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THE CENTER FOR INTEGRATIVE GENOMICS (CIG) AT A GLANCE

The Center for Integrative Genomics (CIG) is a department of the Faculty of Biology and Medicine (FBM) of the University of Lausanne (UNIL). Its main missions are to pursue cutting edge research, to deliver the highest quality teaching to students, and to inform the public at large. It encompasses 14 research groups working on genome structure and function using a large number of techniques and experimental systems, as well as two core facilities dedicated to providing the latest equipment and knowledge in genomics and proteomics to researchers at the UNIL and beyond (see chapter “core facilities”). The CIG research groups are involved in numerous collaborative research projects and programs both within Switzerland and at the international level (see chapter “research”).

To train tomorrow’s scientists, CIG members are involved in the teaching program of the UNIL and contribute to developing new education programs. The Center proposes seminars, lectures, and scientific meetings for the scientists of the Lemanic region and beyond. Moreover, its members organize and actively participate in activities geared to the public at large (see chapter “education”).

The CIG is currently composed of more than 200 members originating from some 30 different countries, who together contribute to the development of its research, its core facilities and its educational activities (see chapter “people”).
From the perspective of the Scientific Advisory Committee (SAC) the CIG continues to be an increasingly dynamic presence within the Swiss and the international scientific communities. During the last several years the ties between the CIG, the UNIL and other scientific institutions in Switzerland have been strengthened as CIG faculty play teaching and administrative roles within the UNIL community and as the CIG collaborates in numerous multi-institute initiatives. A noteworthy example is the new UNIL/CIG/Swiss Institute for Bioinformatics/Vital IT doctoral program in Integrative Experimental and Computational Biology (IECB) with its aim to train a new generation of biologists proficient in both laboratory benchwork and computational analysis.

The CIG continues to appoint and promote faculty of the highest caliber and to recruit first-rate trainees to its laboratories. The SAC considers the diversity of the scientific programs within the CIG to be one of its major strengths. Research in contemporary biology has become increasingly multi-disciplinary and the diverse programs of the CIG foster interactions between fields and unexpected synergies between laboratories as well as providing a unique training environment for graduate students and postdoctoral fellows. The shared-use core facilities required to support these diverse research technologies (e.g. Protein Analysis, Genome Technologies) appear to be up-to-date, well-managed, and widely-used by the CIG and UNIL departments.

During our last visit in June 2012 the SAC met with the CIG leadership, the Dean of the Faculty of Biology and Medicine, technical staff, administrators and assistants (graduate students and postdoctoral fellows). We noted that a number of issues raised during previous visits, primarily concerning the desire for increased involvement of assistants, administrators and technical staff in decision making processes at the CIG, are being satisfactorily addressed. In addition avenues for more open communication have been established and an ombudsman has been appointed to help resolve issues arising among assistants and faculty. Moreover, the director and faculty have approved implementation of a rigorous faculty review plan that will continue to ensure allocation of space and resources based primarily on scientific excellence.

While the CIG is clearly capable of building on its considerable strengths, it nonetheless faces a number of challenges in the near future. For example, hiring and promotion of CIG faculty and the launching and maintenance of new scientific initiatives will require increased, and relatively stable, financial support from both external funding sources and the UNIL. In addition, it will be important for the institute to become more proactive in identifying future employment opportunities for talented CIG postdoctoral fellows and graduating students especially given the limited number of available academic positions. Increasing interactions with the biotechnology and pharmaceutical industry may be useful in this regard and additionally provide avenues for translation of basic science discoveries.

Overall, the Advisory Committee views the CIG as a vibrant and collegial institution that has succeeded in attracting excellent scientists at every career level.

Robert N. Eisenman
President the Scientific Advisory Committee
How to ensure that a department remains highly productive and competitive? In my last director’s report, I wrote about the CIG considering implementing some form of faculty evaluation process. This is now set and done! The CIG faculty has voted favorably on a proposal for a review, every five years, of its tenured professors, based on letters from external experts and a formal review by the CIG Scientific Advisory Committee, with consequences on space and resources. This is an impressive illustration of the dedication of the CIG faculty, who accepted to be regularly reviewed with the goal of allowing the CIG to use its resources in the best possible way in the long term.

Evaluation of tenured faculty is an important tool in keeping a department dynamic, but there is a second, at least as important and perhaps even more important, way to prevent stagnation, which has to do with hiring and promotions. A standard career path for a successful academic research scientist goes something along these lines: as a student, one learns how to perform research, and as a post-doctoral fellow, one learns how to develop and direct one’s own research project, with which one can obtain an independent position. As a young assistant professor, one demonstrates the skills required to build one’s own research group and thus to oversee several research projects that, ideally, synergize with one another. As an associate professor, one can continue developing one’s research group, often with more means than as an assistant professor. Already however, one spends time contributing to the running of the institution, a tendency that increases as a full professor, with the price that one has less time to follow research projects on a day-to-day basis. The important concept here is that when one does well, there is a possibility to climb the ladder and to evolve in one’s career.

It is incredibly important that young people joining a department be assured that, if they deserve it, they can progress in their career, i.e. they can be tenured and then promoted. Promotions should be based on performance, not on the number of years one has spent in a particular position, not on age (neither too old or… too young!), and certainly not on departmental budgets. This is important not only to maintain the motivation of faculty already in the department, but also to attract new young faculty, who want to know that they are joining a meritocracy– that, if they do well, their accomplishments will be recognized.

The counterpart of endorsing faculty promotions when deserved is that retiring associate and full professors should not be replaced by associate or full professors, as is often the case in Swiss universities, but, except in exceptional circumstances, by tenure-track assistant professors. Indeed, this is the only way to maintain a department with faculty at all career stages and with the accompanying diversity of skills, from a focus on outstanding research to broader academic service. Thus, this system avoids the sclerosis of a department where departing senior faculty are replaced by senior faculty, and where deserving junior faculty stay for too many years in the same position because of considerations external to their merit.

Nouria Hernandez, CIG Director
An important event was the retirement of the founding Director of the CIG, Professor Walter Wahli, which was marked by the 2012 CIG symposium being held in his honor. For this occasion, we had the privilege to have Sir John B. Gurdon not only give a talk to his colleague biologists but also deliver the John Grace Lecture to a laypeople audience, this a few months before winning the Nobel Prize in Physiology or Medicine!

