the labs of Henry Markram and Carl Petersen. In 2009, the official organisation of the competition was transferred to the International Neuroinformatics Coordinating Facility (INCF). R. Naud from the EPFL-LCN and Dr. R. Ritz from the INCF worked out the details of the competition. Since the idea of competitions in neural modelling is a rather novel idea in Neuroscience, it led to a “perspective” article in Science (Gerstner & Naud).

The work on single-neuron modeling involves collaborations with the labs of Henry Markram and Carl Petersen.

**Modeling synaptic plasticity.**

We have developed a model that combines induction of synaptic plasticity with consolidation of synapses. The model of induction accounts for induction of Long-Term Potentiation under protocols of voltage-dependent and Spike-Timing Dependent Plasticity and leads to the tagging of the synapse. The model of consolidation combines a bistable dynamics with a triggering process for protein synthesis and accounts for a large variety of plasticity protocols. We also studied consequences of plasticity in a recurrent network. (Nature Neuroscience 2010)

**Network Simulation.**

In two collaborations with the labs of Michael Herzog and Carl Petersen, we simulate properties of networks of neurons.
**Selected Publications**


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**Team Members**

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- Henning Sprekeler
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- Chantal Mellier

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*Hand movement simulated in a learning net of spiking neurons.*
Introduction
The theme of our research is the neuroanatomical bases of emotional, social and cognitive difficulties in autism. Our lab is also interested in examining the pathophysiology and the possible role of the cerebellum in migraine.

Keywords
Functional and anatomical brain imaging, cognition, emotion, autism, plasticity, migraine, cerebellum.

Results Obtained in 2010
Our lab has been working at not only performing research on autism spectrum disorders, but also on informing the public about this condition, by organizing meetings with parents’ associations to provide a better understanding of autism.

In collaboration with the team of Genetics at the CHUV and the Center for Integrative Genomics at UNIL, we were the recipients of the Leenaards prize for Scientific research. The project awarded will study the phenotype, including behavioral, anatomical and functional profile, of a newly described copy number variant of the chromosome 16p11.2, strongly associated with autism and obesity. From this collaboration, a paper has already been published in Nature describing for the first time an association between a genetic microdeletion and obesity. Our collaboration has also led to the award of a Synergia grant, extending our research to an animal model.

Our team collaborated with the team of Genetics at the CHUV and Novartis to study the effect of a treatment by mGluR5 antagonist in Fragile X syndrome. Fragile X syndrome is the most common cause of inherited mental retardation and affects one in every 5000 children worldwide. In a paper recently published in Science Translational Medicine, our team, led by Sebastien Jacquemont at the CHUV, showed that patients with Fragile X who improved in their behavior when taking this drug had a specific ‘fingerprint’ on their DNA, and that there was a correlation between a response to treatment and the methylation status of the FMR1 promoter gene, mutated in Fragile X.

Autism spectrum disorders (ASD) are characterized by difficulties in social interactions, and in emotion expression. We are pursuing our research into the understanding of the neuroanatomical and functional bases of this disorder.

Diffusion spectrum imaging (DSI) is a technique allowing to observe the fine structure of the white matter circuitry in the brain. Using DSI, our group was able to investigate the anatomical structure of the Papez circuit in healthy humans. Papez circuit is an important anatomical substrate for both memory and emotions, and it is structurally altered in psychiatric, neurodegenerative and epileptic diseases, and these findings show that DSI tractography allows to perform non-invasive imaging of this complex circuit in vivo, and can be used as a tool for disease monitoring. In parallel, we are pursuing, in collaboration with our group at the Harvard Medical School in Boston, our research on migraine, its physiopathology and its long-term effect on the brain.
Selected Publications


Jacquemont S, Curie A. et al. (2011) Epigenetic modification of the FMR1 gene in fragile X leads to a differential response to the mGluR5 antagonist AFQ056. *Science Translational Medicine* 3 (64) : 64ra1.


Team Members

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Introduction
In humans, vision is the most important sensory modality. Surprisingly, the mechanisms of even the simplest forms of visual processing, such as spotting a pen on a cluttered desk, are largely unknown. For this reason, robots are still “object blind”. Our research aims to understand how and why humans can cope with visual tasks so remarkably well.

The Herzog lab continues to study a wide variety of areas. A “snapshot” of each topic is provided below.

Keywords
Vision Research, Spatio-temporal Vision, Schizophrenia Research, Psychophysics, TMS, EEG, Modelling.

Results Obtained in 2010
-Schizophrenia is a heterogeneous disease strongly influenced by genetic disposition. However, each gene contributes only little to the risk to suffer from the disease. For this reason, trait markers, so called endophenotypes, are of primary interest. We have developed such an endophenotype based on visual psychophysics. Schizophrenic patients performed worse than healthy controls. Interestingly, also the relatives of the patients performed worse indicating a genetic basis of performance deficits (Chkonia et al., 2010).

-There is no perception without perceptual learning. We have to learn to see. Perceptual learning is often assumed to occur on low, retinotopic levels of visual processing. We showed that perceptual learning can also occur on high, non-retinotopic stages (Otto et al., 2010).

-A clearly visible target presented in peripheral vision appears strongly distorted when flanked by neighbouring elements (crowding). Most work on crowding has focused on basic visual interactions. We found evidence that crowding can, surprisingly, be modulated by high level Gestalt factors (Sayim et al., 2010).

-fMRI is a powerful technique to localize brain activity. Temporal resolution is however limited. EEG, to the contrary, has a high temporal but limited spatial resolution. Using high density EEG and powerful inverse solution techniques, we could show that, in a variety of visual paradigms, EEG can localize brain areas fairly well (Plomp et al., 2010; see figure below).

-Transcranial magnetic stimulation (TMS) is an invasive technique interfering with brain dynamics with a great temporal precision. Using TMS, we showed that feature integration in the human brain takes about half a second. TMS can selectively interfere with feature processing during this epoch. When features do not interfere, TMS cannot change their processing (Rüter et al., 2010).

-In a common effort of three EPFL laboratories, we tested various tennis rackets made from different materials and how they are rated by expert tennis players. Carbon outclassed wood! (Overney et al., 2010).
Selected Publications


Team Members

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Introduction

Our mission:
To understand the molecular pathogenesis of Parkinson’s disease so that we can eventually develop novel targeted therapies and neuroprotective strategies to prevent or delay disease progression.

Our Research Goals:
To elucidate the relationship between the process of protein misfolding and aggregation and neurodegeneration and to understand the molecular mechanisms through which disease-associated mutations and post-translational modification in the gene products associated with neurodegenerative diseases induce neuronal dysfunction and neurodegeneration.

Keywords
Neurodegeneration, Parkinson’s disease, Alzheimer’s disease, amyloid, aggregation, toxicity, fibrils, phosphorylation, kinases, macrophage migration inhibitory factor, protein synthesis, protein biophysics.

Results Obtained in 2010

α-Synuclein aggregation in Parkinson’s disease and related disorders:
Our group continues to be one of the leading research groups investigating the biochemistry of α-syn, the molecular determinants of its aggregation and the structural basis of its toxicity. During the past year, we expanded these efforts and developed an integrative approach to elucidate the roles of post-translational modifications in modulating α-syn aggregation and toxicity in vitro and in vivo. Our studies provided novel insight into the role of diseases-associated phosphorylation, ubiquitination, and tissue-mediated cross-linking of α-syn in regulating the structure, aggregation, and membrane binding of α-syn in vitro. In addition, with the goal of identifying novel kinases and phosphatases involved in α-syn phosphorylation at S129, we showed that S87 is phosphorylated in vivo and that levels of pS87 are elevated in PD and related synucleinopathies. Currently, significant efforts are focused on elucidating the role of these modifications in regulating α-syn aggregation and toxicity in vivo using primary neurons, slice cultures and the AAV-based rat model of Parkinson’s disease.

Amyloid formation in Alzheimer’s disease:
Our work on amyloid-β focuses on elucidating the molecular determinants that govern its oligomerization, fibrillation and toxicity. More specifically, we were able to i) provide a molecular understanding of how the ratio of Aβ42/Aβ40 may influence amyloid formation and clearance in vivo; ii) identify the Aβ toxic species; and iii) develop mechanism-based novel inhibitors that target specific steps in the Aβ amyloid pathway. Many of these advances were made possible by our successful development of reproducible protocols for the preparation and characterization of distinct hydrodynamically defined Aβ species. Recent studies from our group demonstrate that Aβ42 toxicity is not linked to specific prefibrillar aggregate(s); rather it is linked to the ability of these species to grow and undergo fibril formation, which depends on the presence of monomeric Aβ42. The possibility that an ongoing Aβ polymerization process, rather than a specific aggregate of defined size or structure, strongly determines Aβ neurotoxicity has important implications for understanding of the role of Aβ aggregation in AD pathogenesis and the design of anti-Aβ therapeutics.

Macrophage Migration Inhibitory Factor (MIF) and autoimmune and inflammatory diseases:
During the last four years we employed chemical and classical genetic approaches in combination with computational and high-throughput screening methodologies to dissect the structure-function relationship of MIF. We identified several novel classes of potent MIF inhibitors that have distinct mechanisms of action and provide the basis for the development of more selective and potent inhibitors of the enzymatic and biologic activities of MIF.
Selected Publications


Our group works at the interface of chemistry and biology to bring to bear the power of chemistry, biophysics, proteomic engineering, and neurobiology to address many of the key outstanding questions and technical challenges in the field of neurodegenerative research.
elucidate a unique mechanism of SIRT2-inhibition as a promising avenue for HD therapy and Huntington toxicity. These data identify SIRT2 inhibition as a promising avenue for HD therapy and elucidate a unique mechanism of SIRT2-inhibitor-mediated neuroprotection.

Introduction
The Laboratory of Functional Neurogenomics (LNGF) uses high-throughput gene expression profiling and other molecular approaches to elucidate new aspects of brain function and neurodegenerative disease. Our research focuses primarily on Huntington’s disease (HD), and the function of the striatum and cerebral cortex, the brain regions involved in HD. Other research interests include brain aging, neural cell type-specific aspects of gene expression, and the development of new tools for gene expression analysis and drug discovery. Understanding diseases with known causes like HD has been viewed as a unique opportunity to elucidate universal mechanisms of neurodegeneration and explore their possible treatment, and we believe that a neuroprotective treatment for Huntington’s disease might not only benefit patients with this disorder, but also be applicable to other, more prevalent diseases.

Keywords
Neurodegenerative disease, Huntington’s disease, striatum, cerebral cortex, motor cortex

Results Obtained in 2010
Sirtuin 2 (SIRT2) inhibition and sterol biosynthesis (Luthi-Carter et al., 2010). Huntington’s disease (HD) has a complex pathogenesis including protein aggregation and the dysregulation of neuronal transcription and metabolism. Our recent work has demonstrated that inhibition of SIRT2 achieves neuroprotection in cellular and invertebrate models of HD. Whereas mutant huntingtin fragments increased sterols in neuronal cells, SIRT2 inhibition reduced sterol levels and decreased nuclear trafficking of the sterol-regulating transcription factor SREBP-2. Importantly, manipulation of sterol biosynthesis at the transcriptional level mimicked SIRT2 inhibition, demonstrating that the metabolic effects of SIRT2 inhibition are sufficient to diminish mutant huntingtin toxicity. These data identify SIRT2 inhibition as a promising avenue for HD therapy and elucidate a unique mechanism of SIRT2-inhibitor-mediated neuroprotection.

Regulation of cortical microcircuit behavior by activity-dependent Brain-Derived Neurotrophic Factor (BDNF) expression and its perturbation in Huntington’s disease (Gambazzi et al., 2010). The specific molecular and neuronal circuit bases for the cortical effects of mutant huntingtin (htt) in HD are largely unknown. To address this issue, we studied the relationship between the molecular effects of mutant htt fragments in cortical cells and the corresponding behavior of cortical neuron microcircuits. We observed that a transcript-selective diminution in activity-dependent BDNF preceded the onset of a synaptic connectivity deficit in ex vivo cortical networks. Decreased BDNF expression was determined to be a significant contributor to network-level dysfunction, as shown by the ability of exogenous BDNF to ameliorate cortical microcircuit burst firing. These data elucidate a novel HD-related deficit in BDNF gene regulation as a plausible mechanism of cortical neuron hypocoordination and cortical function deficits in HD. Moreover, the novel model paradigm we have established is well suited to further mechanistic and drug screening research applications.

Abnormal cortical neuron gene expression in Huntington’s disease brain (Zucker et al., 2010). Motor dysfunction, cognitive impairment, and regional cortical atrophy indicate cerebral cortical involvement in HD. To address the hypothesis that abnormal corticostriatal connectivity arises from polyglutamine-related alterations in cortical gene expression, we isolated layer 5 cortical neurons by laser-capture microdissection and analyzed transcriptome-wide mRNA changes. Layer 5 motor cortex neurons of transgenic R6/2 HD mice demonstrated numerous transcriptomic changes, including decreased expression of mRNAs encoding the Lin7 homolog b (Lin7b), a finding that was confirmed in human HD brain. Given that Lin7b is a scaffold protein implicated in synaptic plasticity, neurite outgrowth, and cellular polarity, its decreased expression may contribute to abnormal corticostriatal connectivity in HD.
Selected Publications


Schematic representation of the mechanisms by which SREBP2 activity is regulated, and putative sites of action of the SIRT2 deacetylase. SREBP2 trafficking to the nucleus may also be regulated by the deacetylation of tubulin, a known SIRT2 substrate (not shown).
Introduction

We investigate the cellular and molecular mechanisms of brain energy metabolism, in particular the interactions between neurons and astrocytes and the role of this interaction in normal brain function (e.g. learning and memory), as well as dysfunctions (e.g. neurodegeneration).

Keywords

Neuroenergetics, neuro-glia interaction, brain metabolism, neuronal plasticity, glial plasticity, high-resolution optical imaging, digital holographic microscopy, cell dynamics, neurodegeneration, sleep, functional brain imaging, dialogue between neurosciences and psychoanalysis.

Results Obtained in 2010

Neuroenergetics and neurodegeneration (Igor Allaman, Mireille Belanger)

Alterations of brain energy metabolism and oxidative stress are key features of Alzheimer’s disease (AD). We have previously demonstrated that alterations of astrocytic phenotype, with regards to glucose metabolism and oxidative-stress status, are induced by aggregated amyloid-beta (Aβ) peptides and pro-inflammatory cytokines (TNFα and Interleukin (IL)-1β), which are key mediators in AD pathogenesis. In particular, both Aβ and TNFα or IL-1β cytokines increased glucose uptake, and its various metabolic fates, as well as glutathione and H2O2 release. In order to gain further insight about the effects on pro- as well as anti-inflammatory mediators on astrocytes metabolism, we have performed a detailed characterization of the effect of different cytokines on selected astrocytic metabolic parameters. As a general pattern we observed that all pro-inflammatory cytokines increased glucose utilization in cultured astrocytes while the anti-inflammatory ones, IL-4 and IL-10, decreased astrocytic glucose utilization. Interestingly, these effects were astrocytic specific because none of these cytokines induced any significant change of the metabolic profile of neurons. When pairs of pro-inflammatory cytokines were co-applied, synergistic modifications of the metabolic profile of astrocytes could be observed for several combinations. In contrast, the anti-inflammatory cytokine IL-10 partially attenuated the effects of pro-inflammatory cytokines. Finally, the modifications of the astrocytic metabolism induced by TNFα+IL-1β and interferon-γ modulated neuronal susceptibility to an excitotoxic insult in neuron-astrocyte co-cultures. Together, our observations demonstrate that pro- and anti-inflammatory cytokines differentially affect the metabolic profile of astrocytes, and that these changes have functional consequences for surrounding neurons.

Astrocytes metabolism and sleep-waking cycle (Jean-Marie Petit, Sophie Burlet, Maxime Baud, Joel Gyger)

Astrocytes play an important role in the neuro-metabolic coupling through two main mechanisms: the glycogen mobilization and the “Astrocyte-Neuron Lactate Shuttle” (ANLS) by which the lactate, produced by the astrocytic glycolysis in response to neuronal glutamate release, is used as alternative energy substrate by neurons.

We first investigated the impact of a 6h sleep deprivation induced by the “gentle sleep deprivation” method or by administration of modafinil (a psycho-stimulant drug) on different parameters of the cortical glycogen metabolism. In these conditions, glycogen levels stayed unchanged in spite of prolonged neuronal activation. This was in accordance to the transcriptional activation and the increase in enzymatic activity of proteins directly involved in glycogen synthesis. These results show that glycogen metabolism, which is specifically astrocytic, undergoes an adaptation in response to a prolonged neuronal activation in the cerebral cortex (Petit et al., Sleep 2010). In a second set of experiments, we investigated the ANLS in a similar sleep deprivation protocol. Since proteins involved in ANLS are present in astrocytes as well as in neurons, we developed an experimental strategy using transgenic mice. In these animals, astrocytes can be isolated from the cerebral cortex using a FACS (Fluorescence Activated Cell Sorting) apparatus. Preliminary results indicate that some mRNA encoding proteins involved in ANLS are regulated in astrocytes following sleep deprivation.
Selected Publications


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Astrocyte morphology in mixed cultures of astrocytes and neurons. Astrocytes were immunolabelled with the astrocytic marker GFAP (Glial fibrillary acidic protein, green). Nuclear staining (DAPI, blue).
Introduction
The Laboratory of Neural Microcircuitry is dedicated to understanding the structure, function and plasticity of the neural "microcircuits" that make up the neocortex – the outer layer of the brain responsible for memory, and other higher cognitive functions which, in humans, makes up more than 80% of the brain.

Keywords
synaptic plasticity, neuronal integration, neural microcircuits, autism, modeling, neural coding, neurons, synapses, patch clamp, electrophysiology,

Results Obtained in 2010
Ever since its creation, the LNMC has been highly active in developing and applying techniques for stimulating and recording from multiple neurons in brain slices. In 2010 and early 2011 this work gave fruit in several important publications. A paper on Nature Neuroscience, written with Christof Koch of the California Institute of Technology, demonstrated how electrical fields, generated by the electrical and chemical activity of neurons, can modulate neuronal activity in ways that do not depend on synaptic activity. This finding introduces a new dimension into our understanding of the neural microcircuits and into circuit modeling. A second paper, this time in PLoS Biology, again used multineuron recording techniques, this time to show how small numbers of inhibitory neurons (pyramidal cells) can coordinate synchronous spiking activity in neighboring neurons. Finally, a paper recently published in PNAS offers important new insights into the underlying structure of neural microcircuits. The paper provides experimental support for the idea, originally advanced by Hebb, that neurons are organized in tightly interconnected assemblies. However, it also gives evidence that patterns of connectivity within these assemblies are under tight constraints, and that the strengths of their synaptic connections tend towards saturation. This suggests that, contrary to Hebb's proposal, neuronal assemblies are not molded by experience — but rather that they represent, innately determined building blocks ("lego bricks") which experience later shapes into complex memories.

2010 also saw two other extremely important results from the lab's activity:

The first was the publication of an extremely detailed study of the development of Thick Tufted Layer 5 pyramidal neurons in rat somatosensory cortex. In this study researchers from the lab painstakingly reconstructed the 3D morphology of neurons at different stages of development, demonstrating major differences between early stages (at which every part of the neuron grows simultaneously) and later stages when growth is limited to certain parts of the neuron. Results from this work will feed efforts to build models of growing neurons – a key step in Blue Brain's modeling strategy.

The second key result came from the lab's autism research group, which in 2010 published a major paper, describing a unifying theory of autism. The "Intense World Theory" proposes that autism is linked to hyper-reactivity and hyperplasticity of neural microcircuits in the neocortex and the amygdala and possibly elsewhere. It goes on to suggest that this underlying neuropathology causes autistic people to live in a world of abnormally intense perceptions, and that many of the classical symptoms of autism are learned strategies to manage their situation.

Markram Lab
http://bmi.epfl.ch

Born in South Africa, Henry Markram obtained his Ph.D. in Neuroscience at the Weizmann Institute of Science, Israel. After a postdoc position in Bert Sakman's lab at the Max Planck Institute, he returned to the WIS where he began to systematically reverse engineer neocortical microcircuitry. This led to important discoveries including Spike Timing Dependent Plasticity (STDP) and Redistribution of Synaptic Efficacy (RSE). Working with Misha Tsodyks, he developed the TM model of dynamic synapses, With Wolfgang Maass he developed the theory of "Liquid Computing". In 2002, he moved to the EPFL to form and direct the Brain Mind Institute. (con't on next page)
Selected Publications


Team Members

Scientists
Dr. Elhamdani Abdeladim
Dr. Markram Kamila

Postdocs
Dr. Logette Emmanuelle
Dr. Pezzoli Maurizio
Dr. Ryge Jesper

PhD Students
Camacho Susana
Delattre Vincent
Favre Monica
Gambazzi Luca Romano
Ghobril Jean-Pierre
Khazen Georges
Muralidhar Shruti
Perin Rodrigo
Riachi Imad

Lab technicians
La Mendola Deborah
Meystre Julie

Administrative Assistant
Christiane Debono

12 Neuron Patch Clamp Recording System used in electrophysiology experiments: (a) pyramidal neurons; (b) region of the brain studied; (c) 3d reconstruction of neurons; (d) recording apparatus; (e) recordings; (f) observed connections among neurons
Introduction
The combination of experiment and theory has long formed the basis of the scientific method. As computers become faster, computer simulations – combining experimental measurements and theoretical models – are beginning to capture the biological complexity of the brain. This is the goal of the Blue Brain Project, now in its seventh year. Over this time the project has constructed a prototype brain simulation facility with the software tools, the knowhow and the supercomputing infrastructure to model the detailed structure of neuronal circuits and to simulate the way they function.

Keywords
Neocortex, simulation-based research, reverse engineering, high performance computing, subcellular, cortical column, mesocircuits

Results Obtained in 2010
For the Blue Brain Project, the main focus of activity in 2010 was the consolidation of the simulation facility. We expanded the facility’s modeling capability to model the subcellular “ultrastructure” of individual neurons. We also expanded the scale of the models we could build, regularly simulating mesocircuits with up to 36 columns and as many as 300 million synapses. Finally we built tools enabling us to perform new kinds of experiments. In particular we learned to simulate local field potentials (the electrical fields resulting from the activities of large groups of neurons). We also expanded the capabilities of our visualization tools, which now allow researchers to view the real time activity of up to 360,000 neurons.

In parallel with this work, we used the capabilities of the facility to gain important new insights into the structure and function of neuronal microcircuitry. In particularly we have constructed model circuits from realistic 3D models of neurons, shown that the circuit’s general pattern of connectivity is highly invariant and demonstrated that this is due to the diversity of the forms of the neurons in the circuit. In other words, we have discovered a profound principle of brain design which helps to explain why the brain is so resilient to damage and why the brains of animals of the same species are all so similar. These results, which have been submitted for publication, also suggest that it is possible to predict many aspects of brain connectivity from knowledge of neuronal morphologies. This possibility enormously facilitates the modeling process.