Professor Walter Wahli has had a remarkable scientific career, with numerous achievements both in research and in the support of science, the CIG being perhaps the most remarkable example of the latter. Fortunately for the advancement of research, Professor Wahli, although retiring from the University of Lausanne, is continuing his activities as a Visiting Professor at the Lee Kong Chian Medical School, the joint medical school being developed by Imperial College London and Nanyang Technological University (NTU) in Singapore. There he will contribute to the development of one of the three main topics of the school, metabolism and metabolic diseases. We are excited that the first Honorary Professor of the CIG thus provides a “direct” link between the CIG and the Lee Kong Chain Medical School, and we wish Professor Walter Wahli the very best for this new endeavor.

**Highlights of 2011-2012**

<table>
<thead>
<tr>
<th>2011</th>
<th>2012</th>
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<tr>
<td>R. Benton is elected EMBO Young Investigator</td>
<td>R. Benton receives the 2012 Friedrich Miescher Award</td>
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<td>A. Reymond receives a SNSF Sinergia grant</td>
<td>Genomics Days at the Genopode</td>
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<td>(principal investigator)</td>
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<tr>
<td>Genomics Days at the Genopode</td>
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<tr>
<td>A. Reymond receives a SNSF ProDoc grant Research</td>
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<tr>
<td>R. Benton receives a HFSP young investigator grant</td>
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<td></td>
<td>R. Benton receives the 2012 AChemS Young Investigator Award</td>
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<td>for research in olfaction</td>
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<td></td>
<td>I. Xenarios presents his “leçon inaugurale” as full Professor ad personam at the CIG</td>
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<td>May</td>
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<td>5th CIG symposium “Genetics of Behaviour”</td>
<td>M. Tafti receives the foundation NRJ award</td>
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<td>2nd Grace lecture, by Ralf Greenspan</td>
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<tr>
<td>W. Wahli receives the FBM Lifetime Achievement Award</td>
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<td>W. Herr receives the first FBM Jürg Tschopp Life Science Award</td>
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<tr>
<td>R. Benton receives the FBM Basic Life Science Research Award</td>
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<tr>
<td>C. Fankhauser presents his “leçon inaugurale” as full Professor</td>
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<td>July</td>
<td>W. Wahli becomes vice-president of the Swiss Science and Technology Council</td>
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<td>Third visit of the CIG Scientific Advisory Committee</td>
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<td>6th CIG symposium “Transcription, from development to nutrigenomics”, in the honor of W. Wahli</td>
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<td>3rd John Grace lecture by John Gurdon</td>
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<td>August</td>
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<td>P. Franken receives a SNSF Sinergia grant (with B. Thorens and I. Xenarios (CIG), and J. Auwerx (EPFL))</td>
<td>R. Benton becomes Associate Professor</td>
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<tr>
<td>D. Gatfield receives a Fondation Mercier pour la Science award</td>
<td>CIG annual retreat</td>
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<td>CIG annual retreat</td>
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<tr>
<td>M. Tafti presents his “leçon inaugurale” as full Professor</td>
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<td>October</td>
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<td>L. Michalik receives a UNIL Medical Teaching Award</td>
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<td>November</td>
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Richard Benton
Associate Professor

For several hundred million years, animal brains have undergone remarkable diversification in their structure and function, as these biological information processors are challenged and optimised (through natural selection of their organismal hosts) by the demands placed upon them in the ecological niche in which they operate. My group is interested in defining the genetic mechanisms and environmental driving forces underlying neural evolution.

We study the Drosophila olfactory system, a well-described and rapidly evolving sensory system in a genetically accessible model organism. Furthermore, genomic and genetic access to closely-related, but ecologically diverse, drosophilids and more distant insect species provides an unparalleled foundation for comparative genetic and functional analysis of their olfactory circuits. We take an interdisciplinary approach to this problem, combining bioinformatics, molecular genetics and cell biology, neurophysiology and behavioural analysis. Understanding how and why particular olfactory molecules, circuits and behaviours have evolved in Drosophila will, we believe, yield general insights into the mechanisms of, and constraints on, brain evolution.

Our recent focus has been the Drosophila olfactory subsystem expressing the ionotropic Receptors (IRs), a divergent, chemosensory subfamily of the synaptic ionotropic glutamate receptors. This model has proven to be fertile ground for illuminating the evolution of chemosensory systems and stimulated diverse, new questions that start to address the mechanistic basis by which changes in these sensory circuits have come about and the selective pressures that have favoured these adaptations.

COMPARATIVE GENOMICS OF OLFACTION

We have performed comprehensive bioinformatic analyses of the IR repertoires in animal genomes to reveal the evolutionary origin, expansion and diversification of this family of chemosensory receptors, and how this relates to individual species’ chemosensory ecology. These analyses have provided an essential foundation for comparative functional studies of both the Drosophila olfactory subsystems (expressing Odorant Receptor (OR) or IR repertoires) and individual IR olfactory pathways.

MOLECULAR BIOLOGY OF ODOUR DETECTION

Through electrophysiological and cell biological approaches in vivo and heterologous cells, we have studied IR complex formation and stoichiometry, and their trafficking, ion conduction and ligand-recognition properties. Our results provide insights into the conserved and distinct architecture of these chemosensory receptors and their synaptic ancestors. In current work, we collaborate with structural biologists to visualise the three-dimensional organisation and dynamics of the apo and odour-bound IR ligand-binding domain by X-ray crystallography and Nuclear Magnetic Resonance to understand the molecular basis and evolution of their odour recognition properties.

Comparative analysis of chemosensory circuits

We have completed a comprehensive neuroanatomical and physiological analysis of the IR olfactory circuits, in which we have identified odour ligands and central circuit organization for the vast majority of IR olfactory pathways. By comparing our findings with the properties of OR circuits, we can begin to explain how and why two complementary olfactory subsystems have evolved in insects. Recently, we have shown that a large number of IRs are selectively expressed not in the olfactory system, but in small subpopulations of neurons in peripheral and internal gustatory neurons, suggesting roles for these receptors in taste detection and internal food assessment. We are currently defining the ligands detected and behaviours controlled by these sensory pathways.

Behavioural functions of IR circuits

We have used simple odour preference assays to define the innate behaviours mediated by IR pathways. We have also analysed social behavioural functions of IRs, prompted by our observation that one drosophilid-specific receptor, IR84a, is expressed in a population of neurons implicated in control of sexual behaviours. We showed that IR84a is essential to promote male courtship of females. Surprisingly, this receptor detects food-derived odours and not fly-derived pheromones. Our results suggest a model in which IR84a has evolved in drosophilids to co-ordinate feeding site selection and reproductive behaviours. This model can explain the long-standing observation that drosophilid fruit flies breed almost exclusively on their food substrates and highlights a direct sensory mechanism in which a species uses an environmental “aphrodisiac” to promote sexual behaviours. Current efforts are directed towards development of novel behavioural assays in which we can precisely control the temporal pattern of odour stimuli, and video-track single or groups of flies in a high-throughput manner. These technical advances are allowing us to describe previously unobservable olfactory-mediated behaviours.

Olfactory circuit evolution

Much of our current work focuses on obtaining mechanistic evolutionary explanations for the organisation and function of the extant Drosophila olfactory system. Through comparative transcriptomics of OR and IR subsystems, as well as individual olfactory pathways within these subsystems, we aim in the future to identify and characterise loci that have driven the developmental and functional diversification of these olfactory circuits. In addition, we are expanding our efforts to genetic, physiological and behavioural analysis of drosophilid species that have distinct chemosensory preferences to D. melanogaster, to identify the genetic basis of their ecologically-important olfactory adaptations.

Richard Benton received his PhD in 2003 from the University of Cambridge for work on the molecular mechanisms of cell polarisation with Daniel St Johnston at The Wellcome Trust/Cancer Research UK Gurdon Institute. For his post-doctoral research, he joined Leslie Voss’s laboratory at The Rockefeller University, New York, studying the molecular biology of odour detection in Drosophila, during which he was supported by fellowships from the European Molecular Biology Organisation and the Helen Hay Whitney Foundation. He joined the Center for Integrative Genomics in September 2007 as Assistant Professor and was awarded a European Research Council Starting Independent Researcher Grant in 2008. He was the winner of the 2009 Eppendorf and Science Grand Prize for Neurobiology. In 2012, he was promoted to Associate Professor and was elected to the EMBO Young Investigator program. He was also the recipient of the 2012 Fried-rich Miescher Award and the Achens Young Investigator Award for research in olfaction 2012.

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starting independent researcher grant
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Human Frontier Science Program (HFSP)
• Young investigator grant
• Long-term fellowship to P. Ramdya
Novartis Foundation for Biomedical Research
Federation of European Biochemical Societies (FEBS)
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Networking activity of nuclear receptors during development and in adult metabolic homeostasis

As they mediate intracellular hormone action, nuclear receptors play a crucial multi-faceted role in coordinating growth during development, and homeostasis at adult stage. Among them, the peroxisome-proliferator activated receptors (PPARs) have an integrative role in controlling the expression of genes regulating the storage, mobilization, and/or utilization of lipids.

Our activities have been centered on revealing and understanding at the molecular levels the phenotypic expressions of PPAR mutations in mice, taking them as leads to explore the physiopathological signiﬁcance and novel therapeutic advances that PPARs carry. In the last two years, we have focused our efforts on two axes. First we used our newly obtained PPARgamma null mice to explore the multifaceted consequences of lipodystrophy, revealing some key paracrine activity of the adipose tissue during development. Second we explore the liver transcription factor network that drives metabolic homeostasis in the adult organism.

**AXE 1: A NEW MODEL OF PPARGAMMA NULL MICE**

The effect of PPARgamma global deletion was not addressed so far because of embryonic lethality due to a placenta defect. In our laboratory, we recently created a new generalized PPARgamma-/- mouse model by preserving PPARgamma expression in the trophoblastic cells.

In accordance with the requirement of PPARgamma for adipocyte differentiation, PPARgamma-/- mice are totally deprived of white and brown adipose tissue. This generalized lipodystrophy provoks in PPARgamma-/- mice an insulin resistance, starting at 4 to 5 weeks of age followed by a severe type 2 diabetes (T2D) associated to metabolic inflexibility. In parallel, an advanced form of diabetic nephropathy develops, with a severe glomerular phenotype. Finally, the liver undergoes an important and spontaneous hepatic steatosis, accompanied by increased cell proliferation. Thus, PPARgamma null mice represent a formidable tool for gaining insight into the mechanisms underlying the pathogenesis of different metabolic disorders that accompanied T2D, such as metabolic inflexibility, diabetic nephropathy and steatohepatitis, for which little “in vivo” models are satisfactory.

PPARgamma null mice allowed us to demonstrate the crucial role of paracrine activities of the adipose tissue. First in the skin, where we demonstrate that the lack of sub-cutaneous adipose tissue provokes a delay in hair morphogenesis and we are now searching the adipocyte-generated paracrine signal that acts onto hair follicle initial development. Around 5 weeks, a phenotype of cicatricial alopecia developed, but this is now due to the lack of PPARgamma in the hair follicle cells, and more particularly in sebocytes. Second in the bone marrow niche, where we show that the absence of adipocytes in the bone marrow itself promotes myelopoiesis and derepresses osteoclastogenesis. Consequently, higher activity of osteoclast altered the stem cell niche and causes a severe cortical porosis in midshaft of long bones. Deletion of PPARgamma also activates LT-HSC differentiated into multi-potential progenitors and mobilizes progenitors into circulation.

**AXIS 2: NUCLEAR-RECEPTOR REGULATORY NETWORK IN LIVER METABOLISM**

The study of the metabolic regulations has long been focused on mechanisms affecting the rate-limiting steps along a given pathway. However, metabolic homeostasis relies on the cross talk between various regulatory pathways. We thus now shifted our exploration towards understanding the role of the nuclear receptors within regulatory networks focusing in the liver, which is the main metabolic organ with respect to energy homeostasis.

In a first project, we explore a subset of nuclear receptors –LXR, FXR, PPARalpha, HNF4 and PXR– in highly differentiated human liver cells. Global gene expression analyses in response to metabolic signals surprisingly revealed that only a small set of differentially expressed genes are shared by the different nuclear receptors studied, whereas GSEA analyses conﬁrmed the important overlap at the pathway level. We are now working on modeling the results, integrating our experimental data into a rebuilt in-silico model of the known interactions between the investigated pathways (see Figure).

The second project along this axis is linked to the SystemsX project CycliX, where we explore how the transcription factors interplay coordinate cell, nutrition, and circadian cycles. Our group focused on exploring the sterol regulatory element binding protein 1 (SREBP1) activity, which is both nutrient-responsive and inﬂuenced by the circadian clock. We evaluated by ChIP-seq SREBP1 binding around the clock, in the liver of wild type mice. The binding of SREBP1 to its target regions showed an oscillatory proﬁle, with a maximum around ZT18, which is consistent with the maximum of RNA expression and nuclear localization of the protein. However, one subgroup of target genes has an expression proﬁle that is strictly following SREBP1 binding, whereas two other subgroups have a temporal expression proﬁle different from SREBP1 association. Thus other transcription factors –linked to circadian expression since in Bmal1KO mice the expression of all SREBP1 target genes are synchronized and follow SREBP1 binding– participate in the regulation of these genes. Thus, our results deﬁne SREBP1 binding pattern in the physiological context of both rhythmic food absorption and circadian rhythm and they give the ﬁrst tools to comprehensively explore how SREBP1 activity is connected to circadian-driven regulatory events.
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The model of the hepatic nuclear receptor network was built based on data available in the literature. Green rectangles represent different stimuli that can influence the activity of distinct nuclear receptors (violet rectangles), which in turn regulate the transcription of a number of target genes (ellipses of arbitrary colors). The behavior of the network is then compared with experimental data, obtained from microarray analysis of gene expression in human hepatic cells, treated with the same stimuli.