The last aspect of the Blue Brain Project’s activity in 2010 was technical development to facilitate collaboration with outside communities. In particular, the project continued work on a Software Development Kit (SDK) that abstracts away from the technological complexity of Blue Brain models (and the underlying supercomputing infrastructure) and provides neuroscientists with a natural way of interfacing the models. Another development of great importance has been the release of Channelpedia (channelpedia.net) – a standardized database of information about ion channels – the proteins that control the flow of ions across the cell membrane and play a vital role in the functioning of neurons.
Selected Publications


Team Members
Group Leaders
Hill Sean
Schuurmann Felix

Postdocs
Graham Joe
Keller Dan
Müller Eilif
Telefont Martin

Engineers
Kenyon John
King Jim

PhD Students
Ramaswamy Srikanth
Ranjan Rajnish
Reinmann Michael
Tauheed Farhan

Internships
Fleischer Pierson
Moor Ruben
Pelko Miha
Schmuecker Niklas

Master's Students
Akiki Shadi
Mohanna Safa

Civilian Service
Nick Ryckx

Senior Scientist
Richard Walker

Secretary
Demiri Bardhyl
Introduction

The Laboratory of Molecular Neurodegenerative Research investigates the pathophysiology of Parkinson’s disease, a chronic neurodegenerative movement disorder. Our laboratory investigates the normal biological function and pathological dysfunction of various proteins, that when genetically mutated, cause an inherited (familial) form of Parkinson’s disease. Our mission is to understand the molecular mechanisms and pathways through which disease-associated mutations in these proteins cause neuronal damage and neurodegeneration. We aim to use this information in the long term to develop novel therapies and neuroprotective strategies to delay or prevent this devastating disease.

Keywords
Parkinson’s disease, parkinsonism, neurodegeneration, genetic mutations, disease models, neuronal cell death, leucine-rich repeat kinase 2 (LRRK2), parkin, α-synuclein, ATP13A2, therapeutic targets

Results Obtained in 2010

Moore Lab
http://moorelab.epfl.ch

Darren Moore
Tenure-track Assistant Professor

Prof. Moore conducted his PhD in molecular neuroscience at the University of Cambridge (1998-2002) and post-doctoral research on familial Parkinson’s disease (2002-05) in the Department of Neurology at the Johns Hopkins University School of Medicine. He spent 3 years on the Neurology faculty at Johns Hopkins as an Instructor (2005-06) and later as Assistant professor (2006-08). Prof. Moore established the Laboratory of Molecular Neurodegenerative Research at EPFL in 2008 to focus on understanding the molecular basis of Parkinson’s disease and related neurodegenerative disorders.

The Moore laboratory focuses its investigations on a number of gene products that when mutated cause familial Parkinson’s disease (PD), including leucine-rich repeat kinase 2 (LRRK2), α-synuclein, parkin and ATP13A2. Mutations in the LRRK2 and α-synuclein genes cause autosomal dominant forms of PD, whereas parkin and ATP13A2 mutations cause autosomal recessive PD. Mutations in the LRRK2 gene were discovered in 2004 and we have been working over the years to model the pathogenic effects of these dominant mutations. In 2010, we continued to develop and phenotype a collection of novel transgenic mice that we recently created to overexpress disease-associated mutated forms of human LRRK2 protein in the brain. These transgenic models develop some key features of PD with advanced age and will prove extremely useful for understanding how LRRK2 mutations cause neurodegenerative disease. At the same time, we have developed a basic model in the baker’s yeast, Saccharomyces cerevisiae, to further understand the molecular pathobiology of LRRK2 and we have used this model to identify genes that can modify LRRK2-dependent phenotypes. We are actively investigating the mechanisms through which the proteins derived from these genes functionally interact with the LRRK2 protein in neuronal and animal models. Finally, our research is attempting to clarify the mechanisms underlying neuronal cell death induced by mutated LRRK2 and here we continue to focus on the role of mitochondrial dysfunction, autophagy, neuronal morphology and proteins or protein complexes that interact with, or are phosphorylated by, LRRK2.

In 2010 we continued with a new project on the ATP13A2 protein. Genetic mutations in ATP13A2 cause familial PD and Kufor-Rakeb syndrome, a juvenile-onset, autosomal recessive disorder characterized by pallido-pyramidal neurodegeneration with severe parkinsonism and dementia. ATP13A2 is a novel P5-type ATPase protein which is thought to transport cations across intracellular vesicular membranes in an ATP-dependent manner. We are attempting to understand the normal function of ATP13A2 in neurons, and we are also creating disease models based upon gene disruption or silencing to replicate the effects of recessive “loss-of-function” mutations.

We embarked upon a new project in 2010 to understand the role of the E3 ubiquitin ligase, parkin, in mitochondrial function. Genetic mutations in parkin cause early-onset, autosomal recessive PD. Recent studies have shown that parkin can mediate the ubiquitination and proteasomal degradation of mitofusin 1, a protein that normally promotes mitochondrial fusion. Our studies reveal some of the molecular details underlying parkin-dependent mitophagy and support a model whereby, during mitochondrial damage, parkin inhibits mitochondrial fusion through degradation of mitofusin 1 to limit mitochondrial refusion and thereby isolate damaged mitochondria for removal by mitophagy.
**Selected Publications**


**Team Members**

**Post-doctoral Fellows**

David Ramonet
Alzbeta Trancikova
Elpida Tsika

**PhD Students**

Alessandra Musso
Agata Podhajska
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**Laboratory Technician**

Liliane Glauser

**Master’s Students**

Sarah Sonnay

**Administrative assistant**

Caroline Rheiner
Introduction
Sensory perception is an active process in which neurons in the brain construct an internal representation of the world. Our goal is to obtain causal and mechanistic explanations for simple forms of sensory perception in mice at the level of individual neurons and their synaptic connections.

Keywords
Sensory perception, Active sensing, Motor control, Somatosensory cortex, Motor cortex, Whole-cell recordings, Optogenetics, Voltage-sensitive dye imaging, Two-photon microscopy

Results Obtained in 2010
Sensory information is actively gathered by animals. For example, we move our fingers over surfaces to feel their shape and texture. Sensory input and motor control are therefore closely associated. Classical studies of mammalian movement control define a prominent role for primary motor cortex. Investigating the mouse whisker system, we found an additional and equally direct pathway for cortical motor control driven by primary somatosensory cortex (Matyas et al., 2010). Whereas activity in primary motor cortex directly evokes exploratory whisker protraction, primary somatosensory cortex directly drives whisker retraction, providing a rapid negative feedback signal for sensorimotor integration. Motor control by sensory cortex suggests the need to re-evaluate the functional organization of cortical maps.

Excitatory neurons of the neocortex send long-range axonal projections to other brain areas. We made local injections of lentivirus encoding GFP into mouse primary somatosensory barrel cortex in order to visualize the axonal projections from this brain region (Aronoff et al., 2010). In addition, we found that adeno-associated virus serotype 6 encoding Cre-recombinase could be injected into Cre-reporter mice to retrogradely label neurons projecting to the injection site. Prominent reciprocal projections are found between primary somatosensory cortex, secondary somatosensory cortex, motor cortex, perihinal cortex and thalamus. Primary somatosensory barrel cortex also projects strongly to striatum, thalamic reticular nucleus, zona incerta, anterior pretectal nucleus, superior colliculus, pons, red nucleus and spinal trigeminal brain stem nuclei. These long-range connections of the barrel cortex with other specific cortical and subcortical brain regions are likely to play a crucial role in sensorimotor integration, sensory perception and associative learning.

Sensory information within a given local region of the neocortex is processed through the synaptic interactions of excitatory and inhibitory neurons and yet we know little about their activity in awake animals. Through single and dual whole-cell recordings combined with two-photon microscopy in the barrel cortex of behaving mice, we directly compared the synthetically driven membrane potential dynamics of inhibitory and excitatory layer 2/3 neurons (Gentet et al., 2010). We found that inhibitory neurons depolarize synchronously with excitatory neurons, but they are much more active with differential contributions of two classes of inhibitory neurons during different brain states. Fast-Spiking GABAergic neurons dominate during quiet wakefulness, but during active wakefulness Non-Fast-Spiking GABAergic neurons depolarize firing action potentials at increased rates. Sparse uncorrelated action potential firing in excitatory neurons is driven by fast, large and cell-specific depolarization. In contrast, inhibitory neurons fire correlated action potentials at much higher frequencies driven by slower, smaller and broadly synchronized depolarization.
**Selected Publications**


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**Team Members**

**Post doctoral**
Alexandros Kyriakatos
Emmanuel Eggermann
Ferenc Matyas
Luc Gentet
Nadia Urbain
Natalya Korogod
Rachel Aronoff
Shankar Sachidhanandam
Sylvain Crochet (visiting scientist with a permanent position at the University of Lyon)
Takayuki Yamashita
Yves Kremer

**PHD Students**
Aurelie Pala
Celine Mateo
Michael Avermann
Shovan Naskar
Varun Sreenivasan

**Master’s Students**
Fred Marbach

**Administrative Assistant**
Séverine Sudre-Janot

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A neocortical column located below the surface blood vessels (grey, top face) is composed of many cells labelled with DAPI (cyan, right face) including inhibitory GABAergic neurons (green, left face). In Gentet et al. (2010) we targeted whole-cell recordings (red recording electrode) to these GABAergic neurons (yellow neuron at the electrode tip).
Carmen Sandi investigates how stress affects brain function, behavior and cognition, with a recent strong interest in understanding stress effects in social behaviors and aggression. Her work has been pioneering in implicating stress hormones and cell adhesion molecules in memory formation and psychopathology. Currently, she is the Chief Editor of the journal Frontiers in Behavioral Neuroscience, Scientific Advisor at the European College of Neuropsychopharmacology, the President of the European Brain and Behavior Society (EBBS) and the Coordinator of the FP7 EU Project MemStick.

**Introduction**

The Laboratory of Behavioural Genetics investigates the impact and mechanisms whereby stress affects brain function and cognition with a focus on learning and memory processes, social behaviors and psychiatric disorders - such as anxiety, depression, and pathological aggression.

**Keywords**

Stress – Learning – Memory – Violence – Neuroplasticity – Cell adhesion molecules – Glutamate receptors

**Results Obtained in 2010**

**The involvement of novel synaptic cell adhesion molecules in stress and cognition**

As coordinators and partners of the FP7 EU project MemStick, we investigate the role of 'synapse-specific' cell adhesion molecules in memory loss observed in models of psychiatric disorders. Chronic stress is a vulnerability factor for the development of a number of neuropsychiatric disorders frequently characterized by both cognitive dysfunction and anti-social behaviors. We have found that the impact of stress on the expression levels of Nectins and Neuroligins in different hippocampal areas correlate with alterations in social motivation and social cognition. Causality for the involvement of Nectins in the social consequences of stress was obtained by means of AAV-mediated Nectin overexpression in the hippocampus. Our results implicate these molecules in stress-induced alterations in mood and sociability, highlighting them as potential targets for the development of novel treatments for stress-induced neuropsychiatric disorders. Furthermore, they emphasize a key role of the social domain in the mediation of stress-induced alterations in mood disorders.

**Stress, anxiety and social hierarchies**

We have shown that stress can have important and long-lasting influences on social relationships by affecting the hierarchy outcome and amplifying the persistence of the memory for the social status that is established in a first encounter between conspecifics. We have identified key neurobiological pathways (glucocorticoids and oxytocin and vasopressin receptors in specific brain regions; i.e., medial amygdala and lateral septum) that mediate the long-term impact of stress in social hierarchies. Currently, we are exploring the role of anxiety trait and the involvement of the nucleus accumbens in the establishment of social hierarchies.

**The impact of developmental stress on psychopathology: A focus on pathological aggression**

Early life stress is an important risk factor for a wide variety of psychopathological alterations. We have developed an animal model that recapitulates the key features of a 'cycle of violence', including the trans-generational transmission of aggression. Exposing male rats to stress during the peri-puberty period renders animals more aggressive at adulthood, a process that involves changes in the activity pattern in the amygdala and the medial orbitofrontal cortex. In addition, these males are more aggressive with the females they cohabitate with, and their offspring show increased aggressive behaviors against other conspecifics. We are currently investigating the biological mechanisms whereby stress triggers this cycle of violence, and we do this at the different key levels (genetic, epigenetic, neurobiological, neuroendocrine, and behavioral) of the process.
Selected Publications


Team Members

Post doctoral
Maria Isabel Cordero Campana
Martina Fantin
Guillaume Poirier
Yannick Sevelinge
Michael van der Kooij

PhD Students
Jorge Castro Cifuentes
Basira Salehi
Marjan Timmer
Stamatina Tzanoulinou
Vandana Veenit

Master Students
Shanaz Diessler
Xavier Fontana
Keerthana Iyer
Emil Polny

Visiting Students
Germán Cuesto Gil
Paulina Jedynak
Stefanie Klampfl
Timothy Leung
Muy Cheng Peich

Lab Technicians
Christelle Albac
Jocelyn Grosse
Grégoire Parchet
Christina Schrick
Coralie Siegmund
Angélique Vaucher

Administrative Assistant
Barbara Goumaz

Stress and anxiety influence the establishment of social hierarchies (tip).
Introduction
In the brain, nerve cells are arranged in intricate neuronal networks, and communicate with each other at synapses, in the process of synaptic transmission. Synaptic transmission is the most important means of fast information transfer between neurons. Therefore, a detailed understanding of the signalling mechanisms at the synapse is an important pre-requisite to understand how information is processed in neuronal circuits.

Keywords
Synaptic transmission, nerve terminal, neurotransmitter, exocytosis, short-term plasticity, synapse development

Results Obtained in 2010
Short-term plasticity during physiological activity.
We have studied the interaction between two opposing forms of short-term plasticity, synaptic depression and short-term facilitation, using the calyx of Held synapse. We showed that pre-depressing the synapse using a brief low frequency train (~ 10 - 20 Hz) reduces transmission, and uncovers a large short-term facilitation in response to a subsequent high-frequency train (Martin Müller, Juan Goutman et al., 2010). This facilitation helps to recruit additional synaptic strength during the onset of high-frequency activity, as it might occur with natural sound stimulation at these auditory synapses.

Role of Synaptotagmin isoforms in the regulation of vesicle fusion.
Synaptotagmin1/2 are the main Ca2+ sensors for fast vesicle fusion. A multitude of additional Synaptotagmin isoforms (Syt3 - Syt17) exists, but their function in regulating vesicle fusion is less well known. In 2010, we identified other Syt isoforms expressed at the calyx of Held synapse, by establishing a novel qPCR-based gene expression approach for single neurons in whole-cell patch-clamp experiments (Le Xiao et al., 2010). We also contributed to investigating the roles of Syt1, Syt2 and Syt7 in glutamate release from inner hair cells, the sensory cells of the auditory system. In these cells, Ca2+-driven vesicle fusion is dominated by another protein (Otoferlin), and the Synaptotagmin isoforms only play minor roles (Beurg, Michalski et al., 2010).

RIM proteins determine Ca2+ channel density at the presynaptic active zone.
Transmitter release at all synapses takes place at small, specialized membrane areas (the «active zone») where Ca2+ channels, docked vesicles and other components of the release machinery are tightly co-localized. However, the molecular mechanisms enabling a high Ca2+ channel density at the active zone were largely unknown. In 2010, we demonstrated the feasibility of Cre-lox based conditional gene deletion at the calyx of Held model synapse. This has allowed us to remove all RIM1/2 isoforms in a tissue-specific manner form the lower auditory system, without endangering the survival of the resulting conditional double k.o. mice. Using direct nerve terminal recordings which are feasible at the calyx of Held, we uncovered a new role of RIM proteins in guaranteeing a high Ca2+ channel density at the presynaptic active zone (Yunyun Han et al., 2011). This conditional k.o. mouse approach at the calyx of Held promises to be very useful for future studies determining the exact roles of further presynaptic proteins in the complex process of Ca2+ - secretion coupling in the nerve terminal.
Selected Publications


Team Members

Post doctoral
Norbert Babai
Olexiy Kochubey
Nicolas Michalski

Phd Students
Elin Falk
Ozgür Genc
Yunyun Han
Shovan Naskar
Le Xiao

Technicians
Heather Murray
Coralie Pernet
Jessica Perritaz

Administrative Assistant
Laure Dayer

Invited Professor
David Perkel
IBI - Institute of Bioengineering

The Institute of Bioengineering sits at the interface of the life sciences and of engineering, being situated in both the School of Life Sciences and the School of Engineering and reporting to both deans. This dual affiliation allows great diversity in hiring faculty from different backgrounds and with different research perspectives, all focused on basic biological sciences using quantitative and systems analyses, as well as translating the biological and biochemical sciences into therapeutics and diagnostics. The dual affiliation also provides a rich educational environment, both at the BS/MS and PhD levels, especially since a joint MS program in Bioengineering has come into effect in the fall of 2010, shared between the two Schools.

In pursuit of basic biological mechanisms, IBI faculty investigate questions such as:
- How the cellular micro-environment controls cellular differentiation and morphogenetic processes;
- How stem cell processes, such as self-renewal and differentiation, are determined; How cell migration and trafficking in complex environments is modulated;
- How complex biological networks such as metabolism, gene expression and protein trafficking are regulated; and
- How biophysical and biomolecular signals interact in controlling cellular behavior.

Our goal is to transform knowledge gained from our studies into clinical applications. To that end, the IBI faculty develop novel technologies in areas including: interventional and diagnostic biomedical micro-devices, synthetic and biosynthetic biomaterials for delivery of small molecule drugs, proteins and DNA, materials in bio-nanotechnology, immunotherapy based on active biomolecules and nanomaterials, novel molecules for photodynamic therapy, and tissue engineering for therapeutics as well as physiological modelling based on biomolecular and stem cell approaches.

‘http://ibi.epfl.ch’
Introduction
The research of the Laboratory of Integrative and Systems Physiology (LISP) aims to understand how regulatory proteins, including nuclear receptors, membrane receptors and transcriptional cofactors, act as sensors for molecules of nutritional, metabolic or pharmacological origin, and translate this into altered gene expression and protein patterns affecting metabolic function.

Keywords
Diabetes, genetics, metabolism, metabolic disease, phenogenomics, transcription

Results Obtained in 2010
The Auwerx/Schoonjans laboratory was amongst the pioneers to unravel the wide-ranging implications of the three PPARs, PPARα, PPARβ/δ, and PPARγ, in metabolic control. Perhaps most striking in this context was our discovery of an association between the PPARγ Pro12Ala gene variant with type 2 diabetes and obesity, identified long before the era of genome-wide association studies, and as such the first gene tied with these common complex diseases. We established how the enterohepatic nuclear receptors, LRH-1 and SHP, govern hepatic lipid and bile acid metabolism, regulate mucosal immune homeostasis, and control fertility via their commanding role on steroid production. We furthermore identified bile acids as endocrine regulators of energy expenditure, through the activation of a novel membrane receptor, TGR5. Finally, We established that transcriptional cofactors, such as the acetyltransferases (SRC2/TIF2 and SRC-3) and the deacetylases (such as SIRT1), fine-tune energy homeostasis by changing the acetylation status of PGC-1α, the master regulator of mitochondria. Since altered signaling by nuclear receptors and cofactors, contributes to the pathogenesis of type 2 diabetes, obesity and atherosclerosis, our research paved the way for novel preventive and therapeutic strategies for these common diseases. The importance of these discoveries is testified by the fact that several compounds targeting these receptors and or cofactors have made it into the clinic. Examples of drugs for which our research contributed to clinical development are the fibrates (that target PPARα), thiazolidinediones (that target PPARγ), PPARγ/δ agonists, bile acids and bile acid derivatives (that target both the TGR5 and FXR), and resveratrol and SRT1720 (which activate SIRT1).
Selected Publications


Team Members

Post doctoral Associates
Carles Canto
Pablo Fernandez-Marcos
Taoufiq Harach
Riekelt Houtkooper
Ellen Jeninga
Chikage Mataki, until Nov ’10
Laurent Mouchiroud
Lilia Noriega
Thijs Pols
Dongryeol Ryu
Raffaele Teperino, until June ’10
Hiroyasu Yamamoto
Jiujiu Yu

PhD Students
Pénélope Andreux
Mitsonura Nomura
Evan Williams, from Sept. 2010

Master’s Students
Genevieve Rydlo
Evan Williams, until Aug. 2010

Lab Technicians
Sabrina Bichet
Thibaud Clerc
Marie-Laure Dénéreaz, until September 2010
Amandine Moriot-Signorino-Gelo
Norman Moullan

Administrative Assistant
Valérie Stengel

Mice treated with resveratrol are protected from obesity.
Introduction
The goal of the Barrandon laboratory is to understand skin morphogenesis, manipulate stem cell fate and translate stem cells from bench to bedside. The laboratory investigates stem cell fate in skin and other epithelia using single cell analysis and serial transplantation. The research aims 1- at understanding epidermal metaplasia, 2- at reconstructing epidermal appendages (hair follicles, sebaceous glands and sweat glands in patients transplanted with autologous epidermal stem cells, 3- at improving engraftment of transplanted epidermal stem cells and 4- at developing ex vivo gene therapy for Recessive Dystrophic Epidermolysis Bullosa, a horrendous hereditary skin disease.

Keywords
Stem cells, metaplasia, micro-environment, skin, thymus, cell and gene therapy

Results Obtained in 2010
Adult (tissue) stem cells are responsible for long-term renewal, regeneration and repair. Hence, they have the capacity to self-renew and to generate a differentiated progeny for an extended period of time (theoretically a lifetime). Human skin is privileged because its stem cells (epithelial and mesenchymal) can be extensively cultured and cloned, genetically manipulated and transplanted. Our current research targets the role of small microenvironmental variations on epidermal stem cell behavior and aims at exploring the potency of p63-expressing epithelial stem cells in stratified epithelia, trachea, bladder and thymus in several species including the human. We have demonstrated that all stratified epithelia of the rat, independent of their primary germ line origin contain clonogenic stem cells that can respond to skin morphogenetic signals by forming epidermis, sebaceous glands and hair follicles, a capacity that is maintained in serial transplantation. On the other hand, p63-expressing cells of the bladder and of the trachea can only form an epidermal like-structure reminiscent of epidermal metaplasia (Claudinot et al., submitted). The thymus contains epithelial cells (TECs) that form a unique 3D structure that does not resemble that of a simple or stratified epithelium, even if some TECs express markers of skin differentiation (Hassall's bodies). We have demonstrated that the thymus of the rat contains a population of clonogenic p63-expressing TECs with astonishing capabilities. These cells maintain a thymic identity in vitro and express MHC class II and Aire (Autoimmune regulator) when incorporated into a reconstituted thymus in vivo. Surprisingly, these cultured cells can adopt the fate of bona fide multipotent stem cells of the hair follicle when exposed to skin morphogenetic signals, a property maintained in serial transplantation. Gene profiling experiments have demonstrated that several transcription factors important for thymus identity were either down regulated or silenced in TECs recovered from skin. This clearly represents an increase in potency and the demonstration that adult stem/progenitor cells can be robustly reprogrammed by micro-environmental cues (Bonfanti et al., Nature 2010). We are pursuing our investigation to determine the extent of TECs potency. Most importantly, stem/progenitor cells of squamous epithelia are particularly exposed to environmental hazards because of their unique location at the interface of the body with the external world. We have demonstrated that a difference as small as 0.5 degree Celsius, e.g. from 36.5 to 37°C, can impact gene expression in cultured human keratinocyte stem/progenitor cells and we have identified mammalian TOR (mTOR) as a transcriptional modulator (Brouard et al., submitted). Our results strongly suggest that stem/progenitor cells can rely on mTOR signaling to balance a changing niche. We are pursuing our investigation to determine the impact of mTOR signaling on cultured human keratinocyte stem/progenitor cells before and after transplantation.
Selected Publications


Blistering of the skin in a patient suffering from Recesive Dystrophy Epidermolysis Bullosa. Deficient Collagen VII is immunostained in red.