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Almost all our food, feed, fuel and fiber ultimately derive from plants. Plant growth depends on photosynthesis, the process in which light energy is harnessed for the synthesis of high-energy carbon compounds. In order to capture light, plants have evolved unique ways of building cells, tissues and organs, a highly diverse metabolism, and a life-long continuation of versatile growth and development. Plants possess numerous photoreceptors enabling them to sense changes in the amount, spectral composition, photoperiod and direction of light. The main goal of our research is to understand how light modulates plant growth and development allowing these sessile organisms to optimize their growth habit depending on the environmental conditions. We use the model plant *Arabidopsis thaliana* and concentrate on two specific light responses: the shade avoidance syndrome and phototropism.

In crowded environments light becomes a limiting resource. Plants sense foliar shade from competitors primarily using phytochrome (phy) photoreceptors to initiate the shade avoidance syndrome. Phytochromes are synthesized as Pr (red-light absorbing). Upon light excitation they are photo-transformed into Pfr (far-red-light absorbing), which is the active conformer that is converted back into the inactive Pr by far-red light. In direct sunlight phytochrome phyB is mostly in its active conformation and inhibits the shade avoidance response. Foliar shade is poor in red light and rich in far-red light leading to inactivation of phyB, which triggers the shade avoidance syndrome. phyB activity is partly mediated by the conformation-specific interaction between Pfr and a family of bHLH class transcription factors known as PIFs (Phytochrome Interacting Factor). We are studying this signaling cascade to understand how a change in the light environment leads to PIF-regulated growth and development.

Phototropism is a directional growth response enabling plants to optimally position their photosynthetic organs (leaves). Phototropin photoreceptors (phot1 and phot2 in *Arabidopsis*) sense light direction to initiate phototropism. These light sensors also control leaf flattening, chloroplast movements and opening of stomata (pores on leaves regulating gas exchange) and thereby contribute to the optimization of photosynthesis. Phototropins are blue-light activated protein kinases composed of two light-sensing LOV (Light Oxygen Voltage) domains and a carboxy-terminal protein kinase domain. We study signal transduction mechanism leading from photoreceptor activation to phototropin-mediated growth responses (phototropism and leaf positioning). These two processes require the PKS (Phytochrome Kinase Substrate) proteins that act early in this signaling cascade and are one focus of our studies.
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- SystemsX.ch
  - RTD project “Plant Growth in Changing Environment”
  - iPhD project (co-principal investigator)

European Commission
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Genetics and energetics of sleep homeostasis and circadian rhythms

In the study of sleep two main regulatory processes have to be considered: a homeostatic process that is activated by and counters the effects of sleep loss and a circadian process that determines the time-of-day sleep preferably occurs. The fine-tuned interaction between the two permits us to stay awake and alert throughout the day and to remain asleep at night. To gain inside into the molecular correlates of the homeostatic process and its interaction with the circadian process we apply a combination of forward, molecular, and reverse genetic approaches in the mouse. Moreover, we have implemented a variety of novel tools and techniques that, e.g., allow us to follow metabolic state over the circadian cycle in individual cells, to image clock gene expression in the mouse in vivo, and to mathematically predict the impact of sleep, waking, and stress on gene expression.

GENETICS OF SLEEP

We use Quantitative Trait Loci (QTL) analysis as a forward genetics tool to map genomic regions that regulate sleep or brain activity as quantified by the electroencephalogram (EEG). The first mouse genetic reference population (GRP) we phenotyped was a panel of recombinant inbred (RI) lines derived from the two strains C57BL/6J and DBA/2J (referred to as the BXD panel). The analyses revealed several genomic regions affecting sleep and EEG traits. Especially EEG traits were found to be under strong genetic control. Thus far, we successfully identified the genes modifying two such traits thereby implicating novel signaling pathways involved in rhythmic brain activity. We now have initiated two more large scale (and longer term) projects to phenotype and QTL map sleep traits in mice. In a first project we use the genetically diverse CFW-outbred mice in an approach similar to a genome wide association study (GWAS) in humans. Of the planned total of 3’000 CFW mice to be phenotyped and genotyped, an approximate 700 have meanwhile passed through the phenotyping pipeline. We employ a novel, non-invasive, and high throughput method to measure sleep, which we helped develop. In a second project, we will further exploit the BXD panel, which has been extended by some 70 new lines, with emphasis on sleep and metabolic phenotypes. Finally, at a European level we recently launched a COST action (“SYSGENET”) to establish a systems genetics network for the study of complex genetic human diseases using mouse GRPs. A specific aim is to house and make available the ‘Collaborative Cross’ GRP in Europe. The Collaborative Cross is a panel of several hundred RI lines derived from eight inbred lines, which will be a particularly powerful community resource to map complex traits.

CLOCK GENES & SLEEP HOMEOSTASIS

Although the circadian and homeostatic processes are thought to operate independently, using reverse (knock out) and molecular genetic (qPCR, micro-array, miRNA arrays) approaches, we found that the genes known to set circadian time (referred to as clock genes) are also involved in the homeostatic regulation of sleep. Thus, in mice lacking one or a combination of two of the core clock components (e.g. Clock, Npas2, Bmal1, Cry1, and Cry2) sleep homeostasis is altered. We also showed that the expression of the clock genes Per1 and Per2 in the forebrain is tightly linked to the prior sleep–wake history. Thus contrary to the prevailing notion that circadian and homeostatic processes are separate, at a cellular level, the same molecular circuitry seems to be implicated in both circadian rhythms and sleep homeostasis. We now focus on the mechanisms that link clock gene expression to time-spent–awake. The observation that the transcriptional activity of CLOCK and NPAS2 depends on and affects intracellular energy charge is an exciting first clue because this would represent a direct molecular link between cellular metabolism and the need for sleep. We are currently investigating this issue at the cellular level using redox–sensitive GFP probes. We have previously established that the sleep–wake dependent changes in Per1 and Per2 are, in part, mediated by their transcriptional regulator NPAS2. Using chromatin immunoprecipitation (ChIP) analyses we now could demonstrate that sleep loss reduces the binding of NPAS2 to the E-boxes of specific target genes. Moreover, we discovered that corticosterone importantly contributes to the transcriptome changes in the brain after sleep loss and that of the Period genes in particular. Using mathematical modeling we were able to quantify the complex relationship between changes in clock gene expression in the forebrain, the sleep–wake distribution, and circadian corticosterone levels. Model predictions are useful in helping to design relevant experiments to unravel these non-linear relationships.
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Molecular mechanisms of circadian gene expression

Virtually all organisms on earth have developed endogenous time-keeping systems, known as circadian clocks, that allow anticipating daily changes in the environment. In mammals, circadian clocks coordinate the daily timing of vital processes such as sleep-wake cycles, locomotor activity, heartbeat, blood pressure, renal plasma flow, body temperature, and the secretion of many hormones. Most of these physiological parameters remain rhythmic even when organisms are exposed to constant environmental conditions, indicating that their timing is indeed controlled by an endogenous circadian pacemaker.

The overall goal of the projects in our lab is to understand the molecular mechanisms underlying circadian rhythmicity and rhythmic gene expression. Over the last two decades, impressive progress has been made in identifying genes and proteins that function within the mammalian rhythm-generating core clock circuitry. Genetic and biochemical studies have thus led to a molecular model according to which transcriptional activators and repressors are organized in negative feedback loops that constitute the clock’s basic rhythm-generating architecture. Core clock transcription factors such as CLOCK:BMAL1 or REV-ERB/ROR are also responsible for driving rhythms in clock output gene transcription, thus relaying the clock’s timing information to downstream rhythmic gene expression and physiology. Microarray studies dedicated to the genome-wide detection of oscillating mRNAs have indicated that (depending on the algorithms used for the detection of rhythmic transcripts) around 2-15% of an organ’s transcriptome is under circadian control.

Interestingly, with the exception of post-translational protein modifications that represent a long-standing research focus in the circadian field, the potential contribution of post-transcriptional mechanisms to circadian clock functions has been barely addressed. Most projects in our lab are thus dedicated to uncover how mechanisms acting on the RNA level are implicated in regulating rhythmic gene expression. To this end, we are currently pursuing two main directions: first, we wish to define the role that microRNAs play as regulators of circadian gene expression, and second, we aim to identify RNA binding proteins (RBPs) that carry novel functions in the circadian clock. The mammalian genome encodes for an estimated 800 RBPs and we hope that circadianly relevant RBPs will serve as exciting entry points into new research directions allowing us to define regulatory control mechanisms at various levels of RNA metabolism.

In the long term, we aim to identify novel players and molecular mechanisms that are important for a functional circadian clock and elucidate their roles in regulating circadian physiology and metabolism by molecular loss- and gain-of-functions studies in mice.

By combining molecular genetics, genome-wide studies and biochemistry in mice and cultured cells we are currently addressing the following specific aims:

- Identify the transcripts whose parameters of rhythmic accumulation (e.g. amplitude, phase) are dependent on miRNAs. To this end, we are assembling a transcriptome-wide, time-resolved atlas of miRNA activity in liver by RNA high-throughput sequencing (RNA-Seq). For these experiments, we make use of a mouse model in which miRNA production in hepatocytes can be inactivated. For the most interesting and physiologically relevant miRNA targets identified in the study, we use cell culture systems and reporter assays for follow-up experiments. Eventually, we wish to address the physiological importance of the identified regulatory mechanisms by loss-of-function studies of individual miRNAs in mice.
- Identify RBPs whose loss- and/or gain-of-function affects the activity of the circadian clock in cultured cells. Through such RBPs, we aim to uncover novel molecular mechanisms by which rhythmic gene expression is regulated, occurring potentially on all post-transcriptional levels, from transcription to mRNA splicing, translation, localisation and degradation.
- Develop novel methodology to facilitate the identification of the “client RNAs” that are bound by our RBPs of interest. Our aim is to establish standardized experimental protocols to facilitate the UV-crosslinking and immunoprecipitation (CLIP) of protein-bound RNAs, followed by their identification by high-throughput sequencing. The approaches we are currently testing rely on the in vivo biotinylation of RBPs that are expressed from BAC transgenes, followed by the purification of protein-RNA complexes using the biotin-streptavidin interaction. In collaboration with other groups, we aim to establish similar biotin-tagging tools also to facilitate chromatin immunoprecipitation (ChIP) and phosphorylation site mapping experiments by mass-spectrometry.
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Synthesis of non-coding RNAs by RNA polymerases II and III: mechanisms of transcription regulation

MECHANISMS OF BASAL AND REGULATED RNA POLYMERASE III TRANSCRIPTION IN MAMMALIAN CELLS.

RNA polymerase (pol) III synthesizes all tRNAs, ribosomal 5S RNA, and small RNAs involved in various cellular processes, among them the maturation of other RNA molecules. Pol III is an essential enzyme and is highly regulated in response to various external stimuli such as nutrient availability and stress. Its activity is high in growing and dividing cells, and relatively low in quiescent cells. We seek to understand how pol III transcription is regulated and how its deregulation can affect an organism.

Small nuclear RNA (snRNA) genes encode non-coding RNAs with structural or catalytic functions in various processes such as pre-mRNA splicing and histone pre-mRNA 3' end formation. They form a family of genes with very similar promoter structures, some of which are recognized by pol III and others by pol II. We are interested in characterizing this family of genes and in determining how snRNA promoters achieve specific recruitment of either pol II or pol III.

One of the aspects we have been focusing on is the determination, genome-wide, of the loci occupied by pol III, both in cultured human cells and in a normal tissue. We have also examined, within the human genome, the loci occupied by the snRNA activating complex SNAPc, a factor required for pol II and pol III snRNA gene transcription. These and other results are summarized below.

TERMINATION OF TRANSCRIPTION BY POL III IN HUMAN CELLS

Pol III terminates transcription at runs of four or more T residues. When characterizing genomic sites of pol III occupancy, we noticed that pol III could be detected sometimes quite far downstream of IRNA genes. We thus examined the relationship between location and strength of pol III terminators, and pol III occupancy downstream of annotated tRNA genes. We found that pol III terminators are often located well past the tRNA-coding regions, and that there is considerable pol III read-through at terminators of less than five T residues. We combined these genomic observations with extensive work performed by the group of G. Dieci (University of Parma), leading to an extensive characterization of pol III termination in human cells.