Team Members

Senior scientists
Brouard Michel
Rochat Ariane

Post doctoral fellows
Bonfanti Paola
Braschler Thomas
Caillier-Veron Maia
Claudinot Stéphanie
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Grasset Nicolas
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Volorio Christelle

PhD Students
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Gorostidi François
Maggioni Melissa
Mosig Johannes
Stolf Daiana

Master Student
Cohen Lionel
Andrey Jérémy
Peterman Katrin

Scientific Collaborators
Bon Anne-Charlotte
Graber Julien

Clinical Trial Collaborator
Savioz-Dayer Emmanuelle

Supporting Staff
Mercier Louis
Vermot Steeve

Supporting Staff COP
Burki Marko
Gomez Luis Da Costa

Administrative Staff
Guex Nathalie
Introduction
We use advanced molecular modeling techniques combined with high-performance computing to investigate biological systems, in particular their function emerging from structure. Our main targets are bacterial and viral systems and their mechanism of resistance towards natural and clinical drugs. We develop new multi scale schemes and models to extend the power of current molecular simulations to tackle problems such as the assembly of large macromolecular complexes and the design of remedies for pathogenic infections.

Keywords
Computational biophysics, biochemistry, and structural biology; bacteria and viruses; multi scale molecular simulations; macromolecular assembly; protein and drug design; high-performance computing

Results Obtained in 2010
In the past decade, the advances of computational structural biology have permitted to extend our knowledge of biological function at the molecular level shedding light on features that are often experimentally inaccessible. During 2010, within this domain we continued focusing on the development of new coarse-grained force fields for molecular simulations of proteins, which can allow a more consistent overlap of quantities derived from the computational and experimental setting. These new models will permit to tackle complex problems such as protein-ligand recognition and protein-protein interactions in large macromolecular networks with unprecedented sampling power and accuracy.

In parallel, we advanced on the structural and dynamical characterization of large macromolecular assembly and function in bacterial nanomachines such as the pore-forming toxin aerolysin from Aeromonas hydrophila (in collaboration with the van der Goot Lab at EPFL), and the PhoQP two-component system from E.coli, which is involved in bacterial chemotaxis. Molecular simulations within this framework were functional to define the functional multimeric state of these systems on the basis of available experimental restraints. Of particular interest in 2010, are our findings about the molecular basis of growth control for the type III secretion system used by bacteria to infect host cells. In particular, the needle length of the Yersinia spp. injectisome is known to be determined by YscP, an early substrate of the injectisome itself. There is a linear correlation between the length of YscP and the length of the produced needle, suggesting that YscP acts as a molecular ruler (Mol Microbiol 2009). However, it is not known whether one single molecule of YscP suffices to control the length of one needle or whether several molecules of YscP are exported in alternation with the needle subunit YscF until the needle length matches the ruler length, which would stop needle growth. To address this question a interdisciplinary computational/experimental approach was adopted. Different strains expressing simultaneously a short and a long version of YscP were engineered by our collaborators (Cornelis’ Lab in Basel) (Figure). The experimentally obtained needle length distribution was compared to the distributions predicted by stochastic modeling of the various possible scenarios of needle growth based on a molecular description of the YscP-needle interactions (Figure). The comparison between predictions and experimental results clearly showed as a single ruler YscP protein controls the needle length and excluded possible mechanisms involving more than one ruler per needle (Figure).
Selected Publications


On the left, needle length distribution predicted for the single-ruler static model (scenario 1) and the multi-ruler dynamic model (scenarios 2 and 3), when merodiploids express simultaneously a short (yscP388) and a long (yscP686) version of YscP (shown in the box). On the right, comparison between experimental and predicted needle length distributions according to the different scenarios. The single-ruler mechanism of needle length control (schematically reported on top) is the only compatible with experiments. (Adapted from PNAS 2010).
Introduction
Gene regulatory networks control gene expression and therefore play a vital role in metazoan development and function. The LSBG is using high-throughput sequencing, large-scale yeast screens, microfluidics, and computational approaches to characterize the gene regulatory networks underlying differential gene expression in Drosophila and mammals.

Keywords
Systems Biology, Gene Regulatory Network, Transcription, Quantitative Genetics, Mouse, Drosophila, Yeast, Genetic Engineering

Results Obtained in 2010
In 2004, we developed a Gateway-compatible yeast one-hybrid system allowing for the first time the screening of regulatory elements for interacting proteins in straightforward fashion (Deplancke et al., Genome Res., 2004). This work has since resulted in the publication of several high-profile papers (Cell, Genes Dev., Genome Res., Mol Syst. Biol.), but was until now limited to C. elegans and still suffered from being quite laborious and expensive.

In parallel with efforts to make this technology available for human and Arabidopsis, the LSBG developed during the last two years an automated platform that enables the high-throughput protein-DNA interaction screening of Drosophila regulatory elements of interest. Because of the availability of a high-quality genome sequence and many genetic tools, Drosophila has one of the best characterized metazoan genomes in terms of functionally annotated regulatory elements. Yet for most of these, it is still not known which TFs are interacting. The ability to screen annotated regulatory elements for interacting TFs should therefore of great value for the Drosophila community.

Compared to our original work in 2004, the Drosophila platform features several important advances and novelties. First, we generated a full-length Drosophila TF ORF clone library containing 692 of the 755 (95%) predicted TFs in versatile Gateway Entry format of which the large majority (81%) are fully sequence-verified. This is to our knowledge one of the most comprehensive, sequence-verified TF ORF libraries to date for any metazoan organism and should serve as a highly valuable resource for the Drosophila community at large. Second, our previous work showed that a haploid yeast-based matrix assay is most optimal in terms of overall protein-DNA interaction coverage, but least optimal in terms of time and cost. To pair optimal coverage with highest possible throughput and lower cost, we engineered a novel robotic platform that completely automates and significantly scales down the haploid yeast transformation process (Figure). Third, to significantly fasten the identification of positives and to eliminate the subjective factor of calling positives by eye, we generated a novel image processing program called TIDY (for Transcription factor-DNA Interaction Detection in Yeast). Fourth, we stringently validated this novel platform achieving a conservative detection rate of 26% of literature-reported protein-DNA interactions in line with results of other yeast-based screens, and finally, we found many novel interactions and provide evidence for several of them that they may be biologically relevant.
Selected Publications


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The Drosophila high-throughput yeast one-hybrid platform: a yeast DNA bait strain is distributed over a 384-well plate after which yeast in each well of this plate is transformed with a different AD-TF clone from the Drosophila Y1H AD-TF library by a robotic yeast transformation platform which additionally spots the 384 individually transformed yeast strains on a permissive agar plate. A colony pinning robot subsequently transfers the yeast colonies onto a permissive and a selective plate, quadruplicating each colony in a square pattern in the process after which TF-DNA bait interactions can be observed as growth on a selective, 3-AT-containing yeast plate.
Hubbell Lab
http://lmrp.epfl.ch

Jeffrey Hubbell was trained as a chemical engineer from Kansas State University (B.S.) and Rice University (Ph.D.) in the United States. Previous to moving to Lausanne, he was on the faculty at the Swiss Federal Institute of Technology Zurich, at the California Institute of Technology, and at the University of Texas in Austin. He is author of more than 250 papers in peer-reviewed journals and inventor on more than 100 patents. He is a member of the National Academy of Engineering, USA

Introduction
We design novel materials for investigation of basic cell biological phenomena such as stem cell self-renewal and differentiation and applications in medicine such as drug delivery, regenerative medicine, and vaccination. We focus on examples where novel materials are necessary to solve the problem, thus working at the interface between materials science and biology.

Keywords
Biomaterials, tissue engineering, protein engineering, extracellular matrix, immunobioengineering, vaccines

Results Obtained in 2010
Regenerative medicine:
The laboratory made exciting advances in engineering matrix-bound morphogens for conjugation in biomaterial matrices for tissue repair and regeneration. We had previously developed a biochemical approach to incorporate morphogenetic proteins into surgical matrices such as fibrin, two of which have now entered into clinical testing in bone repair and chronic wound healing in more than 500 patients in collaboration with corporate partners. We have further developed this concept, engineering extracellular matrix proteins, based on fibronectin, to comprise a promiscuous growth factor-binding domain proximal to an integrin-binding domain. The growth factor-binding domain was observed to bind to more than 20 growth factors from very diverse families. Synergistic signaling between the bound integrin and the bound growth factor receptor was observed in numerous growth factor receptor systems, and synergistic effects on tissue repair and regeneration were observed with chronic wound repair, driven by enhanced angiogenesis, and bone repair, driven by enhanced mesenchymal stem cell infiltration, in mouse models. Using such approaches of engineered extracellular matrix protein-based morphogen templating, it was possible to induce tissue morphogenesis much more effectively and at much lower doses than with the free morphogenetic proteins.

Vaccines and immunotherapeutics:
In collaboration with the Laboratory for Lymphatic and Cancer Bioengineering (Prof. M.A. Swartz), the laboratory demonstrated that nanoparticles can be used as a vaccine platform for targeting cells in the lymph nodes draining dermal site and the lung, in addition to secondary lymphoid tissues in the nasal cavity. This, combined with advanced design of the polymeric nanoparticle surfaces, has enabled a new generation of vaccines, highly stable and very economical, for use in both the developing and the developed world. The team has demonstrated that ultra-small particles, smaller than biological particles, can be swept into the lymphatics within a few minutes of injection, drain to the lymph nodes, and are collected there for antigen presentation. Particularly favorable antigen conjugation schemes were developed for promotion of MHC I presentation and induction of potent CD8+ T cell responses, very impressive protection of mice versus influenza and Mycobacterium tuberculosis challenge was demonstrated, much more impressive than with free antigen delivered with the same adjuvants. From a materials perspective, our focus is on self-assembling block copolymers that form polymer micelles, upon the surface of which antigens are conjugated, or polymer vesicles, in the core of which antigens are encapsulated. Given that our interest is in inducing cellular immunity for chronic disease, our materials are designed to enhance mechanisms of antigen cross-presentation. In addition to inducing cellular immunity, we are also keenly interested in polymeric vaccine forms to tolerize versus cellular immunity, harnessing the tolerogenic antigen presentation that occurs with antigen from apoptotic cells yet using simple biomolecular and polymer conjugate forms that are clinically tractable.
Selected Publications


A critical-size bone defect in the calvarium of the rat was used to evaluate bone repair in response to BMP-2 and PDGF-BB co-delivered with an engineered fibronectin fragment (left) or free (right). Clearly, engineering the extracellular milieu enhanced growth factor efficacy.

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Introduction

Stem cells can hardly be grown in a culture dish (‘ex vivo’), posing a substantial hurdle for their clinical use. We develop and apply innovative bioengineering tools that allow studying and controlling stem cell behavior in a rationale fashion. These technologies have the potential to be translated into clinical settings, for example to expand rare hematopoietic stem cells to treat blood cancers.

Keywords

Stem cells, self-renewal, single cell analysis, niche, hydrogel engineering, microfluidics

Results Obtained in 2010

A complex mixture of extracellular cues delivered by support cells is critical for adult stem cell maintenance and the regulation of self-renewal in their micro-environment, termed niche. Despite recent progress in the identification of relevant niche proteins and signaling pathways in mice, to date, many adult stem cell populations cannot be efficiently cultured in vitro without rapidly differentiating. To address this important issue, we have developed novel stem cell culture technologies that allow fate changes of individual stem cells to be monitored in vitro, under near-physiological conditions and in real time. These artificial niches were fabricated from ‘smart’ poly(ethylene glycol) (PEG) hydrogels that allow key biochemical characteristics of adult stem cell niches to be mimicked and the physiological niche complexity deconstructed into a smaller, experimentally amenable number of distinct signaling interactions. Moreover, because many adult stem cell populations are inherently heterogeneous and current state-of-the-art culture techniques do not permit efficient dynamic analyses of fates of large numbers of single cells, 2D and 3D hydrogel patterning techniques were developed that allow to confine and microarray single stem cells for high-throughput experimentation. In order to mimic cell-cell interactions typical of niches without the complexity of co-culture, we have for example invented protein micropatterning methods for hydrogels allowing to expose confined stem cells to tethered protein cues, singly or in combination, or to overlapping protein gradients. These artificial niches have been utilized to explore the fate of individual mouse hematopoietic stem cells (HSC), neural stem cells and muscle satellite cells. For example, time-lapse microscopy of several thousand single HSC cultured in micro-wells for several days, combined with subsequent image analyses allowed growth kinetics of selected populations to be statistically analyzed. Retrospective transplantation experiments in mice were performed in order to correlate proliferation kinetics with self-renewal function. A pronounced difference in cell division kinetics, that is predictive of their in vivo blood reconstitution potential, was observed when we compared the behavior of standard multipotent progenitors with long-term repopulating HSC. Furthermore, microfluidic chip technology was developed to sequentially capture single HSC after multiple divisions (see figure) to assess their fate for example by multigene single cell qRT-PCR. Ongoing experiments are geared towards the identification of the role of niche factors in directing the symmetry of stem cell divisions. Our efforts to systematically ‘deconstruct’ stem cell niches may serve as a broadly applicable paradigm for defining and reconstructing artificial niches to accelerate the transition of stem cell biology to the clinic.

Dr. Matthias Lutolf was trained as a Materials Engineer at ETHZ where he also carried out his Ph.D. studies on the development of a novel class of biomolecular materials for tissue engineering (awarded with ETH medal, 2004). In 2005, Lutolf joined the Baxter Laboratory in Stem Cell Biology at Stanford University to work on hematopoietic stem cells; research sponsored by SNSF and Leukemia and Lymphoma Society fellowships. In 2007 Lutolf won a European Young Investigator (EURYI) award to start up his independent research at EPFL.
Selected Publications


(A) Microfluidic device for following progeny deriving from single HSC (note dime for size comparison). On one chip, 256 parental HSC can be spatially trapped and pedigree tracked over up to 4 divisions (16 traps per column). The entire chip is constantly perfused to replenish cell culture media, change micro-environmental conditions or perform other analyses (e.g. immunostaining). (B) Self-regulating (fluidic) cell trapping principle. (C) Optimized single cell trapping efficiency (close to 100%). (D) Successful re-trapping of daughter cell generated by division of a single HSC.

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Introduction
Our lab is interested in quantitative and systems biology. We work on various problems including circadian biology, developmental patterning, transcription regulatory networks, and single cell imaging. To study these systems we apply theoretical, computational and experimental methods.

Keywords
Circadian transcription, chronobiology, circadian clocks precision, fluctuations and bursting in gene expression spatio-temporal model of patterning in the early Drosophila embryo

Results Obtained in 2010
Circadian gene regulation:
Temporal mapping of BMAL1 binding sites in mouse liver reveals genome-wide daily rhythms in DNA-binding and uncovers output functions controlled by the circadian oscillator. The circadian clock is a timing system that allows organisms to keep behavioral, physiological, and cellular rhythms in resonance with daily environmental cycles. In mammals, such clocks use transcriptional regulatory loops in which the heterodimeric transcription factor BMAL1/CLOCK plays a central role. While defects in the circadian clock function have been associated with diabetes, obesity or cancer, the molecular links between the circadian clock and output pathways are poorly characterized. Here, we mapped DNA-binding sites of BMAL1 in mouse liver during one circadian cycle. Our temporal analysis revealed widespread daily rhythms in DNA-binding with maximum levels peaked at midday, with strongest sites found mainly at core circadian genes. Interestingly, BMAL1 targets were highly enriched for genes involved in carbohydrate and lipid metabolism, but also for transcription factors, in particular nuclear receptors. Our results suggest that the mammalian clock uses BMAL1 to control both directly and indirectly transcriptional output programs. DNA specificity of BMAL1 binding revealed the importance of tandem E-box elements, which may favor strong binding and precise timing of daily gene expression. Taken together, our work strengthens BMAL1’s primary function as master regulator of the core circadian oscillator, while contributing in a more distributed fashion to a variety of output programs.

A 3D model of the developing Drosophila embryo.
The early patterning of the Drosophila embryo is one of the most advanced models for systems biology approaches. For years, dynamical models for the gap gene network have been calibrated from spatio-temporal expression patterns. These models are usually restricted to a one-dimensional segment running anterior-posterior (A-P) on the side of the embryo. Recently, experimental progress provided mRNA and protein expression atlases (cf. The Berkeley Drosophila Transcription Network Project) measured on the whole surface of the syncytium (Figure). This now opens the possibility to model the early segmentation process on the real geometry of the embryo. Unlike previous models, we explicitly model mRNA and proteins, which is important due to delays in the accumulation of the regulators. Our best-fit network clearly indicates the importance of nonlinear regulation by Hunchback. In addition, we validated our model by comparing predictions with mutant data for the gap genes and bicoid dosage mutants showing shifts in the domains of the gap genes. We not only demonstrate that modeling segmentation in fly embryos is now realistic on the embryo surface, but also show that it can uncover novel features of the gap gene network. Taken together, we believe that whole organism scale, data driven modeling, opens new avenues for systems biology of development.
Selected Publications


The expression data for the gap genes at stage C14, i.e. after 14 nuclear divisions. Left to right : hb, Kr, gt ,kni,; top row is the mRNA, bottom row the proteins. These data serve as input to our extended model.
Introduction
The lymphatic system is an important regulator of fluid balance, innate immunity and peripheral tolerance. We are fascinated by this network of vessels that drain fluid, antigens, and cells from the periphery, through the lymph nodes, and back into the blood. By uncovering its complex roles in immunity and tolerance, we hope to understand and ultimately manipulate its participation in cancer progression and metastasis.

Keywords
Lymphatic, lymph node, immunity, tolerance, tumor, metastasis, interstitial flow, mechanobiology

Results Obtained in 2010
In 2010, we contributed new fundamental understanding of the lymphatic micro-environment in immunity and cancer, and of how dendritic cells (DCs) interpret different types of cues in this complex biomechanical environment. We also contributed to the mechanobiology of lymphatic endothelium, demonstrating the importance of flow on lymphatic function as well as on tumor cell migration in the lymphatic micro-environment.

DC homing to lymphatic vessels and positioning within the lymph node is regulated by gradients of the CCR7 ligands CCL21 and CCL19; however, it was unclear how DCs interpret gradients of these competing chemokines in complex 3D environments. Using a novel 3D chemotaxis chamber in which stable, well-defined gradients can be rapidly established, we demonstrated that DCs differentially respond to CCL21 and CCL19, which lead to different receptor recycling kinetics, and can respond to gradients as small as 0.4% (Haessler et al, PNAS, in press). These data represent the first quantitative analysis of DC chemotaxis in 3D environments.

In the context of solid tumors, we had previously shown that CCL21 was secreted by a number of invasive tumor cells (Shields et al, Cancer Cell, 2007), and we explored the implications of this on host immune response to the tumor, since CCL21 would attract various types of immune cells as occurs in the lymph node. We discovered that CCL21 secretion by tumors helps promote immunological tolerance (Shields et al, Science, 2010). By attracting dendritic cells and T cells to the tumor margin which express lymphoid stromal-like characteristics driven to CCL21 secretion – the overall result was more of an immune suppressive, and tolerogenic, response compared to tumors with knocked-down CCL21. These data suggest that tumor CCL21 can help direct the education of naive T cells within the tumor margin, along with regulatory T cells, leading to immune escape.

With regards to interstitial flow mechanobiology, we introduced a new mechanism of interstitial flow as a modulator of tumor cell migration in the tumor micro-environment, specifically by modulating TGF-β release from the matrix and the subsequent cross-talk between stromal fibroblasts (seen in the tumor periphery) and cancer cells, which follow migrating fibroblasts in the tumor margin (Shieh et al, Cancer Res, 2011). We also found that transmural flow directly activates lymphatic endothelial cells, modulating their chemokine and adhesion molecule expression that in turn promoted DC transmigration into lymphatic vessels (Nateva et al, Circ Res, 2010).

We also continued to develop and characterize lymph node-targeting nanoparticles for immunomodulation in collaboration with Jeffrey Hubbell’s lab. Specifically, we characterized the uptake, processing, and presentation of antigen delivered by nanoparticles to dendritic cells (Hirosue et al, Vaccine, 2010), the control of complement deposition according to surface chemistry (Thomas et al, Biomaterials, 2010), and demonstrated its potential in mucosal vaccination and ability to enhance adjuvant effects (Stano et al, Vaccine, 2010).
Selected Publications


Activated antigen-presenting cells (White, MHCII) are seen interacting with lymphatic (green, LYVE-1) and blood capillaries (red, CD31) in mouse skin after exposure to inflammatory stimulus. Type IV collagen (blue) surrounds both as well as adipocytes and nerves. Photo credit: Dr. Witek Kilarski
Introduction
Mammalian cells are now considered the most versatile and productive system for the manufacture of recombinant proteins for pharmaceutical applications. The major goal of the Laboratory of Cellular Biotechnology is the development of novel and/or improved tools for gene transfer to cultured mammalian cells and subsequent high-level expression of recombinant proteins from such cells in innovative and scalable production systems (bioreactors).

Keywords
Recombinant protein expression - Mammalian cell culture – Bioreactor – Bioprocess control – Gene transfer - DNA integration - Microinjection - Stable cell line development – Orbital shaking

Results Obtained in 2010
Research at the LBTC is situated on the crossroads between biology and engineering, and it addresses the expression of recombinant proteins from suspension cultures of mammalian cells, which is the major approach to therapeutic protein production. We are investigating two major thematic areas: (1) gene delivery and transient gene expression in animal cells and their respective impacts on the host cells physiology and genetics (2) orbital shaking technology and novel bioreactor systems.

The main results obtained in 2010 are summarized below.

Transient gene expression (TGE) and stable transgene integration. TGE allows to express a fully glycosylated recombinant protein at very high titers (1 g/L for IgGs) in HEK-293 cells only 2-3 weeks after gene cloning. We have studied the cellular uptake and disassembly of PEI-DNA complexes in mammalian cells and we combined with this, our knowledge of the cellular metabolism of cells in batch cultures in bioreactors. To study stable integration of recombinant genes into the genome of a host cell we have focused on the Chinese hamster ovary cell line (CHO), which is the most widely used cell line in the biotech industry. We have investigated the cytogenetics of CHO-derived stable cell lines generated using different DNA delivery techniques, including transposon-mediated and lentivirus-mediated gene integration. Understanding transgene integration at the molecular level will allow us to develop strategies to prevent the widely observed phenomenon of gene silencing, which lowers productivity in cell clones over time. Lentiviral vectors and transposon (integrase) mediated DNA delivery is hoped to improve the integration of DNA into the actively transcribed chromatin of the host cells genome. In 2010 we succeeded in generating high producing, stable CHO cell lines by lentivirus-mediated gene transfer.