LOCI ASSOCIATED WITH RNA POL III IN MOUSE LIVER

In previous work, we characterized the loci associated with pol III and some of its transcription factors in human cultured cells. We found pol III on known pol III genes as well as on about seventy novel loci of unknown function. We also found that out of 522 human annotated tRNA genes, only about 60% were occupied by pol III. To determine whether this pattern was specific to cultured cells, we localized pol III in a normal tissue, mouse liver. In addition to known pol III genes, about forty other loci, all of unknown function, were clearly occupied by pol III. Moreover, like in cultured human cells, only about 60% of the 433 annotated tRNA genes were occupied by pol III.

To explore why only a subset of tRNA genes are occupied by pol III, we examined correlations with various genomic features and individual gene properties. High pol III occupancy was strongly correlated with the presence of H3K4me3 upstream of the transcription start site and with CpG content, but not with H3K36me3. Further, genes close to pol II-occupied transcription start sites were more likely to be highly occupied by pol III. Genes with optimal A and B box promoter elements and, surprisingly, optimal terminators were more highly occupied by pol III. Thus, multiple factors including genomic environment and features intrinsic to each gene contribute to high pol III occupancy.

CHARACTERIZATION OF POL II AND III SNAPc-BOUND PROMOTERS

The human pol II and III snRNA promoters contain a distal sequence element (DSE) that enhances transcription and a proximal sequence element (PSE) required for basal transcription. In pol III snRNA promoters, there is in addition a TATA box, which determines RNA pol III specificity. The PSE recruits the five-subunit complex SNAPc, one of the few basal factors involved in both pol II and pol III transcription, which nucleates the appropriate preinitiation complex. The DSE often recruits the factors Oct-1 and ZNF143.

Although model snRNA promoters have been extensively studied, it was unclear how broadly SNAPc is used, to what extent the highly similar pol II and pol III PSE-containing promoters are selective in their recruitment of the polymerase, and how generally the use of the basal factor SNAPc is coupled to that of the activators Oct-1 and ZNF143. We localized, genome-wide, four of the five SNAPc subunits as well as pol II and pol III and so defined a set of some seventy SNAPc-dependent transcription units. Although most loci were primarily bound by one or the other polymerase, the RPPH1 (RNase P RNA) gene was occupied by both enzymes. Localization of Oct-1 and ZNF143 showed widespread usage of these activators by PSE-containing promoters, and these activators were recruited in G1 before the polymerase.
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The RPPH1 gene can be occupied by either pol II or pol III. UCSC browser view of the RPPH1 gene showing BRF2 (a pol III transcription factor), GTF2B (a pol II transcription factor), pol III (POLR3D subunit), and pol II (POLR2B subunit), occupancy.

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Two complete sets of instructions contained within the genomes we inherit from our parents are responsible for directing a single cell - the zygote - to become an adult human being. This process results from controlled patterns of gene expression that are maintained as well as changed during many rounds of cell division, differentiation, and death. Control of gene transcription is fundamental to these processes, with genetic and epigenetic defects in transcriptional regulation often leading to human disease including cancer.

HCF-1
To investigate these processes, we study a key regulator of human cell proliferation that is also implicated in embryonic stem cell maintenance and cancer. This protein, called HCF-1 for herpes simplex virus host-cell factor-1, binds to many promoters indirectly by recognizing a large number of site-specific DNA-binding proteins and recruits a plethora of chromatin-modifying activities resulting in both activation and repression of transcription. It also undergoes an unusual proteolytic maturation process that generates two associated HCF-1 subunits that regulate different phases of the human cell cycle: the N-terminal subunit, called HCF-1N, permits cells to progress into S phase for genome replication and the C-terminal subunit, called HCF-1C, is required for proper segregation of the replicated genome into the two daughter cells in M phase.

Over the past two years, we have focused on the mechanisms by which the HCF-1N and HCF-1C subunits are generated and maintained as a heterodimeric complex.

AN ENZYME RESPONSIBLE FOR GLYCOSYLATION GENERATES THE HCF-1N AND HCF-1C SUBUNITS
One of the surprises of the sequencing of the human genome at the turn of the century was the paucity of genes found. This finding gave added emphasis to the importance of the diversity of gene products a single gene can provide. One of these mechanisms is the post-translational modification of proteins, which provides diverse strategies for the control of protein function. Modifications that involve the addition of a chemical group (e.g., phosphorylation) are generally reversible, whereas modification by proteolytic processing is considered irreversible. The cellular O-linked beta-N-acetylglucosamine transferase (OGT) modifies a large number of proteins by the addition of the sugar N-acetylglucosamine (GlcNAc) to serine or threonine residues in the form of O-GlcNAc. We have discovered that OGT is also involved in proteolytic processing as — in addition to O-GlcNAc modification of HCF-1 — OGT is responsible for the generation of the HCF-1N and HCF-1C subunits through proteolysis.

HCF-1 is cleaved at any one of six 26 amino acid repeated sequences called the HCF-1PRO-repeat. OGT binds the HCF-1PRO-repeat and subsequently O-GlcNAcylates the HCF-1C subunit and cleaves the HCF-1N-repeat. This process is critical for HCF-1 function as HCF-1 cleavage via a heterologous signal fails to activate M-phase functions of the HCF-1C-subunit.

To probe the mechanisms of HCF-1 glycosylation and proteolysis, we have performed mutational analyses of both the OGT enzyme and the HCF-1 substrate. These studies have revealed that glycosylation and proteolysis are distinguishable enzymatic properties of OGT and that cleavage of the HCF-1PRO-repeat as well as HCF-1N glycosylation are exquisitely sensitive to the nature of the amino acid — a glutamic acid — at the cleavage site. These studies reveal a novel nexus between protein modification mechanisms — proteolytic cleavage and O-GlcNAc modification of HCF-1 — that provide a link between metabolic regulation by OGT and cell-cycle regulation by HCF-1.

AN INTERDIGITATED FN3 STRUCTURE MAINTAINS HCF-1N AND HCF-1C ASSOCIATION AND FACILITATES TRANSCRIPTIONAL REGULATORY COMPLEX FORMATION
In collaboration with Dr. J.-J. Song of KAIST, South Korea, we have elucidated the 3-dimensional structure of the principal element responsible for HCF-1N and HCF-1C, heterodimer complex formation. This structure represents a stable inter-digitated Fn3 module. Fn3 modules are composed of seven beta strands in a sandwich-like structure; the HCF-1 Fn3 module consists of the stable inter-digitation of three beta strands from the HCF-1N subunit and four from the HCF-1C subunit. We find the inter-digitated nature of this module surprising because, contrary to long-standing beliefs, it suggests that HCF-1N and HCF-1C subunit association is stable in the cell.

HCF-1 was discovered by virtue of its ability to stabilize a transcriptional regulatory complex induced by the viral protein VP16 on herpes simplex virus immediate-early promoters. An additional surprise of the HCF-1N and HCF-1C structural studies is that a nuclear localization signal (NLS) positioned at the C-terminus of HCF-1 stabilizes the VP16-induced transcriptional complex. These unexpected results show that an NLS can have two activities: one for cellular localization and the other for transcriptional regulatory complex formation.
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CAPTION:
Cell

Caption: Cell

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Functional evolutionary genomics in mammals

Around 300 million years ago, mammals arose from ancestral amniotes, the first fully terrestrial group of vertebrates that originated from amphibian predecessors ≈340 million years ago and also includes present-day reptiles and birds along with their extinct kin. Ever since, mammals have evolved shared traits that include lactation, hair and relatively large brains with unique structures, but also distinct lineage-specific anatomical, physiological and behavioral characteristics relating to differences in reproduction, life span, cognitive abilities and disease susceptibility. A central goal in evolutionary biology is to understand how phenotypic differences arise between species, and of particular interest are molecular changes underlying distinct mammalian traits, most notably those of humans. While mutations affecting the sequence of the gene product (i.e., the encoded protein or RNA) may underlie phenotypic innovation, regulatory mutations affecting gene expression probably explain most phenotypic differences between species. Recent technological developments based on high-throughput sequencing technologies now afford genome-wide comparative analyses of transcription and regulatory programs across divergent species.

In 2009, we embarked on a major new series of projects that are related to various aspects of gene expression evolution in mammals and center around integrated comparative analyses of large-scale transcriptomic and genomic data for organs from a wide range of mammalian species and vertebrate “outgroup” species (e.g., birds and amphibians). In the past two years, we have completed and published several initial studies relying on these data. For example, we identified numerous expression changes of protein-coding genes likely underlying mammalian species- or lineage-specific traits (e.g., the complex human/primate brain), and we reconstructed molecular changes associated with the evolutionary origin of our sex chromosomes, such as mechanisms underlying X chromosome dosage compensation (Brawand et al. Nature 2011; Julien et al. PLoS Biol. 2012). We also completed a study pertaining to the birth and expression evolution of microRNA genes in mammals (Meunier et al. Genome Res. 2012). A number of transcriptome evolution studies are under-way, including a study in which we unravel the functional evolution of long noncoding RNA genes across tetrapods.
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Molecular control of skin homeostasis

The skin is the barrier that protects the organism from various insults. Due to its peripheral localization, it is prone to be damaged, for instance by mechanical injury or UV radiations. Damage to adult tissues initiates a cascade of event aimed at restoring the organ function. With a few exceptions, most species including human are only able to repair the injury in a life saving process, which does not replace the damaged organ and leads to scaring. The repair program is largely based on rapid and specific changes in gene expression, and on the secretion of signaling molecules. It involves multiple cell types, cell-cell and cell-matrix interactions. Interestingly, the molecular and cellular mechanisms implicated in repair share many common characteristics with the development of skin cancers, carcinoma (of epithelial origin) or melanoma (of melanocyte origin).

We study the molecular and cellular events involved in the regulation of skin homeostasis and pathologies, along the following axis:

- The control of repair and carcinogenesis by the nuclear hormone receptors PPARs and by miRNA
- The transcriptional control of the skin vascular functions by PPARs

PPARalpha, beta and gamma are nuclear hormone receptors discovered in the early 1990’s, whose major known functions at the time we initiated our study was the regulation of energy metabolism.

Using various mouse lines in which the expression of PPARs is modified, we have observed that skin repair is delayed in the absence of PPARalpha or PPARbeta. We demonstrated that PPARalpha controls the inflammatory reaction during skin healing, whereas PPARbeta, which expression in keratinocytes is regulated by TNFalpha, TGF-beta1 and C/EBP, controls many properties of the keratinocytes that are essential for rapid wound closure (survival, proliferation and migration). PPARbeta also regulates the interactions between the epidermal and dermal compartments, thereby activating hair follicle growth and maintaining a balanced proliferation of the keratinocytes. More recently, in collaboration with the group of W. Wahli (CIG), we obtained data showing that PPARbeta-null mice develop less and smaller skin carcinoma upon UV-exposure. Interestingly, we demonstrated that in the wild-type animals, skin carcinoma formation is favored by PPARbeta, through the activation of the proto-oncogene c-src, the activation of the EGF-R/Erk1/2 signaling pathway and the increased expression of EMT markers in the UV exposed keratinocytes. Whether PPARs are also involved in the development of melanoma is under current investigation.

In addition of orchestrating keratinocyte functions, PPARbeta also regulates skin blood vessel homeostasis. In the adult organism, healthy vessels are quiescent, but remain highly dynamic structures. Vessel permeability is increased in pathological situations such as cancer or anaphylactic shock, and the vasculature is able to repair through angiogenesis after wounding. We have observed striking defects of angiogenesis during skin repair in the PPARbeta-null mice, as well as impaired acute permeability in response to VEGF or histamine treatment. We are addressing the mechanisms by which PPARbeta controls adult skin vessel permeability and angiogenesis.

Finally, based on the evidence that miRNA are important regulators of skin homeostasis, we have recently initiated the study of miRNA importance in skin repair and cancer.

Our projects raise fundamental biological questions of importance in the field of tissue repair and cancer. Answering these questions has and will extend our knowledge of the molecular mechanisms governing these processes. Furthermore, our project is also relevant to the search for innovative therapies. PPARs have already proven to be valuable therapeutic targets in the context of metabolic diseases. Recent advances also suggest that miRNA are targets of choice for therapeutic intervention. Our findings will thus pave the way for future research towards clinical applications in the field of tissue repair and cancer.
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Genome structure and expression

Recent technological advances and the completion of the sequencing of multiple vertebrate genomes have demonstrated that mammalian genomes are more fluid than we had previously anticipated. Our goal is to gain a clearer understanding of how variation, in particular genome rearrangements (copy number variants (CNV), translocations and inversions), influence gene expression and phenotypes. In the laboratory we combine genome analysis, genome annotation, expression studies, cytogenetics and transgenic technologies towards this aim.