The orbitally shaken (OS) bioreactor technology for mammalian cell cultivation, designed in our lab, has been scaled-up to 1'000 L. Orbitally shaken cylindrical vessels (with nominal volumes from 50 mL to 250 L) are being extensively studied in order to characterize the hydrodynamics of this type of agitated systems. A scale-up factor for the OS bioreactors could be determined by mixing time analysis in small scale experiments. In collaborations with Prof. Alfio Quarteroni (Chair of Modelling and Scientific Computing) and Dr. Mohamed Farhat of the Laboratory of Hydraulic Machines, a fluid dynamics model of the OS bioreactor could be determined and tested.

Overall, our research provided useful insights for understanding cell cultivation in suspension, gene integration and protein expression. These studies are of general interest in cellular biology and biotechnology.
Selected Publications


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Kamiar Aminian is currently Professor of medical instrumentation and he is teaching in the area of electronics, sensors and instrumentation, medical devices, biomechanics, and sports. He is the inventor of Physilog® system for movement analysis and owner of 5 patents (or patent pending) in the field of movement analysis based on inertial sensors and author of more than 300 publications in international journals, conference proceedings and book chapter. He received the 2008 Venel Award of Swiss Society of Orthopedics for his contribution to functional evaluation of shoulder pathologies by means of a new wearable system.

Research Interests
The multidisciplinary research of the Laboratory of Movement Analysis and Measurement aims to transfer bioengineering findings into clinical applications. We are particularly interested to characterize sport performances and pathologies affecting motor function such as osteoarthritis, frailty, pain or movement disorder by studying the movement ability. Our research involves biomechanical instrumentation for measuring and modeling human biodynamics in daily conditions, during spontaneous activity or physical exercises. Based on body worn sensors, we design wearable systems and algorithms for long-term monitoring of physical activity and gait analysis, for the estimation of the 3D joint kinematics and kinetics, and for the sport performance evaluation. Based on these features and instruments new metrics are defined and validated to provide early diagnosis and objective clinimetry for outcome evaluation in orthopedics and aging, to assess the change of motor function with disease and rehabilitation, to characterize improved performances in sport, and to classify movement disorders.

Selected Publications

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Georg Fantner is an assistant professor for bio- and nano-instrumentation in the Interfaculty Institute of Bioengineering (IBI), with affiliation in the department of science and technology (STI). His research focuses on developing and using novel nanoscale characterization methods to answer questions in life science, with a specific interest in cell membranes and protein-membrane interactions. Prof. Fantner has a strong background in atomic force microscopy, biomaterials and microfabrication. He received his BS and MS from the Technical University Graz and did a post doc in the biomolecular materials lab at the Massachusetts Institute of Technology.

Research Interests

Our research aims to advance nanoscale measurement technology for life science applications, with a special focus on high speed Atomic Force Microscopy. Using this novel technique, we study the structure of cell membranes and lipid model membrane system with nanometer resolution and two orders of magnitude faster than previously possible. The high spatial and high temporal resolution allows us to study how membrane disrupting toxins, such as antimicrobial peptides, pore forming proteins or antimicrobial polymers interact with the membrane. Other research interests are the dynamics of lipid patch organization, molecular interactions in organic/inorganic nanocomposites such as bone, and protein induced mineralization. On the technology development side, we work on the integration of high speed AFM with fluorescence microscopy, micro- and nano-fluidics for sample handling and NEMS cantilever design.

Selected Publications


Fantner Lab - coaffiliated STI

http://lbni.epfl.ch/
Research Interests
The Laboratory of Life Sciences Electronics aims at (i) developing and characterizing integrable sensing techniques for sensing bimolecular events and interacting with living matter, (ii) contributing to the development of 3D compatible novel microfabrication technologies for the implementation of biochips.

Detection and quantification of very small amounts of biological species are the common issues of fundamental areas of health-care and life sciences, ranging from early detection of diseases to the development of personalized medicine. CLSE focus on applications such as point-of-care solutions for therapeutic drug monitoring and on the interactions between amyloids and lipid bilayers membranes.

CLSE employs widely electrode-based sensing coupled with electrochemical and impedance techniques in fields such as high-throughput integrated biomolecular sensing, flow cytometry, neural recording.

Among other techniques under investigation, silicon nanowires (SiNWs) have showed the potential to become a general platform for ultrasensitive label-free detection of biological and chemical species in multisensing applications. CLSE also investigates integrable optical detection techniques such as transmission surface plasmon resonance.

Selected Publications

Hatzimanikatis Lab - coaffiliated SB

http://lcsb.epfl.ch

Vassily Hatzimanikatis
Associate Professor
School of Basic Sciences

Dr. Vassily Hatzimanikatis received his PhD (1996) and MS (1994) in Chemical Engineering from the California Institute of Technology, and his Diploma (1991) in Chemical Engineering from the University of Patras, Greece. Positions held: Group leader (ETH Zurich); Research Scientist (DuPont), Senior Scientist (Cargill); Assistant Professor (Northwestern University).

Vassily has written over 70 technical publications and he is co-inventor in three patents and patent applications. He is associate editor of the journals Biotechnology & Bioengineering, Metabolic Engineering, and Biotechnology Journal. He serves on the editorial advisory board of four biotechnology journals.

Honors and Awards: Fellow of the American Institute for Medical & Biological Engineering (2010); DuPont Young Professor (2001-2003); the Jay Bailey Young Investigator Award in Metabolic Engineering (2002); the ACS Gaden Award (2011).

Research Interests
Computational biotechnology focuses on the development of mathematical models and systems engineering frameworks for accelerating the design and purposeful manipulation of complex cellular processes.

The Laboratory of Computational Systems Biotechnology (LCSB) develops expertise in the formulation of mathematical models of cellular processes and in the development of process systems engineering methods for the integration and analysis of experimental information from different levels. However, most of this information is partial and it is subject to uncertainty. Researchers in LCSB develop methods that can account quantitatively for the uncertainty in the available information and can provide guidance on solving problems in biotechnology and medicine.

LCSB is one of the leading laboratories in the study of energetics and thermodynamics of complex cellular processes. Research in LCSB has also pioneered the development of computational methods for the discovery of novel metabolic pathways for metabolic engineering and synthetic biology. The applications areas of research in LCSB are: metabolic engineering and metabolic diseases, bioenergetics, protein synthesis, lipidomics, and drug discovery for infectious diseases.

Selected Publications


Auke Ijspeert is an associate professor at the EPFL in the Institute of Bioengineering, and head of the Biorobotics Laboratory. He is also Adjunct faculty at the Department of Computer Science at the University of Southern California. He received his engineering degree in physics from the EPFL, and did his PhD in artificial intelligence at the University of Edinburgh. With his colleagues, Dr Ijspeert has received the Best Paper Award at ICRA2002, the Industrial Robot Highly Commended Award at CLAWAR2005, and the Best Paper Award at the IEEE-RAS Humanoids 2007 conference. He was the Technical Program Chair of 5 international conferences (BioADIT2004, SAB2004, AMAM2005, BioADIT2006, LATSIS2006), and has been a program committee member of over 40 conferences. Prof. Ijspeert is also an associate editor for the IEEE Transactions on Robotics.

Research Interests
Our research is at the intersection of robotics and computational neuroscience. It addresses the topics of movement control, sensorimotor coordination, and learning in autonomous robots with multiple degrees of freedom (from snake robots to quadruped robots to humanoid robots). Our ambition is two-fold: (1) to program and design robots that exhibit motor skills with the same efficiency, adaptivity, and robustness as animals, and (2) to get a better understanding of the functioning of animals using numerical simulation and robots as scientific tools.

Together with neurobiologists (Jean-Marie Cabelguen and Sten Grillner), we have developed mathematical models of the neural circuits controlling locomotion in lower vertebrates. We have demonstrated how a primitive neural circuit for swimming like the one found in the lamprey can be extended by phylogenetically more recent limb oscillatory centers to explain the ability of salamanders to switch between swimming and walking. These models have been tested in an innovative salamander-like robot capable of swimming and walking.

We also develop a dynamical systems approach for controlling movements in robots. For instance, we designed the concept of dynamical movement primitives: nonlinear dynamical systems with well-defined attractor properties that can learn demonstrated discrete or rhythmic movements. Our methods are applied to various robots (quadruped, humanoid and reconfigurable modular robots) and more recently to lower limb exoskeletons for patients with locomotor deficiencies.

Selected Publications


Team Members
Postdoctoral Researcher
Crespi, Alessandro
Möckel, Rico
Morel, Yannick
Sprowitz, Alexander

PhD Students
Ajallooeian, Mostafa
Bicanski, Andrej
Bonardi, Stéphane
Dégallier, Sarah
Gay, Sébastien
Karakashliotis, Konstantinos
Knüsel, Jérémie
Pouya, Sapa
Tuleu, Alexandre
van den Kieboom, Jesse
Vespignani, Massimo

Administrative Assistant
Fiaux, Sylvie
Research Interests

The visualization and characterization of biologically relevant molecules and activities inside living cells continues to transform cell biology into a truly quantitative science. However, despite the spectacular achievements in some areas of cell biology, the majority of cellular processes still operate invisibly. Further progress will therefore depend increasingly on the development of new (fluorescent) sensors and chemical probes to target and characterize these activities. Our research addresses this need by developing and applying chemical approaches to observe and manipulate protein function in living cells. For example, we have introduced general methods for the covalent and specific labeling of fusion proteins with chemically diverse compounds that open up new ways of studying proteins (i.e. SNAP-tag, CLIP-tag and ACP-tag). We are pursuing the further development of such approaches and their application to biological problems that cannot be resolved by traditional approaches.

Selected Publications


Brigitte Jolles-Haeberli
Adjunct Professor
School of Engineering
Director of CBT

Research Interests
We promote and support the transfer of findings from the basic science laboratory to clinical application with a strong relationship between clinicians and engineers for each specific project. Our team develops medical devices and wearable systems to characterize human mobility and locomotion in daily conditions. Based on these instruments, we provide objective clinical metrics for diagnosis and outcome evaluation of treatments as well as useful parameters to increase sport performances. We also carry out work in tissue engineering of musculoskeletal tissues, implant and joints biomechanics, drug delivery systems and mechanobiology. A combination of biomechanical and biological approaches is used to describe and understand different clinical problems of interest such as bone loss following total joint arthroplasty, arthritis or intervertebral disc degeneration. Based on these analyses, original solutions are developed such as fetal cell therapy, scaffolds with high mechanical properties or orthopaedic implants used as drug delivery systems.

Selected Publications


Center Groups
LBO Lab
LMAM Lab for Orthopaedic & sport medicine activities

Administrative Assistant
Sabrina Martone
Prof. Maerkl received two bachelor degrees, one in biology and one in chemistry, from Fairleigh-Dickinson University in New Jersey, USA. He then joined the California Institute of Technology, Biochemistry and Molecular Biophysics Option as a graduate student where he worked in the laboratory of Prof. Stephen Quake. After completing his PhD in 2008 he accepted a tenure track position in the Institute of Bioengineering at the EPFL. Prof. Maerkl is currently the lead PI of the DynamiX SystemsX.ch RTD. Prof. Maerkl coaches the EPFL iGEM team and teaches the course Genome & Network Architecture.

Selected Publications


Team Members

Post-doctoral
Luis Miguel Fidalgo
Jose Garcia-Cordero
Marcel Geertz (Shore lab U. Geneva)

PhD Students
Matthew Blackburn
Nicolas Denervaud
Henrike Niederholtmeyer
Jean-Bernard Nobs
Arun Rajkumar
Sylvie Rockel

Master’s Students
Valoise Mendoh Mangoua

Administrative Assistant
Helen Chong
Research Interests
Our research can be summarized in four main areas:

- Genetic regulation by cell growth factors and tissue regeneration [http://www.unil.ch/Jahia/site/biotech/pid/37429]
- Expression of genes of biotechnological interest in mammalian cells [http://www.unil.ch/Jahia/site/biotech/pid/37430]
- Characterization and modeling of genomic and epigenetic regulators [http://www.unil.ch/Jahia/site/biotech/pid/38548]
- Development of more efficient and safer gene therapy vectors [http://www.unil.ch/Jahia/site/biotech/pid/37432]

Selected Publications


Team Members
Laboratory Assistants & apprentice:
- Alessia Cochard
- Yves Dusserre
- Jacqueline Masternak

Technical staff:
- Ione Gutscher
- Daniel Peter
- Armindo Teixeira

Maître assistant:
- Nicolas Niederländer

Post Doctoral Fellows:
- Junhua Qiao
- Niamh Harraghy
- Stéphanie Renaud
- Matthieu Delanoy

PhD students:
- Simone Edelmann
- Kaja Kostyrko
- Deborah Ley
- Stefano Majocchi
- Iaroslav Shcherba
- Ruthger Van Zwieten

Administrative Assistant
- Ms Nassim Berberat
José del R. Millán explores the use of brain signals for multimodal interaction and, in particular, the development of brain-controlled robots and neuroprostheses. In this multidisciplinary research effort, Dr. Millán is bringing together his pioneering work in the two fields of brain-machine interfaces (BMI) and adaptive intelligent robotics. He received his Ph.D. in computer science from the Univ. Politècnica de Catalunya (Barcelona, Spain) in 1992. Among other honors, his research on BMI was nominated finalist of the European Descartes Prize 2001 and he has been named Research Leader 2004 by the journal Scientific American for his work on brain-controlled robots.

**Research Interests**

The Defitech Foundation Chair in Non-Invasive Brain-Machine Interface (CNBI) carries out research on the direct use of human brain signals for controlling devices and interacting with the environment. In this multidisciplinary research, CNBI is bringing together its pioneering work in the two fields of brain-machine interfaces and adaptive intelligent robotics. A brain-machine interface (BMI) monitors a subject’s brain activity, extracts specific features from the brain signals that reflect his/her intent, and translates these features into actions —such as moving a wheelchair or selecting a letter from a virtual keyboard, without use of muscles or peripheral nerves. CNBI focuses on non-invasive methods for recording brain activity, in particular using electroencephalographic (EEG) signals recorded from electrodes placed on the scalp. The goal of CNBI is to develop principled methods to design intelligent brain-actuated devices that people can efficiently operate them in a natural and intuitive manner over long periods of time. Such neuroprosthetic devices allow interaction by exploiting brain signals associated to different aspects of voluntary behavior.

**Selected Publications**


Research Interests

The projects developed at the LBO are at different levels from basic to applied researches with an overall strategy to bring the developed research to clinical application, the so-called translational research. The core aspect is to use and develop biomechanical descriptions to understand or develop new strategies in the field of musculo-skeletal system. In particular, our projects are organized in four categories: mechano-transduction, tissue engineering, biomechanics of joints and implants, and drug delivery system. A particularity of the LBO is to involve surgeons in most of the developed projects, allowing us to obtain a more effective way for the translational aspect of our research. Translation also means valorization, so we still continued our long lasting collaborations with several industries such Tornier, Stryker or Symbios. In particular, we also obtained financial support from the KTI to develop new solutions in orthopedic implants with some of these companies.

Selected Publications


Team Members

Group Leaders
Prof. Lee A. Laurent-Applegate
Dr. Alexandre Terrier

Post-doctoral fellows
Dr. Nathalie Krattinger
Dr. Xavier Larrea
Dr. Hicham Majd

Lab assistants
Sandra Jaccoud
Corinne Scalialetta

Engineers
Vittoria Brighenti
Damien Joss
Silvio Ramondetti
Patricia Scheuber

PhD students
Philippe Abdel-Sayed
Salim Darwich
Michael Gorthacow
Jérôme Holleinstein (UCSD)
Ulrike Kettenberger
Nassajian Moghadam Mohamadreza
Alireza Roshan Ghias
Marion Röthlisberger
Arne Vogel

Master students
Yannick Bastin
Fabien Duc
Michael Ducrot
Aurelien Gallice
Florian Herzog
Fabienne Meier
Andreas Schmocker

Administrative Assistant
Virginie Kokocinski
Research Interests

The activities of the Optics Laboratory primarily focus onto two research areas. First, we work within the field of Optofluidics, where the objective is to develop novel photonic devices and analytical methods by fusing integrated optics and microfluidics. Typical examples involve on-chip molecular spectroscopy, where individual components such as light sources, filters and switches have been developed. In parallel, we have also explored the importance of surfaces in optofluidics, primarily focusing on the manipulation of DNA, the use of plasmonic nanoparticles of advanced mass transport and the employment of electrical fields for flow and bio-entity control. Such methodologies are currently employed to address challenges within the field of biophysics.

The second research focus is in nonlinear optics and consists of two different research axes: new microscopy techniques for imaging in diffusive media such as biological tissue, and imaging in nonlinear media. In regards to the former, we are exploring nanoparticles that consist of non-centrosymmetric crystal structures as sources of second-harmonic generation (SHG); these nanoparticles have shown great promise as imaging probes due to their coherent and stable signals. In regards to the latter, we investigate how to optimize image transmission through non-linear media. This technique is promising for both enhanced resolution imaging, but also novel methods to analyse the non-linear properties of liquid media.

Selected publications


Team Members

Post-doctoral Fellows
Ye Pu
Andreas Vasdekis
Jae-Woo Choi
Chia-Lung Hsieh

PhD students
Wuzhou Song
Alexandre Goy
Julien Cuennet
Ioannis Papadopoulos
Xin Yang
Grégoire Laporte
Jianhang Yang

Administrative Assistant
Carole Berthet

Demetri Psaltis was educated at Carnegie-Mellon University where he received the Bachelor of Science degree in Electrical Engineering and Economics in 1974, the Master’s in 1975, and the PhD in Electrical Engineering in 1977. In 1980, he joined the faculty at the California Institute of Technology, Pasadena, California and he served as Executive Officer for the Computation and Neural Systems department from 1992-1996. From 1996 until 1999 he was the Director of the National Science Foundation research center on Neuromorphic Systems Engineering at Caltech as well as the director of the Center for Optofluidic Integration. In 2007, he moved to the EPFL where he is professor and director of the optics laboratory and also the Dean of School of Engineering.

He has authored or co-authored over 400 publications in these areas. Dr. Psaltis is a fellow of the IEEE, the Optical Society of America and the Society for Photo-optical Systems Engineering (SPIE). He received the International Commission of Optics Prize, the Humboldt Award, and the Gabor prize. He is the co-founder of Ondax.
Aleksandra Radenovic earned a degree in physics from the University of Zagreb before joining Professor Giovanni Dietler’s. There she earned her Doctor of Sciences degree in 2003. She then undertook postdoctoral study at the University of California, Berkeley. From July 2008 she is an assistant tenure tracked professor at the institute of Bioengineering.

Research Interests
The research of the Laboratory of Nanoscale Biology focuses on developing tools and probes for single-molecule biophysics. The group uses optical tweezers, AFM, single-molecule fluorescence, PhotoActivated Light microscopy PALM and nanofabricated structures to study biomolecular systems and advance new nanotechnology. Current experimental work in our lab focuses on two interconnecting areas:

Nanofabricated probes and platforms for single-molecule biophysics experiments
Including nanofabricated SHG nanocylinders, solid-state nanopores, local nanoelectrodes for molecular sensing and sequencing

DNA nanotechnology
Our main focus is to implement DNA origami structures into nanoelectronics. We use graphene nanoribbon templates onto which different DNA origami structures can self-assemble and would enable us to register individual molecular nanostructures, to electronically address them, and to integrate them into functional devices.

Local probe studies of single biomolecules
For example RNA polymerase, DNA binding proteins, membrane proteins such G protein-coupled receptors (GPCRs).

Selected Publications


Team Members
Post Doctoral
Scarselli Marco
Traversi Floriano

PhD Students
Annibale Paolo
Brando Serena
Dutto Fabrizia
Raillon Camille

Master students
Matia Greco

Administrative Assistant
Chong Helen
Nikos Stergiopulos studied Mechanical Engineering at the National Technical University of Athens, Greece and obtained his Ph.D. in Biomedical Engineering from Iowa State University in 1990. His research interests are Hemodynamics, Cardiovascular Mechanics and Medical Implant Technology. He has authored more than 100 publications and holds more than 15 patents in medical technology. He co-founded EndoArt, world leader in telemetric implants for the treatment of congenital heart disease and morbid obesity and Antlia SA, developer of implantable drug delivery pumps.

Research Interests

The Laboratory of Hemodynamics and Cardiovascular Technology (LHTC) focuses is on the relation between blood flow and the development, progression and regression of cardiovascular disease. Development of vascular implants and non-invasive or mini-invasive technologies for the diagnosis and treatment of disease is also a major objective.

Selected publications


Team Members

Nikos Stergiopulos
Full Professor
School of Engineering

http://lhtc.epfl.ch

Nikos Stergiopulos
Full Professor
School of Engineering

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Research Interests
Our goal is to advance our understanding of the human body, in particular of brain function in health and disorder using non-invasive imaging techniques. To that aim, we pursue the development and integration of innovative methodological tools from signal and image processing at various stages of the acquisition, processing, and analysis pipeline. The first highlight of our research is on temporal dynamics of spontaneous brain activity; e.g., we showed fractal organization of the rapid switching between scalp topographies in spontaneous EEG and how it interlinks with fMRI that is governed by slow hemodynamics. The second highlight is the analysis of functional brain networks using multi-scale graph models and techniques from pattern recognition to interpret and predict cognitive and clinical conditions based on signatures of functional connectivity.

Selected publications


Hubert van den Bergh obtained a BA in chemistry at Williams College Massachusetts USA, a PhD in physical chemistry at Cambridge University UK, and did postdoctoral work in physics at the Max Planck Institut für Strömungsforschung in Göttingen Germany. He is professor at EPFL and a member of the Council of the Swiss National Science Foundation. He was awarded the prize of the Swiss Chemical Society, the Ruzicka Prize and the prize of the Swiss Biomedical Technology Society.

Research Interests
Hubert van den Bergh has contributed in the fields of basic chemical kinetics (including the development of the T-jump method in the gas-phase and molecular beam investigations of the cage effect), laser- and beam-induced chemical vapor deposition, and air pollution studies (modeling and measurements). The atmospheric measurements by LIDAR include a Raman system for measuring H2O vapor and temperature that was delivered to the Swiss Meteorological Institute for routine daily round the clock measurements. Other contributions include a novel method for the separation of isotopes by laser-induced inhibition of condensation, which has led to the large scale separation of Uranium isotopes now in use at Wilmington NC by GE, Hitachi and Cameco. Contributions to photomedicine include part of the development of Visudyne® technology for the treatment of wet age-related macular degeneration (FDA approval in 2000) with Novartis and QLT, the development of Hexvix® for the detection and removal of early stage bladder cancer (FDA approval in 2010) with Photocure and GE Healthcare, and the development of a fluorescence endoscope with Wolf GmbH in Germany.

Selected publications
Gabriel D., Zuluaga M.F., van den Bergh H., Gurny R., and Lange N. (Accepted). It is all about proteases: from drug delivery to in vivo imaging and photomedicine, Current Medical Chemistry.


Hubert van den Bergh
Full Professor
School of Engineering

Van den Bergh Lab - coaffiliated STI
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GHI - Global Health Institute

Since its foundation in 2006, the Global Health Institute (GHI) has been contributing to the understanding, diagnosis, prevention and treatment of infectious diseases, which account for half of the deaths in the developing world and still claim 18 million human lives every year. The GHI comprises 9 groups, all engaged in different facets of research linked to human health but with strong emphasis on diseases of truly global importance such as HIV/AIDS, tuberculosis and malaria. The current workforce comprises ~120 students, postdoctoral-fellows, technicians and scientists, representing 22 different nations.

The research portfolio at the GHI includes a balanced mixture of basic and translational work. Mechanisms of host-pathogen interactions and innate and acquired immunity against disease are being studied using multidisciplinary approaches. A unique feature of the GHI is its ability to tackle crucial world health issues by harnessing cutting edge technologies developed at EPFL and elsewhere. Among these the nanotechnologies, micro-engineering and informatics are proving particularly powerful at underpinning drug discovery and vaccinology as well as more mechanistic research.

In 2010, the Indian Institute of Science (IISc) in Bangalore and the GHI established a partnership in the area of infectious disease research with the aim of exchanging students and personnel and developing collaborative projects. The GHI was also the recipient of a Landolt chair for sustainable development.
Introduction
There is increasing concern about the (re-)emergence of infectious agents and the threat this poses to human health. Knowledge of how bacteria acquire pathogenic traits is of fundamental importance. Our research focuses on evolution mediated by horizontal gene transfer and is exemplified using the human pathogen Vibrio cholerae, the causative agent of the disease cholera, as a model organism.

Keywords
Bacterial evolution, horizontal gene transfer, environmental reservoirs, regulatory circuits

Results Obtained in 2010
As recent studies by our lab and others supported the notion of extensive horizontal gene transfer (HGT) in the human pathogen V. cholerae, it is of major importance to understand the mechanisms underlying such DNA exchange strategies. Natural competence for transformation, as one out of three modes of HGT in bacteria, describes the physiological state in which the bacterium takes up free DNA from the environment. This DNA can be used for the acquisition of new alleles / genes leading to genetic diversity and evolution.

Natural transformation of Vibrio cholerae as a tool
Our research is based on the knowledge of how pathogens thrive in their natural reservoirs. Bacteria of the genus Vibrio for example are often associated with chitinous surfaces of aquatic invertebrates. Within this association, the bacteria develop the state of natural competence and initiate the transfer of genetic material. In the laboratory we mimic this environmental niche using natural and artificial chitin surfaces, respectively. In a recent study we analyzed the natural competence-inducing conditions in further detail and provided an optimized protocol to transform V. cholerae and other Vibrio species. We also established experimental setups to knock-in and knock-out genes in V. cholerae by chitin-induced natural transformation in combination with the Flp recombination system of yeast. This method allows us to use the horizontal gene transfer process in order to genetically manipulate pathogenic and non-pathogenic bacteria of the genus Vibrio.

Regulation of natural competence for transformation
In the initial study on natural competence of V. cholerae, we suggested that cell-to-cell communication, known as quorum sensing (QS) in bacteria, is essential for chitin-induced natural transformation. We followed up on this suggestion and discovered that intrageneric communication of V. cholerae is primarily important in this context. In contrast, interspecies QS systems play a minor role. We also showed that heterologously produced or chemically synthesized autoinducers, the signalling molecules involved in QS, activate natural competence. This is a striking finding given recent developments in the field, which recommend the use of autoinducers as therapeutics to treat or to prevent the disease cholera. Based on our results such treatments might contribute to the onset of horizontal gene transfer. Given the bacteria-rich environment of the human gut, autoinducer-induced evolution within this niche might create hypervirulent strains of V. cholerae. Therefore, caution should be taken for administering autoinducers as therapeutics.

We are also following up on the complex regulatory circuit of natural competence using transcriptional reporter fusions and single-cell microscopy. This will allow us to distinguish between population-wide transcriptional profiles and those genes that are only transcribed in distinct subpopulations.

Mechanistic aspects of the DNA uptake process
To fully understand the process of natural competence for transformation it is not only crucial to elucidate the regulatory circuits but to also investigate the mechanistic and dynamic aspects of the DNA uptake process itself. We therefore initiated a collaborative study, which will be based on epifluorescence and super-resolution microscopy.

Melanie Blokesch studied biology at the Ludwig-Maximilians-Universität in Munich, Germany, graduating with a major in microbiology. Her doctoral work, performed at the same institution, dealt with bacterial hydrogen production and was supervised by Prof. Dr. Dr. h.c. August Böck. Her thesis was awarded the Prize for Junior Scientists by the German National Academy of Sciences, Leopoldina and the Thesis Award by the Association for General and Applied Microbiology. After a 4-years postdoctoral stay in Prof. Dr. Gary Schoolnik’s group at Stanford University in the USA, Melanie Blokesch joined EPFL in 2009.
Selected Publications


Whereas the bacterium *Vibrio cholerae* is a human pathogen, its primary habitats are estuaries and coastal waters. Within this environmental niche it often associates with the chitinous exoskeleton of zooplankton (left). *V. cholerae* bacteria (orange-colored rods) sense the degradation products of the chitin polymer (I) and form biofilm structures on the surface (II). Horizontal gene transfer takes place within these biofilms (III).
Introduction

We are using a multidisciplinary approach to tackle major public health problems such as tuberculosis. Finding new drugs and understanding disease mechanisms are among our priorities.

Keywords

Tuberculosis, leprosy, drug discovery, pathogenesis

Results Obtained in 2010

TB Drug Discovery

We are leading a major effort to discover new drugs for the treatment of TB as part of the New Medicines for Tuberculosis Project, NM4TB, funded by the European Commission. In 2010, we continued the characterization of the 1,3-benzothiazin-4-ones (BTZ), a new class of antimycobacterial agents that kill Mycobacterium tuberculosis in vitro, ex vivo and in murine models of TB. The most advanced compound, BTZ043 is a candidate for inclusion in combination therapies for both drug-sensitive and extensively-drug resistant TB. We have shown that all clinical isolates are killed by BTZ043 and also demonstrated that the killing mechanism is due to the formation of a covalent adduct with the essential enzyme decaprenylphosphoryl-β-D-ribose 2’-epimerase, which produces key components of the mycobacterial cell wall.

Protein secretion and pathogenicity

The ESX-1 protein secretion system is the major virulence determinant operating in M. tuberculosis and has been lost by the vaccine strains M. bovis BCG and M. microti. ESX-1 is required for the export of small helical-hairpin proteins belonging to the ESAT-6 family as well as other effector proteins of unknown function. ESX-1 mediates host cell entry of tubercle bacilli and triggers intercell spread. We are using an integrated approach involving biochemistry, genetics, X-ray crystallography and electron microscopy to establish the organization, architecture, structure and function of this ATP-driven secretory apparatus. The figure shows the 3D-structure of EspR a transcriptional regulator that controls expression of ESX-1 genes. EspR, a homodimer, has an atypical DNA-binding mechanism.

A regulatory map of the M. tuberculosis genome

We have adopted an integrated approach to studying gene regulation by using chromatin-immunoprecipitation of DNA-binding proteins in conjunction with high density oligonucleotide-based microarrays or high-throughput sequencing to map the genome. Using this approach we mapped all the RNA polymerase binding sites in the genome under different growth conditions in two different strains. In parallel the genome-wide distribution of EspR regulatory sites was established. Regulatory information is being incorporated into TubercuList, the genome server dedicated to M. tuberculosis http://tuberculist.epfl.ch/, for which we are the official curators.

Phylogeography of leprosy

Despite the highly successful implementation of multi-drug therapy by the World Health Organisation, leprosy remains a serious public health problem in several countries probably due to our inability to identify infectious cases early enough. One of our goals is the development of an epidemiological tool to monitor transmission of the disease. This uses comparative genomics, particularly SNP (single nucleotide polymorphism) analysis of patient isolates, to monitor the phylogeography of leprosy. In collaboration with the WHO, we are also coordinating a worldwide effort to monitor the emergence of drug resistance.
Selected Publications


EsPr dimer with monomers placed vertically and colored in cyan and dark blue. Note the N-terminal DNA-binding domain forming a typical helix-turn-helix and the C-terminal dimerization domain.
Introduction
Our team has pioneered and brought important contributions to the fields of signal transduction, cell cycle control, and kinome characterisation in malaria parasites, and has developed extensive expertise in protein kinase biochemistry and Plasmodium reverse genetics. Active collaborations have been established with pharmacology and structural biology laboratories with the purpose of developing drug discovery activities based on plasmodial protein kinase inhibition.

Keywords
Malaria, kinomics, protein kinase, phosphorylation, signaling, antimalarial drug discovery

Results Obtained in 2010
Since our arrival at EPFL at the end of 2009, we completed the functional characterization of a number of P. falciparum protein kinases that are involved in the control of parasite proliferation in red blood cells of the human host. These include:

• a homologue of the mammalian Aurora kinases, a family of enzymes that control several cellular processes during eukaryotic cell division. We showed that all three plasmodial Aurora-related kinases are essential for parasite viability, and localize to distinct locations within the cell. One of these enzymes, PfARK1, transiently associates with spindle pole bodies (the plasmodial equivalents of the centrosome), which enabled us to directly demonstrate that nuclei within a single P. falciparum schizont divide asynchronously (Reininger et al., Mol. Microbiol., 2011).

• a tyrosine kinase-like kinase that is also essential for parasite viability, and whose enzymatic activity requires an oligomerisation accessory domain (Abdi et al, Cell. Mol. Life. Sci., 2010).

• an essential transcriptional cyclin-dependent kinase, which we showed associates with histone deacetylase activity in parasite extracts (Halbert et al., Eukaryot. Cell, 2010).

We also achieved significant progress in our understanding of the function of several additional kinases involved in the control of parasite proliferation, notably:

• the casein kinase 2 homologues, for which a role in chromatin assembly is strongly suggested by (among other lines of evidence) the identification of components of protein complexes purified from transgenic parasite lines expressing tagged α and β PfCK2 subunits;

• an atypical cyclin-dependent kinase that has no orthologue in the mammalian kinome, and whose knock-out causes a slow proliferation rate phenotype.

In parallel with the above studies, which are focused on individual proliferation-related enzymes, we have pursued and almost completed the systematic “knocking-out and tagging” of the entire P. falciparum 65-member kinome. This identified 35 enzymes as essential for asexual proliferation in erythrocytes, pointing them out as prioritized targets for drug discovery.

Finally, we showed that the kinomics of the infected erythrocyte system is not restricted to parasite-encoded kinases: we demonstrated that a PAK→MEK pathway present in the red blood cell is activated upon infection with P. falciparum. Furthermore, the effect of highly selective allosteric inhibitors of the MEK and PAK kinases (which have no homologues in the parasite’s kinome) on the parasite in culture strongly suggests that this host cell pathway is essential for parasite maturation in the erythrocyte. This observation may have considerable implications in the context of strategies for antimalarial drug discovery (Sicard et al, Cell. Microbiol., 2011).
Selected Publications


Recommened by Faculty of 1000


An artist’s view of an infected erythrocyte rupturing and releasing Plasmodium merozoites. Generated by Sciencevisuals (www.sciencevisuals.com).
Introduction
The intestinal mucosa represents an interface between the body and the external environment and is constantly exposed to environmental micro-organisms. Amongst these commensal bacteria are present in vast numbers (10^{12} per gram of intestinal contents) in all individuals at all times. Worms (helminths) can also establish chronic infections within our intestines and were present in a near ubiquitous manner throughout mammalian evolution. Today intestinal helminths still infect approximately 1/3 of the worlds population, with the heaviest infections found in children living in poor communities within developing countries.

Our work aims to investigate; i) how we protect ourselves from exaggerated infections with helminths or systemic dissemination of intestinal bacteria, and ii) how these organisms can modulate the responsiveness of our immune system. In particular we would like to understand why and how alterations in our exposure to specific intestinal bacteria species or worms can cause disease and predispose us to auto-immunity and allergy.

Keywords
Immunology, intestine, soil-transmitted helminths, commensal bacteria, antibodies, Th2 immune responses, cytokines, allergy, vaccination.

Results Obtained in 2010
In 2010 we continued work on mammalian protective immune responses against intestinal helminths. Specifically we have uncovered a novel role for IgG1 and IgE antibodies in regulating the production of basophils in the bone marrow following helminth infection. We have also shown that antibody-coated basophils can contribute to the killing of helminth parasites. This work is still in progress and will continue into 2011. We have also begun work on two new projects. In the first one, we are generating monoclonal antibodies specific for helminths and hope to use these antibodies to uncover novel helminth antigens that could be useful for vaccine design. In the second, we are investigating the potential of helminth-derived antigens to directly modulate host immune cells.

2010 also saw the completion of two ongoing projects related to host immune modulation by commensal bacteria. In the first project, entitled ‘Dysregulation of allergic airway inflammation in the absence of microbial colonization’, we investigated the role of intestinal bacteria in modulating allergic responses. For this purpose we developed a novel model of experimental asthma in mice reared under normal conditions (specific pathogen free, SPF) or within specialized isolators that prevent colonization with any type of micro-organisms including intestinal bacteria (germ-free, GF). Our data showed that germ free mice develop exaggerated allergic asthma and that this can be reversed by re-colonization of GF mice with the complex commensal flora of SPF mice. Exaggerated asthma correlated with increased eosinophilia, exaggerated local production of T cell derived cytokines, elevated IgE production and an altered number and activation status of lung antigen presenting cells. These data provides experimental evidence supporting the ‘hygiene hypothesis’ that states that decreased exposure to micro-organisms is responsible for the increasing incidence of allergies observed in developed countries. We now intend to use this model to test the ability of specific intestinal bacteria (probiotics) to prevent allergic disease.

In the second project, we investigated the impact of a novel tumour necrosis factor super family (TNFSF) member, HVEM, on inflammatory bowel disease (IBD). IBD is a chronic disease in which the patient mistakenly generates an immune response against his or her own intestinal bacteria. We used mice deficient in HVEM to demonstrate that HVEM signalling to innate and adaptive immune cells is crucial for the development and maintenance of pathological inflammatory responses within the intestine. These data identify HVEM as a potential new target for the treatment of IBD.
Selected Publications


Asthmatic inflammation in the lungs of control or allergen exposed animals with or without intestinal bacteria. Note the increased severity of the inflammatory cell infiltrate in the lungs of animals that do not have intestinal bacteria but are exposed to allergens.

Team Members

Post doctoral Fellows
Corinne Schaer
Mario Zaiss

PhD Students
Tina Herbst
Ilaria Mosconi

Master’s Students
Raphael Duvoisin
Blaise Dayer

Senior Technical Assistant
Manuel Kulagin

Administrative Assistant
Marisa Marciano-Wynn
Introduction

Our group develop an integrated approach of host-pathogen interactions in model insect Drosophila analysing the basis of microbial infection and corresponding host defence responses using both genetic and genomic tools.

Keywords

Innate immunity, gut homeostasis, host-pathogen interactions, Drosophila genetic

Results Obtained in 2010

The gut combines and integrates very different physiological functions required for maintaining the equilibrium of the whole organism. In addition to its role in digestion, it is the main entry route for pathogens, and a reservoir for resident bacteria that must be tolerated. Finally, the intestinal epithelium undergoes a constant renewal required to maintain the integrity of this barrier. However, little is known about how these functions are regulated and coordinated, or what mechanisms are required to ensure gut homeostasis upon exposure to external challenges such as bacterial infection.

In recent years, Drosophila has emerged as a powerful model to dissect host-pathogen interactions, leading to the paradigm of antimicrobial peptide regulation by the Toll and Imd signaling pathways. The strength of this model is due to the availability of powerful and cost effective genetic and genomic tools, as well as its high degree of similarity to vertebrate innate immunity. Using an integrated approach, our goal will be to study the mechanisms that make the gut an efficient and interactive barrier despite its constant interaction with microbes. We will also focus our attention on the regulatory mechanisms that restore normal gut function upon challenge with bacteria. This project will utilize integrated approaches to dissect not only the gut immune response, but also gut homeostasis and physiology in the presence of microbiota, as well as strategies used by entomopathogens to circumvent these defenses. We believe that the fundamental knowledge generated on Drosophila gut immunity will serve as a paradigm of epithelial immune reactivity and have broader impacts on our comprehension of animal immune defense mechanisms and gut homeostasis.
Selected Publications


In the cover image, we observed that ingestion of Gram-negative bacteria Erwinia carotovora provokes in Drosophila a massive increase in epithelial renewal via increased intestinal stem cell proliferation and differentiation. Domains of cell proliferation in the Drosophila midgut are revealed by the expression of an Escargot-GFP reporter. Nuclei are stained in DAPI (blue).
Introduction
Research in the McKinney lab is focused on mechanisms of microbial persistence in the face of environmental assaults, particularly antibiotics and host immunity. Better understanding of microbial persistence mechanisms will lead to new strategies to prevent and cure infectious diseases.

Keywords
microbiology; micro-engineering; tuberculosis; persistence; antibiotics; timelapse fluorescence microscopy; microfluidics; micro-electromechanical systems (MEMS)

Results Obtained in 2010
Bacterial cells behave as individuals. Mutation and genetic exchange are important drivers of bacterial individuation, but these genetic events are relatively rare. At much higher frequencies, genetically identical cells display metastable variation in growth rates, response kinetics, stress resistance, and other quantitative phenotypes. These cell-cell differences arise from non-genetic sources, such as stochastic fluctuations in gene expression and asymmetric partitioning of components at cell division. Temporal variation at the single-cell level generates phenotypic diversity at the population level. This diversity is critical for bacterial persistence in changing environments because it ensures that some individuals will survive potentially lethal stresses that would otherwise extinguish the population. Our research focuses on the pathogenic species Mycobacterium tuberculosis. We use timelapse fluorescence microscopy with custom-made microdevices to study the real-time dynamics of bacterial behavior at the single-cell level.

Counter-Immune Mechanisms
This project is focused on the mechanisms that M. tuberculosis deploys to resist elimination by the host immune response. We identified a signal transduction pathway that mediates bacterial resistance to immune-related stresses, e.g., reactive oxygen and nitrogen species. We found that resistance to these stresses is linked to regulation of a prominent family of cell wall proteins of unknown function. We are exploring the mechanistic role of these proteins in stress resistance and immune evasion.

In Vivo Metabolism
This project is focused on the metabolic pathways required for growth and persistence of M. tuberculosis in the mammalian host. Computational modeling of M. tuberculosis metabolism has generated surprising new insights into the metabolic capabilities and vulnerabilities of M. tuberculosis, including the identification of a novel pathway for ATP production that is present only in mycobacteria. We are testing our computational findings in wetlab experiments.

Antibiotic Tolerance
This project is focused on the epigenetic basis of cell-cell variation in antibiotic-mediated death and persistence. Our findings challenge conventional models of antibiotic “mode of action”, which postulate that growth rate determines cell fate (death or persistence) at the single-cell level. Instead, we find that the fate of individual cells is not correlated with growth kinetics but is instead linked to stochastic expression of death-modulating factors. We are studying the underlying mechanisms of stochastic gene expression and their impact on cell fate.

Growth Dynamics
This project is focused on the physiology of slow growth, which is a hallmark of persistent infections, and the scaling rules that link cell growth and cell cycle kinetics. We find that mycobacteria display extreme cell-cell variation in biomass doubling time, cell division time, size at division, symmetry of division, etc. These findings challenge the conventional notion that each cell’s phenotype is uniquely determined by the sum of its genotype and its environment. We are studying the mechanistic basis of cell-cell variation in the kinetics of cell growth and division.
Selected Publications


Single-cell dynamics of mycobacterial chromosome replication and segregation. The chromosomal origin of replication was visualized by fusing an origin-binding protein to a fluorescent reporter protein (red foci). Using timelapse microfluidic-microscopy, we found that chromosome duplication and movement were remarkably accurate in time and space, which suggests the existence of a mechanism that coordinates chromosome replication/segregation and cell division.

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Introduction
Our research focuses on interactions between viral pathogens and their hosts, and on the exploration of genetics from both fundamental and therapeutic perspectives. Our laboratory is particularly interested in innate defenses against retroelements such as HIV and in the role of epigenetics in shaping the expression of mammalian genomes.

Keywords
Molecular virology, HIV, endogenous retroelements, mammalian genetics, epigenetics, KRAB zinc finger proteins, KAP1, transcriptional repression

Results Obtained in 2010
About 1'200 of the 20'000 genes contained in the human genome encode for transcriptional regulators, including some four hundred KRAB-containing zinc finger proteins (KRAB-ZFps). KRAB-ZFps are tetrapod-restricted, sequence-specific DNA binding transcriptional repressors, which act by triggering the formation of heterochromatin through their universal cofactor KAP1. KRAB-ZFP genes have been subjected to intense positive selection during evolution. A few years ago, we decided to explore the roles and mechanisms of action of the KRAP/KAP gene regulatory system, which until then had largely remained a terra incognita.

Our functional studies led us to discover that KRAB-ZFps and KAP1 are responsible for the early embryonic silencing of endogenous retroviruses. Close to half of the human genome is derived from retroelements, amongst which endogenous retroviruses (ERVs) closely related to the human immunodeficiency virus. Although essential motors of evolution, these highly mutagenic genetic invaders need to be tightly controlled, an action exerted through their transcriptional repression at the earliest embryonic stages by KRAB/KAP1. Our ongoing work indicates that this regulatory system, although it most likely first developed as an antiviral defense mechanism, has now been co-opted to function as a master regulator of mammalian homeostasis.

In parallel we pursued mechanistic analyses. We developed an ectopic repressor assay, allowing the study of KRAB-mediated transcriptional regulation at hundreds of different transcriptional units. By targeting a drug-controllable KRAB-containing repressor to gene-trapping lentiviral vectors, we could demonstrate that KRAB and its corepressor KAP1 can silence promoters located several tens of kilobases (kb) away from their DNA binding sites, via spreading of repressive chromatin marks. This finding not only suggests auto-regulatory mechanisms in the control of KRAB-ZFP gene clusters, but also provides important cues for interpreting future genome-wide DNA binding data of KRAB-ZFps and KAP1.

Finally, this year was marked by the completion of a methodological project pursued in collaboration with Kai Johnsson’s laboratory. Protein turnover critically influences many biological functions, yet methods have been lacking to assess this parameter in vivo. We succeeded in illustrating how chemical labeling of SNAP-tag fusion proteins, derived from a mutant of human O6-alkylguanine-DNA alkyltransferase (AGT) that permits specific and irreversible labeling with O6-benzylguanine (BG) derivatives carrying molecular probes, can be exploited to measure the half-life of resident intracellular and extracellular proteins in living mice. These results open broad perspectives for studying protein function in living animals.
Selected Publications


Visualization of SNAP-tag-expressing tumor in mice.

Tumor-bearing mice were labeled in vivo with different doses of a fluorescent compound and signal was imaged several hours after the probe administration.

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Introduction
Our laboratory has three main focuses. First, we are interested in the functioning of protein toxins, which are molecular weapons produced by pathogenic organisms to manipulate the behavior of the host they infect. Second, we study fundamental processes in biology such as how proteins fold and how they are transported inside cells. Finally, we are interested in understanding the molecular basis of a rare genetic disease called Hyaline Fibromatosis syndrome.

Keywords
Bacterial virulence factors, toxins, anthrax, pore-forming toxins, cellular microbiology, cell biology, structure of membrane proteins, Systemic Hyalinosis, Hyaline Fibromatosis

Results Obtained in 2010
Pore-forming toxin aerolysin
Pore-forming toxins (PFTs) are molecules that are produced as soluble monomeric proteins but finally form multimeric transmembrane pores in the target cell membrane. In a multidisciplinary approach in collaboration with two groups at the EPFL, Matteo Dal Peraro (Molecular dynamics) and Felix Naef (computational biology), we have addressed the two following questions: What drives the folding of the prototypical pore-forming toxin aerolysin into its soluble monomeric state rather than into the pore conformation? What is the limiting step in pore formation? Through a combination of molecular dynamics simulation and various experimental approaches, we showed that a ~40 residue C-terminal peptide acts as an intramolecular chaperone essential for aerolysin folding. This peptide not only drives biosynthetic folding, but also controls the assembly of the quaternary pore structure. By analyzing pore-formation at the single cell level using live microscopy and analyzing the stochasticity of the pore formation process, we found that release of the C-terminal peptide is the rate-limiting step and that this must occur in each monomer to render it competent for oligomeric assembly. Slow availability of these “activated” monomers leads to sequential assembly of the pore-forming complex.

Consequences of Hyaline Fibromatosis Syndrome mutations
Hyaline Fibromatosis Syndrome is a human genetic disease caused by mutations in the anthrax toxin receptor 2 (or cmg2) gene, which encodes a membrane protein thought to be involved in the homeostasis of the extracellular matrix. Little is known about the structure and function of the protein and the genotype-phenotype relationship of the disease. Through the analysis of 4 patients, we have characterized, lead to folding defects and thereby to retention of the mutated protein in the endoplasmic reticulum. Mutations in the Ig-like domain prevent proper disulfide bond formation and are more efficiently targeted to ER associated degradation. Promisingly, we have also found that CMG2 can be rescued in fibroblasts of some patients by treatment with proteasome inhibitors and that CMG2 is then properly transported to the plasma membrane and signaling competent, identifying the ER folding and degradation pathway components as promising drug targets for Hyaline Fibromatosis Syndrome.
Selected publications


Structure of the proaerolysin monomer (1PRE). The C-terminal peptide (CTP), bound to domain 4, is shown in dark blue. B: Spaced-filled representation of a snapshot of domain 4 showing the hydrophobic pocket in gray and the CTP residues involved in the hydrophobic interactions in yellow.

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ISREC - Swiss Institute for Experimental Cancer Research

ISREC has seen a year of important developments and progress. A faculty search launched in 2009 has culminated in the hiring of three new Assistant Professors:

- Oliver Hantschel, who comes from the Center for Molecular Medicine of the Austrian Academy of Sciences in Vienna, will develop a research program centered on structure-function relationships of oncogenic kinases, in particular the 3D structural effects of mutations conveying acquired resistance to kinase inhibitory anti-cancer drugs; a major focus is on the Bcr-Abl oncogene that drives development of chronic myelogenous leukemia (CML).

- Etienne Meylan, from the Massachusetts Institute of Technology (MIT) in Cambridge, USA, will study mechanisms and therapeutic targeting of lung cancer, using genetically engineered mouse models of de novo lung carcinogenesis in conjunction with translational studies of human lung tumors.

- Michele De Palma, coming from the San Raffaele Scientific Institute in Milan, will study tumor-infiltrating leucocytes that stimulate tumor angiogenesis, seeking to delineate the regulation, recruitment, and effector functions of these pro-angiogenic inflammatory cells.

All three new ISREC faculty members will establish their research groups in the Life Sciences (SV) building on the EPFL campus during 2011.

Several faculty have received honors and awards in 2010: Melody Swartz was awarded the Robert Wenner Prize; Freddy Radtke and Douglas Hanahan were elected to EMBO; and Denis Duboule received a Dr Honoris Causa from the Ecole Normale Supérieure and the Grand Prix International of INSERM.

ISREC’s faculty maintains a balanced emphasis on fundamental research into biological systems and basic and translational cancer research, seeking to elucidate mechanisms that on the one hand are subverted to facilitate tumor growth and progression, and on the other orchestrate normal biological processes in development and organ function. We continue to contribute to the missions of EPFL in teaching undergraduate and graduate students, and in mentoring young scientists toward careers in academics and biotechnology. ISREC continues as the home base for the Swiss National Center of Competence in Research (NCCR) in Molecular Oncology, focused on characterizing the complex organization and functional importance of the tumor-organ micro-environment, in model systems and in clinical samples. The institute is significantly involved on behalf of the EPFL in the design and implementation of a new multi-institutional regional cancer center, involving the University of Lausanne, its Hospital and biomedical faculty, the (Independent) ISREC Foundation, and in turn other institutions. This cancer center whose mission will be to innovate, via trans-disciplinary interactions and collaborations, will progress in the exciting frontier of discovering and then translating principles about mechanisms of the disease into improved treatments for human cancer.

Looking ahead, in 2011 ISREC is presenting the next installment of the annual Life Sciences Symposia September 7-10. The topic will be “Hallmark and Horizons of Cancer”, with a world class roster of speakers, and a program aimed to foster interactions and to highlight exciting cancer science from the participants, including short talks and posters. The program is available at http://isrec2011.epfl.ch/. For further information about ISREC and its faculty, please see http://isrec.epfl.ch/.
Introduction

Our group recently observed in a mouse model of colon adenocarcinoma that inactivation of two genes involved in the Wnt pathway results in abrogation of traits characteristic of stem cells and associated with invasiveness and drug resistance. The main focus of our current research is to explore whether inhibiting the function of these genes in human cancer cells can revert such traits and may lead to a novel therapeutic approach.

Keywords

Wnt pathway, Bcl9/Bcl9l, intestinal tumorigenesis, epithelial-mesenchymal transition, cancer stem cells

Results Obtained in 2010

Canonical Wnt-signaling regulates critical processes during embryonic development and adult tissue renewal, and aberrant activation of this pathway is associated with colorectal and other cancers. Oncogenic mutations in the Wnt pathway cause ligand-independent pathway activation, due to the inappropriate stabilization of β-catenin, leading to aberrant transcription of β-catenin/TCF target genes. Wnt signals may result in different outcomes, dependent upon tissue origin and cellular context, and stimulate cell proliferation, as well as control cell fate and differentiation. Wnt signaling has also been implicated in the regulation of epithelial-mesenchymal transition (EMT). EMT has been associated with invasive and metastatic tumor behavior, and there is growing evidence suggesting a relationship between EMT, the emergence of cancer stem cells (CSCs) and drug resistance. Targeting pathways that regulate EMT and/or CSC traits may therefore prove of particular clinical relevance, with regard to preventing invasion and metastasis, and for precluding the outgrowth of therapy-resistant tumor cells.

We recently described phenotypic changes in a mouse model of colon adenocarcinoma suggesting that the Wnt signaling components Bcl9/Bcl9l mediate a sub-program of the Wnt pathway (Deka et al., 2010). Thus, a subset of Wnt target genes associated with a mesenchymal phenotype, intestinal stem cells and colon cancer progression was strongly down-regulated in Bcl9/Bcl9l-mutant tumors. Consistent with the EMT state of wild-type tumor cells, the basement membrane appeared disintegrated as assessed by laminin staining, whereas Bcl9/Bcl9l-mutant tumor cells were aligned on a contiguous laminin membrane. Follow-up experiments showed that the EMT phenotype observed in this tumor model is dependent upon continuous Bcl9/Bcl9l expression and can be abrogated when ablation of Bcl9/Bcl9l is induced in established tumors (see Figure). Collectively, these observations indicated that Bcl9/Bcl9l are critical for the expression of a subset of Wnt target genes relevant to controlling EMT- and stem cell-associated traits.

The main focus of our current research is to explore to what extent these observations apply to human Wnt-activated cancers. We have selected a panel of Wnt-activated human cancer cell lines exhibiting EMT- and stem cell markers and make use of RNAi and dominant-negative expression of Wnt signaling components to inactivate BCL9/BCL9L function. We will address to what extent inhibiting BCL9/BCL9L function affects expression of Wnt target genes, and mesenchymal and stem cell-related traits. We will focus on assessing to what extent shifts in these gene expression patterns are associated with attenuated invasive and metastatic properties and enhanced susceptibility to chemotherapy.
Selected Publications


Collaborations

These projects are carried out in part as collaborations with the groups of Prof. Konrad Basler, Institute of Molecular Biology, University of Zürich and Dr. Pascale Anderle, Swiss Institute of Bioinformatics. Other collaborations include the groups of Prof. Mariann Bienz, MRC, Cambridge, UK, Prof. Rudolf Grosschedl, Max-Planck-Institute of Immunobiology, Freiburg, Germany, Prof. Thomas Rando, Stanford University School of Medicine, California, and Prof. Ivan Stamenkovic, Department of Experimental Pathology (IUP), CHUV, Lausanne.

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Immunofluorescence staining of mouse colon adenocarcinomas. Wild-type tumor cells stain for the mesenchymal filament vimentin (green) and show a discontinuous basement membrane (laminin; red). Bcl9/Bcl9l-mutant tumor cells express no vimentin and are aligned on a continuous laminin layer.
Introduction

Our laboratory studies the relation between small viruses with DNA genomes and cancer. On one hand, some cancers, notably cervical carcinoma, are caused by viruses of this type—human papillomaviruses. On the other, we try to use different viruses to specifically target tumour cells—oncogenic virotherapy.

Keywords

adenovirus, papillomavirus, cancer, DNA damage response, cell cycle, cell death

Results Obtained in 2010

Viruses against cancer

We use the helper-dependent parvovirus adeno-associated virus (AAV) as a biological probe to study DNA damage signaling pathways in cancer cells. We found that infection with AAV, wild-type or UV-inactivated, triggers a damage response that can lead to death of p53-defective tumour cells. AAV therefore provides a unique opportunity to study this response without actually damaging the cellular DNA. Understanding the tumour-suppressive activity of AAV may lead to novel approaches to cancer therapy.

Why are transformed cells susceptible to AAV infection?

Given the variety of applications of AAV-based viral vectors in the treatment of genetic disorders, numerous studies have focused on the immunogenicity of recombinant AAV. In general AAV vectors appear not to induce inflammatory responses. We have found that, in U2OS osteosarcoma cells, AAV2 can initiate part of its replicative cycle in the absence of helper virus leading to production of the cytotoxic viral Rep proteins. This does not occur in untransformed cells. We set out to test whether the cellular innate antiviral defences control this susceptibility and found that AAV2 induces type I IFN production and release in non-specialized normal human fibroblasts, but fails to mobilize this defence pathway in the U2OS cells. This permissiveness is in large part due to impairment of the viral sensing machinery in these cells. Our investigations point to Toll-like receptor 9 (TLR9) as the intracellular sensor that detects AAV2 and triggers the antiviral state in AAV-infected untransformed cells. Efficient sensing of the AAV genome and the ensuing activation of an innate antiviral response are thus crucial cellular events dictating the parvovirus infectivity in host cells.

What cellular changes, in addition to HPV infection, lead to cervical cancer?

Human papillomavirus (HPV) infection is considered to be a primary hit that causes cervical cancer. However, infection with this agent, although needed, is not sufficient for a cancer to develop. Additional cellular changes are required to complement the action of HPV. We studied the role of a candidate for one of these changes, the Hedgehog (Hh) signalling pathway, in cervical cancer. The Hh pathway has a promoting role in several cancers, including basal cell carcinoma, medulloblastoma and rhabdomyosarcoma, where mutations of Hh pathway components have been found. Moreover, an autocrine requirement of Hh ligand has been reported for several other cancer cell types.

We found that components of the Hh pathway are expressed in the cervical cancer cell lines tested, indicating the possibility of an autocrine Hh signalling loop in these cells. Furthermore, we found that inhibition of Hh signalling pathway reduces survival of cervical cell lines and induces their apoptosis, as seen by the upregulation of pro-apoptotic protein cleaved caspase 3. We also found that Shh ligand induces proliferation and promotes migration of some of the cervical cell lines studied. Together, our results indicate a pro-survival and protective role of Hh signalling in a panel of cervical cancer cells, and suggest that inhibition of this pathway might be a therapeutic option against cervical cancer.
Selected Publications


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Confocal microscopic visualisation of the juxtaposition of promyelocytic leukemia bodies (PML) and AAV replication proteins (Rep) in AAV-infected nuclei. DNA stained with DAPI.
**Introduction**

Breast cancer strikes one out of eight women in Switzerland. A woman’s risk to get breast cancer is linked to her lifetime exposure to endogenous and exogenous hormones. Early pregnancies have a protective effect and breast cancer risk increases with the number of menstrual cycles experienced prior to a first pregnancy. Hormones also influence the course of the disease. We study how hormones control the breast in vivo, in particular the mechanisms by which they elicit cell proliferation and changes in structure of the breast tissue, to gain insights into the genesis of the disease and to develop new preventive and therapeutic strategies.

We have established the role of estrogens, progesterone and prolactin in mammary gland development and analyze the mechanism by which the hormones control local developmental signaling pathways in the breast (summarized in scheme 1).

**Progesterone-induced cell proliferation**

We unveiled a critical connection between progesterone and the receptor activator of NF-kB-ligand (RANKL), in paracrine regulation of mammary epithelial cell proliferation. We demonstrated that PR positive and negative mammary epithelial cells proliferate by distinct mechanisms, with the former requiring cyclin D1, and the latter relying on RANKL. Interestingly, hormone receptor status is the major biological determinant of breast cancer biology and clinical management.

Excitingly, systemic administration of a RANKL inhibitor blocks proliferation of hormone receptor negative cells in the mouse mammary epithelium. This has potential clinical implications; if RANKL has a similar growth stimulatory role in the human breast and in hormone receptor positive and/or negative breast cancers; it will be a good drug target. A specific antagonist of this TNF-family member (denusomab) is in Phase 3 clinical trials to treat different diseases, so that the testing of our hypothesis is straightforward.

**Notch and p63 antagonism in cell fate specification**

The question of how cell lineages are specified and maintained in the breast epithelium is of utmost importance as different cell types of origin contribute to the heterogeneity characteristic of breast cancers. We combined experiments with primary human breast epithelial cells in vitro with mouse in vivo studies to address this issue and demonstrated that Notch signaling is physiologically required for establishing/maintaining the luminal cell lineage. We identified downmodulation of the p53 homolog, Dnp63, as underlying mechanism of this Notch signaling function and established that Dnp63, whose function in the mammary epithelium was hitherto unknown, is required for the maintenance of basal cell fate.

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**Cathrin Brisken**  
Tenure-track Assistant Professor

Cathrin Brisken received an MD and a Doctorate in Biophysics from the University of Göttingen in 1993. She worked as a postdoc and research scientist at the Whitehead Institute, MIT, Cambridge, USA. She was assistant professor at the MGH Cancer Center, Harvard University before joining the NCCR Molecular Oncology at ISREC in 2002. In 2005 she was appointed Tenure Track Assistant Professor at EPFL. Cathrin Brisken is a member of various scientific advisory boards and of the “Hinterzartener Kreis”.

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**Scheme 1:** Schematic representation of the hormonal control of mammary gland development (black) based on our previous work.

**Scheme 2:** Progesterone induces cell proliferation by two distinct mechanisms. Firstly, it elicits proliferation of hormone receptor positive cells by a cyclin D1 dependent mechanism. Second, it stimulated hormone receptor positive cells to secrete the protein RANKL which turns makes neighboring cells proliferate.
Selected Publications


Reviews:

Brizken, C., O’Malley, B. (2010)


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Scheme 3. Notch and p63 control cell fates. P63 is a hallmark of progenitor cells and myoepithelial cells. Activation of Notch signaling downmodulates p63 expression thereby driving cells towards a luminal cell fate.
Introduction

Using genetic mouse models and biochemical approaches, the Constam lab investigates how TGFβ and Wnt signaling pathways are regulated to control progenitor cell proliferation and differentiation, since perturbations in these pathways cause multiple diseases, including cancer.

Keywords

Development and cancer; stem cell fate; polycystic kidney diseases; cilia and planar polarity signaling; protein processing and trafficking; microRNA.

Results Obtained in 2010

To initiate and maintain tumor growth and metastasis, cancer cells depend on growth and survival signals which normally sustain progenitor and stem cell compartments during development and adult tissue homeostasis, inflammation and tissue regeneration. Among these signals, secreted TGFβ and Wnt proteins are of key interest as they act as potent stem cell or differentiation factors depending on the context.

To elucidate how such paradoxical activities are kept in balance, our lab is studying the role of the TGFβ family member Nodal in coordinating the proliferation and subsequent differentiation of pluripotent cells in the mouse blastocyst. Previously, we have shown that Nodal signaling with the coreceptor Cripto in the epiblast is controlled by the proteolytic activities of the proprotein convertases (PC) Furin and Pace4 to regulate Smad2 and Smad3 transcription factors (Constam, 2009a). Furin and Pace4 are secreted and cleave the Nodal precursor protein in vitro, and they are expressed in the epiblast micro-environment before and during gastrulation. However, a paracrine function for PCs has not been directly demonstrated. To assess whether Furin and Pace4 directly act on epiblast cells, we generated a transgenic cell surface-linked indicator of proteolysis (CLIP) that can image PC activities in vivo. CLIP consists of secreted CFP that was fused to membrane-bound citrine via the Furin/Pace4 recognition motif RQRR. CLIP imaging revealed wide-spread cell surface fluorescence of citrine, whereas the CFP moiety was efficiently cleaved off already in the inner cell mass of preimplantation blastocysts and its derivative, the epiblast. By contrast, in double mutant blastocysts lacking Furin and Pace4, CFP remained at the cell surface together with citrine (Figure). Cleavage of CLIP in Furin-/-,Pace4-/- double mutants was also impaired in the epiblast during gastrulation (Mensnard and Constam, 2010). These findings demonstrate that Furin and Pace4 are active and functionally overlap in the mouse embryo already at the time when Nodal promotes pluripotency, and that the epiblast remains exposed to PCs during gastrulation. CLIP thus emerges as a specific biosensor to explore PC functions in the crosstalk between pluripotent cells and their micro-environment, and in other tissue contexts.

In parallel, we characterized a new role for the RNA-binding protein Bicaudal-C in renal tubule morphogenesis. Previously, we reported that Bicaudal-C inhibits canonical Wnt signaling at the level of Dishevelled and that a targeted mutation induces polycystic kidney disease (Maisonneuve et al. 2009). Identification of target RNAs now shed new light on the underlying mechanism.
Selected Publications


The fluorescent reporter substrate CLIP reveals the presence of redundant Furin and Pace4 activities in mouse blastocysts. (A) Schematic representation of CLIP. In the control transgene CLIPm, the PC recognition motif RQRR is mutated to block cleavage. (B) Box plot and (C) images of cell surface CFP/YFP ratios of transgenic blastocysts from Furin and Pace4 wild-type, single mutants and double knockout (DKO) embryos. CLIPm transgenic embryos are shown for comparison. Bar, 50 μm.

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Introduction

The aim of this research is to understand how genes are regulated during mammalian embryonic development. We are particularly interested in studying the relationships that exist between genomic organization (e.g. gene topology) and the control of transcriptional activity, both at the genetic and epigenetic levels, by using one of the Hox gene locus as a paradigm. These genes are involved in many important processes during embryonic development, and are mis-regulated in a variety of human genetic syndromes. We thus hope to understand some basic rules of long-distance gene regulation, which will be extrapolated to other normal and pathological contexts.

Keywords

Embryos, development, evolution, transcription, epigenetic regulation, Hox gene clusters, enhancers

Results Obtained in 2010

SystemsHox.ch; an in vivo System Approach to Hox Genes Regulation in Vertebrates.

We like to understand the relationships between genomic topology and the control of transcription, using the HoxD locus as a paradigm. We take a system approach in the mouse, combining tools of genetics, evolutionary genomics and biochemistry to try and model various modes of large-scale gene regulations occurring during development and in embryonic stem cells. Over the past years, we have produced a large series of mutant stocks carrying deletions, duplications or inversions and we now analyze these mutant mice in the context of large-scale (several 100 kb) regulations. We focus our research on several target tissues where Hox gene functions were co-opted along with the emergence of tetrapods, such as the limbs, the external genitalia and the caecum and try and define the similarities and differences in the ways Hox genes are regulated into these various contexts, by using technologies such as ChIP-seq and 4C-seq. The aim is to understand these regulatory mechanisms and to see whether they share some basic principles, which may allow us to reconstruct a ‘phylogeny of regulation’, i.e. to establish the successive steps, in the acquisition of regulatory controls, leading to the intricate situation we can witness today at these paradigmatic genomic loci.

Hox gene clusters are surrounded by gene deserts, rich in highly conserved non-coding sequences. It is generally believed that such deserts are instrumental in organizing long-range regulations and, over the past several years, we have built the tools necessary to address this question. We found that many vertebrate specific traits, which emerged along with the 2R genome duplication such as the limbs, the teguments or the gut regionalization are indeed largely controlled by global enhancers located within these gene-deserts.
Selected Publications


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The 4C and ChIP technologies. Tissues are dissected out from fetuses, either non-expressing (brain) or expressing (limbs) the Hoxd13 gene. The points of contacts between Hoxd13 and the centromeric landscape are determined after cross-linking, re-ligating and sequencing. The profiles are shown in black and are compared with the presence (in blue) of H3K27ac marks, as obtained by classical ChIP, which indicate the presence of potential regulatory sequences (present in the limbs, yet absent from the brain). Coincidences between the peaks indicate the presence of important enhancer elements with a fair probability (pictures from T. Montavon)
Introduction
Correct cell division is fundamental for proper development and for self-renewing tissues in the adult organism. Using a unique combination of genetic, functional genomic, cell biological and live imaging approaches, we seek to decipher the mechanisms governing fundamental cell division processes.

Keywords
Cell biology, developmental biology, centrosome duplication, asymmetric cell division

Results Obtained in 2010
We focus our work on two fundamental cell division processes: centrosome duplication and asymmetric cell division. In other work, we have notably developed a robust algorithm for the automated segmentation and standardization of early C. elegans embryos (see Figure).

Centrosome duplication.
The centrosome is the principal microtubule-organizing center of animal cells and comprises two microtubule-based centrioles. The centriole and the procentriole are characterized by a universal nine-fold radial symmetry, but the mechanisms by which this architecture is achieved were not understood. We, as well as others, identified five proteins required for procentriole formation in C. elegans: the kinase ZYG-1, as well as the coiled-coil proteins SAS-4, SAS-5, SAS-6 and SPD-2. These five proteins have relatives in other metazoans. In collaboration with the laboratory of Michel Steinmetz (Paul Scherrer Institute), we established that C. elegans SAS-6 forms rod-shaped homodimers and that oligomerization of such homodimers is essential for centriole formation in C. elegans and in human cells. Moreover, we generated a structural model of the SAS-6-related protein Bld12p from C. reinhardtii. In this model, nine homodimers of Bld12p form a ring from which radiate nine coiled-coil rod domains. Furthermore, we demonstrated that recombinant Bld12p can self-assemble into such structures. Overall, our findings reveal the structural basis of the universal nine-fold symmetry of centrioles.

Asymmetric cell division.
Asymmetric division is crucial for generating cell diversity. Accurate spindle positioning is critical for proper asymmetric cell division. Previously, we proposed that asymmetric spindle positioning in C. elegans results from two Gα-proteins recruiting the GoLoco protein GPR-1/2 and the coiled-coil protein LIN-5 to the cell cortex. The LIN-5/GPR-1/2/Gα complex serves to recruit the minus-end directed microtubule motor dynein to the cell cortex. Together with microtubule depolymerization, dynein allows pulling forces to be exerted along astral microtubules, thus ensuring proper spindle positioning. The distribution of GPR-1/2 at the cell membrane is asymmetric during mitosis, with more protein present on the posterior, but how this asymmetry is achieved was not understood. We established that the distribution of the Gβ subunit GPB-1, a negative regulator of force generators, varies across the cell cycle, with levels at the cell cortex being lowest during mitosis. Furthermore, we uncovered that GPB-1 traffics through the endosomal network in a manner that is more pronounced on the anterior, under the regulation of polarity cues. In addition, we demonstrated that GPB-1 depletion results in the loss of GPR-1/2 asymmetry during mitosis. Overall, this leads us to propose that modulation of Gβγ trafficking plays a critical role during asymmetric division of one-cell stage C. elegans embryos.
Selected Publications


Introduction

Our goal is to understand how the pancreas forms during development. The long term medical purpose is to use this information to generate replacement cells for patients suffering from diabetes and to understand pancreatic cancer progression.

Keywords

Development, embryo, pancreas, diabetes, endoderm, Wnt, Planar cell polarity, patterning, beta-cell, chick, mouse, architecture

Results Obtained in 2010

Regulation of pancreas organogenesis: role of the bHLH transcription factors Ptf1a and Ngn3.

We investigated the mechanisms by which Ptf1a maintains and expands pancreas progenitors. We compared the transcriptome of early pancreas progenitors lacking Ptf1a to that of wild type progenitors and analyzed the chromatin regions bound by Ptf1a using ChiP-sequencing. Our experiments show that Ptf1a directly regulates a very large number of effector genes. However, its activities are also relayed by a network of 5 crucial transcription factors which regulate each other, thereby robustly maintaining pancreas progenitors.

Pancreas progenitors differentiate into exocrine cells and multiple endocrine cell types whose main function is the regulation of glucose homeostasis. The transcription factor Ngn3 is absolutely necessary to generate endocrine cells and to promote their migration from the epithelium. We recently identified targets of Ngn3 which mediate its ability to trigger migration (Gouzi et al., 2011) and differentiation. In particular we found that Ngn3 induces planar cell polarity genes and are currently using mouse mutants for this pathway to study its function during development.

Regulation of endocrine differentiation by intercellular communication pathways

The differentiation of specific endocrine cells in the pancreas is controlled by distinct transcription factors. In 2010, we found that β-cell differentiation does not proceed in a deterministic manner, but that it is regulated by communication between cells through the canonical Wnt pathway. Following a burst of glucagon-positive α-cells, insulin-producing β-cells first appear at E11.5 coinciding with the expression of the RNA-binding protein Bicc1 in progenitors. We showed that deletion of Bicc1 inhibits β-cell differentiation downstream of Ngn3, and that this defect is accompanied by ectopic activation of Wnt/β-catenin signaling. In sharp contrast, inversin truncation mutants, opposite to Bicc1 KOs, behave as overactive alleles resulting in decreased Wnt signaling and increased β-cell differentiation. Interferences with canonical Wnt signaling show that this pathway must be blocked for β-cells to differentiate and that Bicc1 expression after E11.5 is instrumental for this purpose. Our study provides a clue how type 2 diabetes risk alleles of the Wnt pathway component TCF7L2 may increase disease susceptibility.

Significance of this work for diabetes and pancreatic cancer

Although the function of the pancreas in controlling glucose homeostasis is compensated by insulin injection in diabetic patients, the physiological effects are inexact and too variable. Among approaches that are currently being explored to find a cure for diabetes are the isolation and propagation of embryonic or adult stem cells that can be engineered to produce endocrine hormones and then transplanted to patients. Our experiments are aimed at identifying the critical cellular transcription factors and signaling molecules that are sufficient to transform cells, including ES and iPS cells, into β-cells. To assist diabetes therapy, we developed optical coherence microscopy in collaboration with the Lasser laboratory (EPFL) to image islets of Langerhans live, in mice (Villiger et al., 2009).

In addition, pre-cancerous and cancerous cells often reactivate the expression of developmental genes. In pancreatic carcinoma many developmental genes are reactivated. Ongoing work on developmental genes may give a better understanding of pancreas cancer development and may point to new therapeutic targets.
Selected Publications


Team Members

Post doctoral
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Embryonic development of the pancreas differentiation of endocrine cells, structure of the adult organ and visualisation of pancreatic islets by optical coherence microscopy. Adult islets are composed of insulin-producing β-cells, glucagon-producing α-cells and 3 other endocrine cell types. All these cells originate from the embryonic epithelial progenitors after delamination and aggregation.
Douglas Hanahan, born in Seattle, Washington, USA, received a bachelor’s degree in Physics from MIT (1976), and a Ph.D. in Biophysics from Harvard (1983). He worked at Cold Spring Harbor Laboratory from 1978-88 as graduate student and then as group leader. From 1988-2010 he was on the faculty of the Department of Biochemistry & Biophysics at UCSF. He has been elected to the American Academy of Arts & Sciences (2007), the Institute of Medicine (USA) (2008), the US National Academy of Science (2009), and EMBO (2010).

Introduction
The Hanahan group investigates tumor development and progression using genetically-engineered mouse models of cancer that recapitulate salient characteristics of human cancers, with strategic goals to elucidate pathogenic mechanisms and develop new therapeutic strategies for translation to clinical trials.

Keywords
Cancer; translational oncology, genetically engineered mouse models of human cancer; transgenic mice; tumor micro-environment; angiogenesis, invasion, and metastasis, pre-clinical trials

Results Obtained in 2010
During 2010 the Hanahan lab became fully operational following its move from UCSF in San Francisco, with the integration of a new research team. The research is focussed on two forms of pancreatic cancer -- ductal adenocarcinoma (PDAC) and neuroendocrine carcinoma (PNET) – involving representative mouse models of de novo, multi-stage carcinogenesis, and translational studies in the human counterparts. Additionally, new efforts are ongoing in mouse models of glioblastoma and melanoma. In 2010 the lab participated in a collaborative study that identified via transcriptome profiling and bioinformatic analysis distinct subtypes of human and mouse PDAC (Collison, Sadanandam, et al, 2011, Nature Medicine). Ongoing cross-filtering mouse and human PNET is similarly revealing heretofore unrecognized molecular genetic subtypes. A continuing project involves the responses and eventual failure of anti-angiogenic therapy, which is manifested in unconventional forms of so-called evasive resistance involving revascularization and/or heightened invasion and metastasis (see Paez-Ribas et al 2009). A study begun at UCSF has been completed at EPFL, in which a multi-kinase inhibitor, brivanib, that targets VEGFR and FGFR signalling, was evaluated in a mouse PNET model; the results indicate that brivanib can limit a particular form of evasive resistance, namely FGF-driven vascularization, encouraging its further clinical evaluation, particularly in the context of developing resistance to selective VEGF inhibitors. Additional projects are focused on parameters of invasion and metastasis. One project is dissecting a polymorphic invasion modifier locus (see Chun et al 2010) that is alternatively suppressive or permissive for development of invasive vs non-invasive PNET, depending on genetic background (C3H vs C57Bl); the goal is to identify the genes in this locus whose differential expression manifest these alternative phenotypes. The results may have implications for prognostic evaluation of human tumors, if similar polymorphic variation is identified in the human population.

Another project is investigating the functional roles and importance of a group of microRNAs that are differentially expressed in benign vs highly invasive subtypes of PNET, previously identified but not functionally assessed in a study that profiled the microRNA transcriptome in the stages of PNET tumorigenesis (Olson et al, 2009). Two other projects are investigating the reprogramming and functional significance of altered cellular energetics and metabolism in PDAC and PNET tumors. One is assessing the role of copper bioavailability in the switch from oxidative phosphorylation to glycolysis, while the second is studying the effects of hypoxic conditions on the growth phenotype of PDAC, which is unusual for its poor vascularization and extensive fibrotic stoma.
Selected Publications


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Targeted cancer therapies eliciting or partially circumventing adaptive resistance to anti-angiogenic therapy. Panel i depicts a pancreatic neuroendocrine tumor in a mouse model of cancer after treatment with a drug that inhibits both VEGF and FGF receptor signaling, leading to a significant angiogenic blockade (green; Meca 32, an endothelial cell marker). In contrast, treatment with a a combin
Introduction
The last years of cancer research have established the concept of tumor stem cells (CSC) as sub-population of cells within a tumor entirely responsible for long-term tumor growth. This has aroused expectations that targeting specifically these cancer stem cells would allow effective tumor eradication. We now provide evidence that these cells are also essential for metastatic disease and identify the interaction between stem cells and their environment as a promising target to block the spreading of cancer to secondary sites.

Keywords
Stem cells, Cancer stem cells, Stem cell niches, Wnt signaling, Metastatic colonization

Results Obtained in 2010
In the last years, we and others have identified hierarchical organization as a basic principle which applies not only to normal tissues but also to tumors. This has lead to the identification of so-called cancer stem cells which are essential for initiating tumor growth and long-term tumor maintenance. We have now expanded this concept and shown that these rare cancer stem cells are also essential for metastatic progression. Moreover, we found that niche signals, i.e. signalling molecules and extracellular matrix components produced by surrounding stromal cells, participate in the control of cancer stem cell function and play an important role in expanding these stem cells. We furthermore found that such niche derived signals are of particular importance during the early phases of metastatic colonization, when cancer cells leave the primary niche and are suddenly exposed to a new environment. Cancer stem cells appear to critically depend on a “known” set of signaling molecules present at the primary site, however missing in the new environment. Consequently, infiltrating cancer cells attempt to reprogram the target organ to generate a supportive niche. Since this is hardly ever successful, many disseminated cancer cells fail to initiate growth at a secondary site. This is in line with earlier reports which described metastasis formation as an overall very inefficient process. We now find that factors that contribute to this inefficiency comprise the low abundance of cancer stem cells that initiate metastasis, incompatibilities with “foreign” niches and the requirement to educate the target organ. Consequently, we were able to show that genetic ablation of essential niche components can render the body resistant to metastasis formation, even when challenged with large amounts of cancer cells. This clearly demonstrates that targeting the stem cell - niche communication could emerge as a viable approach to metastasis prevention and intervention. It is in particular the early metastatic colonization phase that can be expected to be sensitive to therapeutic intervention as the dependence of the cancer stem cell for niche signals is highest. We suggest that targeting the stroma-derived cancer stem cell niche holds the promise to be less prone to rapid genetic changes in cancer cells and therefore could turn out as a favorable regimen to avoid resistance and therapy escape. We have developed antibodies which can target stem cell niche molecules and interfere with cancer stem cell expansion. We are optimistic that such antibody-mediated therapies can be further developed and may be used for the benefit of cancer patients in the future.
Selected Publications


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Introduction
We have generated mice with a conditional deletion of the ferritin H gene. Ferritin H is necessary for iron storage and detoxification, and its absence provokes oxidative stress, which in turn can damage DNA, a known cause of cancer. Our mice also contribute to the understanding of hereditary diseases of iron overload and anemia.

Keywords
Conditional knock-out mice for ferritin H, oxidative cell damage, iron physiology, mRNA degradation, RNA-protein interactions

Results Obtained in 2010
Analysis of ferritin H knock-out mice
Iron is an essential metal for life and at the same time a hazard since, in its free form, it catalyzes the formation of hydroxyl radicals, which are a cause of cell damage and mutations in DNA. Therefore, body iron absorption from nutrients and free iron in cells are delicately controlled in order to avoid the excess or deprivation of iron. In the human population, an excess of iron is observed in the hereditary disease of hemochromatosis, which is accompanied by tissue damage in liver, heart and pancreas. It can be the cause of liver cancer. We study the role of ferritin in the regulation of iron physiology. Ferritin, a complex composed of ferritin H and L chains, stores excess free iron and thereby protects cells against radical formation. We have generated mouse strains with a conditional deletion of the ferritin H gene in various tissues of adult animals using the Cre-lox strategy.

This year we have completed and published a study which shows that ferritin H is required for the control of intestinal iron absorption. Iron enters duodenal enterocytes from the intestinal lumen by divalent metal transporter 1 (DMT1)-mediated transport across the apical brush border membrane after reduction to Fe2+ by duodenal cytochrome b (Dcytb). Its export at the basolateral membrane is mediated by ferroportin followed by its reoxidation to Fe3+ by hephaestin. The control of iron absorption requires hepcidin, a polypeptide hormone secreted by the liver in response to high body iron levels. We have investigated the conditional deletion of the ferritin H gene in the intestinal mucosa. Deleted mice showed increased serum and tissue iron levels, compared to control mice. As expected for iron-loaded animals, they had induced liver hepcidin mRNA and reduced duodenal DMT1 and Dcytb mRNA levels, while ferroportin and hephaestin mRNA levels were unaffected. In spite of these feedback controls, intestinal ferroportin protein and 59Fe-absorption were increased more than two-fold on average. This was accompanied by IRP2 inactivation and increased ferritin L protein expression, suggesting an increased intracellular free iron-pool in the intestinal cells and the likely possibility that ferroportin mRNA translation was IRP-dependently derepressed. Our results demonstrate that hepcidin-mediated regulation alone is insufficient to restrict iron absorption in mice and that intestinal ferritin H is also required, presumably to limit iron efflux from intestinal cells (Figure).

Mechanisms of rapid mRNA degradation
In parallel we study rapid mRNA degradation as it occurs in a large number of mRNAs that harbor instability elements, such as AU-rich sequences, in their 3’-untranslated regions. We explore methods to enrich RNA-protein complexes from cells or tissues by immunoprecipitation in view of identifying interaction sites by high-throughput sequencing.
**Selected Publications**


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**Team Members**

Post doctoral
Claude Schweizer (from March 2010)

PhD Student
Ramona Batschulat

Scientific collaborator
Barbara Grisoni-Neupert (to July 2010)

Specialist technician
Larry Richman

Administrative assistant
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Regulation of intestinal iron absorption in normal (A), iron-loaded (B) and ferritin H-deleted mice (C). We conclude that ferritin sequesters part of the free iron on its transport across intestinal cells and thereby reduces the gradient which drives iron export.
Introduction
Telomeres are the physical ends of eukaryotic chromosomes. They mediate chromosome stability and function as cellular clocks and tumor suppressors. Our laboratory aims at gaining a detailed understanding of telomere structure and function. Our work should provide fundamental insight into these fascinating biological structures in addition to delineating novel approaches to attack telomere function in cancer cells.

Keywords
Telomeres, telomerase, long non-coding RNA, TERRA, cellular senescence, genome stability

Results Obtained in 2010
Telomerase is a cellular reverse transcriptase that uses an internal RNA template to synthesize telomeric repeats at chromosome ends. Telomerase counteracts telomere shortening that occurs due to the end replication problem and nucleolytic processing of telomeric DNA. In humans, telomere length is set in most tissues early in embryogenesis as telomerase is repressed later in life. Short telomeres that accumulate with increasing numbers of cell division cycles induce cellular senescence and this is thought to counteract growth of pre-malignant lesions in our body. Most cancers re-express telomerase to overcome this growth barrier. Our work during 2010 concentrated on the question of how the telomerase enzyme is recruited to chromosome ends by telomere binding proteins and how telomerase is regulated by TERRA, a large non-coding (lnc) RNA which is transcribed at telomeres.

Activation and recruitment of telomerase to chromosome ends
Activation and recruitment of telomerase to chromosome ends are not well understood in complex eukaryotes including humans. Therefore, we developed assays to measure association of human telomerase with chromosome ends by chromatin immunoprecipitation, and our collaborators from the Terns-lab (University of Georgia) could for the first time detect human telomerase at chromosome ends by fluorescence in situ hybridization. We defined two critical steps that are required for telomerase maturation. First, we could show that Cajal bodies, subnuclear structures implicated in ribonucleoprotein assembly are critical for telomerase maturation and the recruitment to telomeres. Second, through downregulation of telomere binding proteins by RNA interference, we identified that the shelterin components TPP1 in association with TIN2 recruit human telomerase to chromosome ends to allow their extension in S phase of the cell cycle.

TERRA lncRNA: a natural ligand and regulator of telomerase
We recently discovered in eutherian mammals and in the yeast Saccharomyces cerevisiae that telomeres are transcribed into lnc RNAs termed TERRA. The identification of TERRA is paradigm-shifting because telomeric heterochromatin had been accepted as being a transcription silencer. TERRA functions may include the regulation telomeric heterochromatin and the regulation of telomerase (see below). We now dissected the molecular structure of TERRA and its regulation during the cell cycle. In addition, we demonstrated that TERRA binds the telomerase enzyme. The UUAGGG-repeat sequences of TERRA base-pair with the RNA template sequence of telomerase in addition to directly interacting with the TERT polypeptide. TERRA acts as a very potent mixed-type inhibitor of telomerase (see figure). Our data suggest that telomerase regulation by the telomere substrate may be mediated via its transcription.
Selected Publications


TERRA inhibits telomerase. (A) TERRA-oligonucleotides inhibit telomerase activity without perturbing repeat addition processivity whereas the small molecule inhibitor BIBR1532 reduces processivity. (B) Upper: Telomerase activity as a function substrate concentration. TERRA causes an increase of Vmax and a decrease of the Km. Bottom: Model for telomerase (E) inhibition by TERRA (I).
Introduction

Our group uses mouse genetics to study the molecular mechanisms controlling self-renewal and differentiation of normal and cancer stem cells in the blood system as well as in epithelial tissues including the intestine and the epidermis. The basic principle of self-renewing tissues is that they constantly produce cells from a stem cell reservoir that gives rise to proliferating transient amplifying cells, which subsequently differentiate and migrate to the correct compartment. These processes have to be under stringent control mechanisms to ensure life-long tissue homeostasis and their deregulation can lead to organ failure and/or cancer. Current attention is focused on the evolutionarily conserved Notch and Wnt signaling pathways, which play pleiotropic roles in different self-renewing tissues and cancer.

Keywords

Notch, Wnt, stem and progenitor cells, self-renewing tissues, differentiation, cancer, genetic mouse models

Results Obtained in 2010

Notch: lineage specifier, oncogene, and stem cell gate-keeper

Notch signaling in T cell development and leukemia

The evolutionarily conserved Notch signaling pathway regulates a broad spectrum of cell fate decisions and differentiation processes during fetal and postnatal life through cell-to-cell signaling. Using conditional gene targeting strategies we demonstrated that Notch signaling mediated by the Notch1-Delta-like 4 (DL4) receptor ligand pair is essential for thymic T cell development. Loss of the Notch1 receptor on hematopoietic bone marrow progenitors or inactivation of the DL4 ligand in thymic epithelial cells leads to a complete block in T cell development coupled with the ectopic appearance of immature B cells in the thymus. Moreover, aberrant Notch signaling is deeply implicated in the pathogenesis of T cell acute lymphoblastic leukemia (T-ALL). More than 50% of all patients have increased Notch signaling due to activating mutations within Notch1. It is largely unknown through which target genes and signaling pathways Notch exerts its normal and its oncogenic properties. Using conditional mouse genetics we recently showed that the well-characterized Notch target gene Hes1 (a basic helix-loop-helix transcriptional repressor) is important for efficient T cell lineage commitment. More importantly our studies showed that Hes1 is critical for development and maintenance of murine and human T cell leukemia (Figure)

Delta-like 1 and Delta-Like 4 mediated Notch signaling are essential for intestinal stem cell homeostasis

The intestinal epithelium is a self-renewing tissue with a high turn over rate and cellular processes such as proliferation, migration and cell death have to be under stringent control to ensure homeostasis of the tissue. The epithelium of the small intestine consists of four principal cell types: absorptive enterocytes, mucus secreting goblet cells, antimicrobial Paneth cells, and hormone secreting enteroendocrine cells. While most differentiated cell types reside within the villus, post mitotic Paneth cells together with proliferating Lgr5+ stem and progenitor cells localize to the crypt compartment. We previously showed that Notch signaling (mediated by Notch1 & 2) is essential for the maintenance of crypt progenitors. Ablation of Notch signaling results in a rapid and massive conversion of proliferative crypt cells into post mitotic goblet cells demonstrating that Notch is required for the high turn over and homeostasis of the intestinal epithelium. More recently we performed lineage-tracing experiments combined with tissue specific gene targeting to show that Notch signaling is also occurring at the level of and is important for the maintenance of Lgr5+ stem cells. Furthermore we identified Delta-like1 and 4 as the physiological Notch ligands of the small and the large intestine.
Selected Publications


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The basis helix-loop-helix transcriptional repressor Hes1 is important for normal T cell development as well as for induction and maintenance of T cell leukemia.
**Simanis Lab**

http://simanis-lab.epfl.ch/

**Viesturs Simanis**  
Associate Professor

Viesturs Simanis has been an Associate professor at EPFL since 2006. Leading up to his appointment at EPFL, Dr. Simanis was a Group leader at Swiss Institute for Experimental Cancer Research (1988 – 2006). He did his Post-doctoral studies with Professor Paul Nurse (London and Oxford; 1984-1988) after his Ph.D with Professor David Lane (Imperial College, London University; 1980 – 1984).

**Introduction**

If the fidelity of the processes involved in cell division is reduced, there is an increased risk that errors will occur in the transmission of genetic information from a cell to its daughters; this can result in the death of the cells, or alter their properties, which can contribute to the development of diseases such as cancer. We study cytokinesis, the division of cells, to understand how it is regulated and coordinated with other events in the cell cycle.

**Keywords**

Cell cycle, fission yeast, cytokinesis, protein kinase, phosphoprotein phosphatase.

**Results Obtained in 2010**

We use a combination of genetics, and cell and molecular biology to study the septation initiation network (SIN): a signalling pathway that regulates cytokinesis in vegetative cells and spore formation in meiosis.

**Identification of regulators of the SIN (Anupama Goyal, Evelyn Lattmann).**

We have used a variety of genetic screening approaches to identify regulators of the SIN, including the isolation of mutants dependent upon high levels of SIN signalling for viability, and isolation of extragenic suppressors of SIN mutants. Consistent with earlier analysis from this lab and others, we have found that phosphoprotein phosphatase 2A and its regulatory subunits play an important role in regulating the SIN.

**The role of dma1 in meiosis: (Andrea Krapp, Elena Cano).**

Meiosis is a specialised form of the cell cycle that gives rise to haploid gametes. In S. pombe, the products of meiosis are four spores, which are formed by encapsulation of the four meiosis II nuclei within the cytoplasm of the zygote that was produced by fusion of the mating cells. The S. pombe spindle pole body is remodelled during meiosis II, and membrane vesicles are then recruited there to form the forespore membrane, which encapsulates the haploid nucleus to form a spore. Spore wall material is then deposited giving rise to the mature spore. We investigated the role of the SIN regulator dma1p in meiosis; we discovered that though both meiotic divisions occur in the absence of dma1p, asci frequently contain fewer than four spores, which are larger than in wild-type meiosis. Staining with DAPI indicates the one or more nuclei do not become encapsulated within a spore. The spores that are produced have an overall viability comparable to a wild-type meiosis, and the overwhelming majority of them are haploid. Imaging of forespore membrane formation in living cells during meiosis indicates that in the absence of dma1p, all SPBs initiate spore formation, but the process proceeds aberrantly on some SPBs. Analysis of double mutants indicates that dma1p acts in parallel to the leading edge proteins and septins to assure proper formation for the forespore membrane. Dma1p also contributes to the temporal regulation of the abundance of the meiosis-specific SIN component mug27p, which may account for the increased size of the spores. Future studies will attempt to determine the nature of the defects leading to a failure of spore formation.
**Selected Publications**


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**Team Members**

**Post Doctoral**
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**psy1p-GFP in dma1-D**

The image shows frames from a time-lapse movie of spore formation in a dma1-D meiosis. Note that three nuclei are encapsulated normally, while the fourth nucleus forms a multi-lobed structure that eventually fails to form a spore.
**Introduction**

Pigment cells are involved in benign changes such as hair graying, albinism, and vitiligo, as well as in cutaneous melanoma, one of the most devastating types of cancer. Pigment cells are an attractive model to study gene regulation, development and interplay between stem cells and differentiating cells.

**Keywords**
Melanocytes, RPE, pigmentation

**Results Obtained in 2010**

Melanocytes in mice differentiate from pluripotent neural crest cells, migrate along the dorsolateral pathway and subsequently proliferate through the dermis horizontally to the ventral region. By midgestation, melanocytes exit from the dermis and invade the epidermis to finally be located in the skin and the hair follicles. Many genes are implicated in specific aspects of melanocyte/melanoblast differentiation and more than 370 loci are currently known to affect pigmentation in the mouse.

One interest of the past year(s) was focused on the role of the Notch signaling pathway and the c-Myc oncogene in melanocyte development and homeostasis. Removal of c-Myc leads to gray hair, which is not progressive, and is caused by a reduction in melanocyte number. Disruption of the Notch pathway by inactivating Notch1 and Notch2, or RbpJk in the melanocyte lineage resulted in a dosage-dependent precocious hair graying, due to an elimination of melanocytes and melanocyte stem cells. The molecular and cellular origin of this phenotype is not known, and we thus have established a FAC5-sorting protocol to isolate melanocytes from embryos. This will enable us to analyse gene expression in Notch-deficient melanocytes in vivo.

We equally addressed the implication of the Notch signaling in the development of another population of pigment cells forming the retinal pigment epithelium (RPE) in mammalian eyes. The constitutive activity of Notch in Tyrp1::NotchIC/+ transgenic mice enhanced RPE cell proliferation, and the resulting RPE-derived pigmented tumor severely affected the overall eye structure. This RPE cell proliferation is dependent on the presence of the transcription factor RBP-Jk, since it is rescued in mice lacking RBP-Jk in the RPE. In conclusion, Notch signaling in the RPE uses the canonical pathway, which is dependent on the transcription factor RBP-Jk. In addition, it is of importance for RPE development, and constitutive Notch activity leads to hyperproliferation and benign tumors of these pigment cells.

Mart-1 (encoded by the Mlana gene in the mouse) is an important melanoma-associated antigen which is widely studied as a target for immunotherapy. Mart-1 is exclusively expressed in melanocytes and the retinal pigment epithelium as reflected by analysis of Mlana::lacZ BAC transgenic mice (Figure). We have used the Mart-1 regulatory sequences to target Cre expression to melanocytes, and have analysed a knock-out of the Mart-1 gene. Preliminary data reveal a coat-color phenotype due to a reduction in eumelanin production.

Friedrich Beermann was trained as biologist at the Universities of Tübingen and Göttingen, where he received his PhD in 1989. He carried out postdoctoral work at the German Cancer Research Center in Heidelberg and joined ISREC in 1992 as group leader and head of the transgenic services. Since 2009, he is a senior scientist at the EPFL. His research has focused on melanocytes and pigment cell biology.
Selected Publications


Aydin, I.T. and Beermann, F. (2011) A MART-1::Cre transgenic line induces recombination in melanocytes and RPE. Genesis, DOI: 10.1002/dvg.20725


Expression from a Mlana::lacZ BAC in pigment cells of skin and eye.

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Introduction
New technologies allow for comprehensive characterization of the molecular processes that cause a healthy cell to become cancerous. These technologies produce vast amounts of data. We develop computational methods that will help to extract insights and knowledge from such data.

Keywords
Computational genomics, transcriptional regulation, sequence analysis methods, ChIP-Seq data analysis, survival prediction from molecular profiles, human biographic data analysis.

Results Obtained in 2010
Computers have become indispensable tools for accessing, visualizing, analyzing, managing, and disseminating biological data. Over the last two decades, high-throughput sequencing and functional genomics projects have generated unprecedented quantities of biological data which can neither manually be processed, nor comprehensively inspected by eye. The emergence of bioinformatics as a research field in its own right is a response to this development.

Cancer can be considered a gene regulatory disease. Normal regulation of genes permits the development and maintenance of a healthy human being. Abnormal regulation leads to various diseases. Cancer cells are maintained in a specific pathological state by gene regulatory circuits. Transcription factors are key elements of such circuits in that they control the expression of other genes while themselves being regulated by the products of genes. Our research aims at an understanding of transcriptional regulatory mechanisms in general, but with a particular focus on those which are affected by genetic lesions that cause cancer.

Transcriptional control mechanisms in higher organisms are poorly understood, despite three decades of intensive research efforts. New hope comes from the recently introduced ChIP-seq technology and related assays based on ultra-high-throughput sequencing. For the first time, we are now able to observe transcription factor-DNA interactions in gene regulatory regions directly.

The development of effective computational tools to mine these data has been the research focus of our group over the last three years. The resulting methods have been successfully applied in a number of research collaborations and are used by many researchers all over the world via the web interface at http://ccg.vital-it.ch/chipseq/. In addition to experimental data-driven approaches, we are also trying to crack the regulatory genetic code through comparative genomics. Specifically, we are studying the evolution of the most highly conserved non-coding sequences across the vertebrate phylum.

Our group has been active in several other areas of too. One project was aimed at improving breast cancer diagnosis based on gene expression signatures. This led to the discovery of a novel breast cancer survival gene, CYB5D1, potentially useful for personalized treatment (Figure). CYB5D1 most probably escaped the attention of researchers before because it was not included in the Affymetrix gene chips used in earlier studies. In a collaboration involving sociologists at the University of Lausanne, we applied algorithms originally developed for the analysis of molecular sequence data to human life trajectories. This highly trans-disciplinary project led to two publications in leading sociology journals. We hope that this proof of concept study will pave the way to successful applications of the same methods to patients’ medical history data in clinical studies.
Selected Publications


Kaplan-Meier plot showing the correlation of CYB5D1 expression with survival in a cohort of breast cancer patients participating in clinical tests (based on data from Sorlie et al., Proc. Natl. Acad. Sci. USA 100, 8418–8423, 2003). Note that this gene is not part of the 70-gene signature derived from expression data which is already in use for breast cancer diagnosis.

Team Members

Post-doctoral
Giovanna Ambrosini
René Dreos

PhD Students
Slavica Dimitrieva, PhD

Administrative Assistant
Sophie Aquilar
Jonathan Knowles was named as Professor of Translational Research at EPFL, Sciences Vie at the beginning of 2010. He is working to help better establish translational research, the critical bridge between bench and bedside at EPFL and other partners in Switzerland and abroad. His interests span all aspects of technology and fundamental biological science particularly in the context of how they could be applied to help patients now, or in the future, and he interacts with a number of groups at EPFL to help bring this about. He believes that better public-private partnerships are essential to bring the advances of technology to society.

Dr. Knowles was Head of Group Research and Member of the Executive Committee at Roche for 15 years until the end of 2009. He was a member of the Chugai Board for seven years. Dr. Knowles was also the chairman of the Corporate Governance Committee of Genentech.

From 1987 to 1997, he was director of the Glaxo Institute for Molecular Biology in Geneva, a privately funded Research Institute with an excellent academic publication record. From 1992 until 1997 until he moved to Roche, Jonathan Knowles was the head of the European Research Division and head of the Glaxo Genetics Initiative.

He was for 5 years the Chairman of the Research Directors’ Group of EFPIA (European Federation of Pharmaceutical Industry Associations) and was the founding chairman of the Board of the Innovative Medicines Initiative, a unique public-private partnership between 28 Pharmaceutical companies, the European Commission and over one hundred of European academic centres with a budget of more than 2 billion Euros over five years.

From the beginning of 2010, Dr. Knowles joined the Board of Caris Life Sciences, an international cutting edge molecular diagnostics company based in Irving, Texas. He is currently a Vice Chairman of Caris, and is focused on the development of revolutionary new blood based diagnostics for cancer and other serious diseases.

Jonathan Knowles is a Member of the European Molecular Biology Organization and also holds a Distinguished Professorship in Personalized Medicine at FIMM (Institute for Molecular Medicine Finland) at the University of Helsinki. He has been appointed to a Visiting Chair at the University of Oxford and is a Visiting Fellow of Pembroke College Cambridge. In 2011, Jonathan Knowles was appointed as a Trustee of Cancer Research UK, one of the worlds leading Cancer Research organisations.

He remains very excited by the short term prospects for more personalised medicine through molecular diagnostics, especially for the treatment of cancer, as he believes this is the best and perhaps only way in which effective new therapies can be created and used.

Contact: jonathan.knowles@epfl.ch
Maurizio Molinari earned a PhD in Biochemistry at the ETH-Zurich in 1995. He worked as a postdoctoral fellow in the laboratories of Cesare Montecucco (Padua, 1996-1997) and of Ari Helenius (Zurich, 1998-2000). Since October 2000, he is group leader at the IRB in Bellinzona. Dr. Molinari has received the Science Award 2002 from the Foundation for study of neurodegenerative diseases, the Kiwanis Club Award 2002 for Medical Science, the Friedrich-Miescher Award 2006 and the Research Award Aetas 2007. Since 2008, Dr. Molinari is Adjunct Professor at the EPFL.

Introduction
The endoplasmic reticulum (ER) is the site of maturation for secretory and membrane proteins in eukaryotic cells. Correctly structured proteins are transported at their intra- or extra-cellular site of activity, while misfolded polypeptides are rapidly degraded to prevent formation of toxic aggregates. We study the mechanisms that regulate protein folding, quality control and degradation in mammalian cells. The characterization of these mechanisms and the capacity to manipulate them will be instrumental to delay progression or even to cure diseases caused by defective functioning of the cellular protein factory (e.g. loss-of-function or gain-of-toxic-function conformational diseases such as cystic fibrosis, several types of tumor and of neurodegenerative diseases).

Keywords
Cell Biology; Protein Folding, Quality Control and Degradation; Endoplasmic Reticulum; Molecular Chaperones; Folding Enzymes; Conformational Diseases.

Results Obtained in 2010
ERAD tuning
Protein folding is error-prone and the rapid clearance from the ER lumen of defective proteins (ERAD) is an integral part of the mechanisms that prevent toxic deposition of misfolded conformers. The uncontrolled activity of the ERAD machinery may result in the inappropriate recognition and degradation of non-native intermediates of ongoing folding programs and may cause loss-of-function diseases. We have proposed a model in which ERAD tuning, i.e. the selective degradation of ERAD regulators maintains efficient protein biogenesis at steady state by reducing the ERAD activity at levels that do not interfere with the maturation of newly synthesized cargo proteins (see accompanying figure). The ERAD tuning mechanisms are hijacked by Coronavirus to generate ER-derived membrane vesicles required for viral replication.

Molecular chaperone Malectin
Molecular chaperone Malectin, a novel ER-resident, stress-induced lectin. Unlike the well-studied lectin chaperone Calnexin, Malectin shows prolonged association with misfolded protein conformers. Our findings are consistent with a role of Malectin in ER retention of defective gene products that might be generated upon aberrant functioning of the ER quality control machinery.

ERAD-LS and ERAD-LM
Structural lesions in the luminal, transmembrane, or cytosolic domains determine the classification of misfolded polypeptides as ERAD-L, ERAD-M or ERAD-C substrates and results in selection of distinct degradation pathways. We showed that disposal of soluble polypeptides with luminal lesions (ERAD-LS substrates) is strictly dependent on the E3 ubiquitin ligase HRD1, the associated cargo receptor SEL1L and two interchangeable ERAD lectins, OS-9 and XTP3-B. These ERAD factors become dispensable for degradation of the same polypeptides when membrane-tethered (ERAD-LM substrates). Thus, tethering of mammalian ERAD-L substrates to the membrane changes selection of the degradation pathway.

Cyclosporine A and Cyclophilin B
Peptidyl-prolyl cis/trans isomerases (PPI) catalyze the cis/trans isomerization of peptidyl-prolyl bonds. We reported that the immunosuppressive drug CsA delays the degradation of select ERAD substrates and we identified CyPB as the ER-resident CsA-target that regulates disposal of misfolded polypeptides characterized by the presence of peptidyl-prolyl bonds in the cis configuration. Our work presents the first evidence for the enzymatic involvement of a PPI in protein quality control in the ER of a living cell.

Alzheimer’s Disease (AD)
In collaboration with the group of Patrick Aeberscher, we have developed a novel technique for chronic in situ delivery of antibodies as an alternative to passive vaccination strategies. A polymer device loaded with genetically engineered C2C12 cells was implanted in the brain parenchyma of APP23 transgenic mice and supported chronic delivery of single chain antibodies that prevented deposition of toxic Aβ aggregate and substantially contrasted the worsening of behavioral, anxiety and memory defects, which are hallmarks of progressive AD.
Selected Publications


- *Highlights, Cell Host & Microbe* 7, 424-426.
- *Leading Edge Microbiology Select, Cell* 142, 5.
- *Recommended by the Faculty of 1000.*


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**Team Members**

Post-doctoral
Riccardo Bernasconi

PhD Students
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Julia Noack

Senior Scientists
Carmela Galli
Tatiana Soldà

Technicians
Verena Calanca
Siro Bianchi

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**ERAD tuning.** At steady-state, EDEM1 and OS-9 associate with an elusive receptor (?) and are released from the ER in LC3-1 coated vesicles defined as EDEMosomes. The EDEMosomal content is degraded in endo/lysosomal compartments. PRase: protease.
Introduction
Our mission is to understand the brain mechanisms underlying vision and object recognition. We are developing new technologies for electrical and fluid brain interfacing, with long range goals of visual prosthesis development.

Keywords
Electrophysiology, Neural basis of behaviour

Results Obtained in 2010
In my recently established laboratory, we have begun detailed electrophysiological characterization of the tree shrew visual system, focusing on how neurons in each of the six cortical layers differ in terms of coding for features of the visual stimulus. For example, we have shown that rapidly flashing stimuli, such as those produced by a cathode ray tube television, produce tightly entrained pulses of neural activity in the primary visual cortex. Entrainment is particularly strong in the input layer IV of the cortex, where signals arrive from the eyes. Intriguingly, this entrained activity does not reach conscious perception, which is continuous and not composed of separate segments. Combining these electrophysiological observations with behavioural studies examining the perceptual capacities of tree shrews will allow us to further explore this apparent dissociation between neural activity and perception. In fact, we have already begun to develop variations of behavioural tests suitable for tree shrew. It has become evident that special care and procedures regarding the handling of these fast-moving, shy animals are needed. Under appropriate conditions however, tree shrews can be trained to participate in behavioural paradigms. For example, we have been able to demonstrate robust preference in exploratory behaviour for novel objects, when compared to familiar objects. We have also performed a series of experiments exploring the effects of cholinergic agents on visual cortical activity with layer specificity. Our studies reveal layer-specific action of iontophoretically applied cholinergic agents, and demonstrate a close homology regarding the function of the visual cortex between tree shrews and closely related primate species. In addition, we are continuing to develop, test and further refine electrical and fluid interface probes in collaboration with Prof. Renaud, thanks to the generous support of the Stoicescu program in Neurotechnology. The continuous interaction between probe design and manufacture and the biological experiments is proving extremely valuable for rapid progress in this direction. Finally, we are developing analytical chemistry methods to study time variation of neurotransmitters and other neuroactive compounds from in vivo samples obtained using microdialysis as well as from tissue extracts. Target compounds include Acetylcholine, and related compounds such as the Carnitines, but also Neuropeptides such as Neuropeptide Y, that have been implicated in learning and memory.

Gregor Rainer
External Adjunct Professor
University of Fribourg

Gregor Rainer is a ESF EURYI investigator, associate Professor at the University of Fribourg and adjunct Professor at EPFL. His original training was in semiconductor physics (University of Vienna), after which he obtained a PhD in systems Neuroscience at M.I.T. He has received a number of distinctions including an APART scholarship from the Austrian Academy of Sciences, an award for outstanding teaching from the Tübingen graduate school in Neurosciences and the Otto Hahn Medal from the Max Planck Society.
Selected Publications


Team Members

Post doctoral
Laetitia Fouillen
Xiaozhe Zhang

PhD Students
Anwesha Bhattacharyya
Felix Bießmann (co-supervision with Prof. Müller, TU Berlin)
Pierre Joris (co-supervision with Prof. Renaud, EPFL)
Abbas Khani
Sara Falasca
Filomena Petruzzello
Julia Veit

Tree shrew primary visual cortex with electrolytic lesions marking recording sites at specific cortical layers.
Introduction

The Institute for Research in Ophthalmology (IRO) develops research in various aspects of vision, from understanding the development of the eye in animal models like the zebrafish to identifying new genes in inherited blinding diseases and characterizing their molecular and cellular pathways for better diagnosis and treatment. Through various collaborations, including Retina Suisse, a lay organization very active in the field of retinal diseases, IRO is shaping a new way in providing molecular diagnosis and understanding the inherited conditions behind some of these diseases.

Keywords
Genetics of eye diseases, retinitis pigmentosa, blindness, glaucoma, age-related macular degeneration, diabetic retinopathy.

Results Obtained in 2010

Research done at IRO is centred on 4 axes: identification of new genes implicated in ophthalmic diseases, understanding their function, developing animal models of eye diseases and developing new therapeutic tools. In 2005, we identified NR2E3, a nuclear receptor involved in autosomal recessive enhanced-S cone syndrome, as an actor in severe autosomal dominant retinitis pigmentosa. We have been able to study a family in which the forms of NR2E3 mutations were co-segregating: a mild recessive and a severe dominant form. In this situation, being a carrier of one single mutation (G56R/normal allele) was more dramatic than carrying two mutations (G56R/R311Q). From our functional analyses, we have been able to show that the G56R mutation acts as a dominant negative and is not rescued by the presence of a normal allele, while a mutated allele could reduce the severity of the disease. If gene therapy would be available today, one would need to treat the dominant form by replacing the normal second allele by a mutated allele! We have also identified new loci and genes in several other diseases: CCMMC (congenital cataract, microcornea, microphthalmia, coloboma syndrome), cone-rod dystrophy with amelogenesis imperfecta (Jalili syndrome), congenital stationary night blindness, a specific form of microphthalmia, and anophthalmia with limb defects (Waardenburg anophthalmia syndrome). At IRO, we use the zebrafish as an animal model in the developing eye. In the Waardenburg anophthalmia syndrome, we analyzed SMOC1, the gene responsible for this disease, and showed a very specific eye expression at the boundaries of the closing choroids fissure.
**Selected Publications**


**Team Members**

Research Associates

Nathalie Allaman-Pillet

Sandra Cottet

Pascal Escher

Raphaël Roduit

Post doctoral

Hasret Bajrami

Gwénaëlle Boisset

Arnaud Boulling

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Nathalie Produit

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Séverine Hamann

Fabienne Marcelli

Lionel Page

Désirée von Alpen

Linda Wicht

Bioinformatics and IT support

Etienne Bagnoud

Sylvain Bolay

Cédric Schöpfer

Laboratory technicians

Céline Agosti

Martine Emery

Tatiana Favez

Isabelle Favre

Carole Herkenne

Sylviane Métrailler

Loriane Moret

Administrative Assistants

Pascale Évéquoz

Sandra Thèodoloz

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In situ hybridization of the head of a 3-day zebrafish embryo using a smoc1 probe. The red dots indicate smoc1 expression on both sides of the choroids fissure.
Research Keywords
Epidemiology, public health, vaccines, drugs and diagnostics

Swiss TPH (Tropical and Public Health Institute) and the EPFL School of Life Sciences have intensified scientific collaboration with the goal to bring together complementary expertise of the two institutions in research on host-pathogen interaction in infectious diseases and the development of new diagnostics, drugs and vaccines. Besides the collaboration in research, exchanges of teaching faculty and students within the MSc courses continued.

Joint research activities with malaria parasites, pathogenic mycobacteria and nematodes as target pathogens have been initiated. Since most of the pathogenic nematodes are difficult to maintain in the lab the free-living nematode Caenorhabditis elegans, widely used as a model in developmental biology, has been selected as tool for the identification of novel anthelmintics and for functional characterization of existing ones. It is planned to perform medium-throughput chemical in vitro screens against C. elegans in order to identify novel anthelmintic scaffolds and synthetic lethal compounds against drug-resistant nematodes.

The three main mycobacterial pathogens, Mycobacterium tuberculosis, M. leprae and M. ulcerans are the etiologic agents of the human diseases tuberculosis, leprosy and Buruli ulcer. It is envisioned that these pathogens will all be studied at different stages of the collaboration between EPFL and Swiss TPH.

Facilitated by access to the BSL3 laboratories at the GHI, a mouse model for Buruli ulcer has been successfully set up. It is now used to study immune responses to M. ulcerans infection and the assessment of vaccine candidates.

An innovative approach aiming to develop tools and methods for the comparative evaluation of candidate small molecules for docking into the binding site of drug target enzymes by engaging volunteer users and their computers has been initiated. As first targets kinases of the malaria parasite Plasmodium falciparum have been chosen.

Welcome To Our New Collaborators!

Michele De Palma
Assistant Professor

Former Home Institution
San Raffaele Institute, Milan
EPFL School of Life Sciences (ISREC) since July 2011

Keywords
Macrophage heterogeneity, tumor angiogenesis, Angiopoietins, microRNAs, targeted gene delivery, tumor-infiltrating monocytes

Jacques Fellay
Swiss National Science Foundation Professor

 Former Home Institution
Duke University, Durham
EPFL School of Life Sciences (GHI) since April 2011

Keywords:
Human genomics of infectious diseases, viral-host interactions, translational genomics

Oliver Hantschel
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ISREC Foundation Chair in Translational Oncology

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Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna
EPFL School of Life Sciences (ISREC) since March 2011

Keywords:
Translational Oncology, Tyrosine Kinase Signaling

Etienne Meylan
Swiss National Science Foundation Professor

Former Home Institution
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EPFL School of Life Sciences (ISREC) since April 2010

Keywords:
Lung cancer, NF-kappaB, glucose metabolism, mouse models
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