THE 16p11.2 REARRANGEMENTS

The 11.2 band of the short arm of human chromosome 16 encompasses several distinct genomic structural variants, including a recurrent interstitial deletion, of a ~600 kb region containing 29 genes. This deletion has a population prevalence of approximately 1/2000, and reaches 0.5% in autism spectrum disorders. It is thus one of the most frequent known single-locus etiologies of neurodevelopmental disorders and ASD. In contrast the reciprocal duplication, which has a similar frequency was associated with schizophrenia. Increased head circumference has also been associated with the deletion, while the duplication is linked to microcephaly. We and others demonstrated that the deletion predisposes to a highly penetrant form of obesity with a 43-fold increased risk to develop morbid obesity. Again, a mirror phenotype is observed in carriers of the reciprocal duplication who are at high risk of being underweight. Modeling in zebrafish allowed to pinpoint that KCTD13, MVP and MAPK3, three genes mapping within the rearrangement interval, epistatically control the head size in teleost fishes.

Thus the rearrangements of the short arm of human chromosome 16 are a unique opportunity to explore molecular, cognitive and behavioral correlates. They are windows to look at the etiology of obesity, its relationship to behavioral or cognitive impairments, and possibly to identify the underlying pathophysiological pathways. They exquisitely demonstrate that rare variants play a role in complex and common traits explaining part of the missing heritability of genome wide association studies.

STRUCTURAL VARIATION AND CHROMATIN

As chromatin structure plays an important role in gene regulation, we anticipate that CNVs will affect the chromatin structure on a large scale, and hence possibly modify the clinical phenotype. However, studies investigating the impact of a structural aberration on long-range chromatin structure have been lacking. To assess the possible mechanism(s) underlying the “neighboring effect” of CNVs, i.e. their influence on the expression of genes that map within their flanks, we compared intrachromosomal interactions and histone modifications in cell lines of patients affected by genomic disorders and control individuals. Using chromosome conformation capture (4C-seq), we observed that a set of genes flanking the Williams-Beuren Syndrome critical region (WBSCR) were often looping together, possibly forming an interacting cluster with each other and the WBSCR. Deletion of the WBSCR disrupts the expression of this group of flanking genes, as well as long-range interactions between them and the rearranged interval. We also pinpointed concomitant changes in histone modifications between samples. We conclude that large genomic rearrangements can lead to chromatin conformation changes that extend far away from the structural variant, thereby possibly modulating expression globally and modifying the phenotype.
Micale L et al. (including Reymond A) (2011) Mutation spectrum of MLL2 in a cohort of kabuki syndrome patients. Orphanet J Rare Dis 6:38
The main interest of our group is directed towards understanding the topological aspects of overall organization of genomes starting with the arrangement of DNA in phage heads and ending with chromosome territories in higher eukaryotes. We try to understand how bacterial topoisomerases actively remove knots from crowded DNA molecules and what are the consequences of so called topological exclusion in shaping chromosome territories. We are also interested in the topological aspects of protein folding with the aim of classification of knotted proteins and understanding of particular advantages provided by knotting of the polypeptide chain. Some aspects of our interests go beyond biology, like for example statistical mechanics studies of knotted polymers or simplification pathways of various knots. However, also these studies have biological or biophysical applications in helping to explain, for example, how DNA topoisomerases can efficiently distinguish knotted DNA molecules from unknotted ones. We also maintain our interest in studies of proteins participating in DNA recombination and DNA repair. During recent years numerical methods used to model behavior of DNA molecules and of chromatin fibers became the main method utilized by our group, although biochemistry and electron microscopy, in particular, remained as an essential part of our research.

ORGANIZATION OF NUCLEAR ARCHITECTURE

We are interested in revealing the underlying physical phenomena responsible for the overall organization of chromosomal territories in interphase nuclei. In particular we try to explain why chromatin fibers belonging to different chromosomes do not intermingle with each other but each forms its own chromosome territory. We try to understand how topological domains are formed and what are the factors that are responsible for high contact frequency between sites belonging to the same topological domain, whereas interdomain contacts are relatively infrequent. We try to understand the mechanism of chromatin insulators such as these provided by CTCF bound to chromatin fibers.

SUPERCOILING AND DNA UNKNOTTING AND DECATENATION

Normal functioning of DNA requires that intermolecular catenation and intramolecular knotting should be quickly resolved by action of DNA topoisomerases. In bacterial cells the level of DNA knotting and catenation is much lower than this resulting from random DNA-DNA passages. The question arises then how DNA topoisomerases are directed to act on DNA-DNA juxtapositions where intersegmental passages specifically lead to unknotting and decatenation rather than to act on juxtapositions where passages can produce knots and catenanes. In bacterial cells the DNA is negatively supercoiled and several earlier reports revealed that DNA supercoiling helps DNA topoisomerases to remove DNA knots more efficiently. To shed light on the role of DNA supercoiling in DNA unknotting, we have modeled knotted DNA molecules that are supercoiled. We observed that supercoiling resulted in very strong localization of knotted portions of the molecules in such a way that the local curvature in the knotted portion was significantly higher than the average curvature in the rest of negatively supercoiled DNA molecules. Since it was known already that type II DNA topoisomerases preferentially bind to DNA portions that are highly curved our result provided the missing link needed to understand how DNA supercoiling directs type II DNA topoisomerases to preferentially act on knotted portions of DNA molecules.

STUDIES OF PROTEIN KNOTTING

The polypeptide chain of some proteins is knotted. In a collaboration project involving mathematicians and biophysicists (Prof. K. Millett, UCSB, USA, Prof. E. Rawdon, Univ. St. Thomas, USA, Prof. J. Onuchic and Dr. J. Sulkowska, UCSD, USA) we analyzed all deposited protein structures for the presence of knots. Our novel form of analysis permitted us to obtain knotting fingerprints of various proteins. We observed that despite large sequence variance the precise knotting pattern is highly conserved within to the same protein family and sometimes the conservation involves separate families. High conservation of knotting patterns naturally suggests that knots in proteins have a unique function that is hard to achieve without knotting. We continue our study aimed to understand the evolutionarily advantage of knotted proteins.

ELECTRON MICROSCOPY STUDIES OF DNA STRUCTURE AND OF PROTEIN-DNA INTERACTIONS IMPLICATED IN THE PROCESS OF DNA RECOMBINATION

In a collaboration project with Dr. T. Lionberger (University of Michigan) we used Cryo-EM to study effects of DNA supercoiling on DNA minicircles. We observed that negative supercoiling in DNA minicircles induces formation of two kinks that are placed 180° apart along the circumference of DNA minicircles. This observation has important implications for gene regulation processes that involve formation of small DNA loops.

Our group has a long time experience in electron microscopy imaging of functional complexes formed with DNA by various proteins.
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Participating in the process of homologous recombination. Our studies contributed in a significant way to understanding the role and the mechanism of action of such proteins as RecA, RuvAB, RAD51, RAD52, DMC1, BRCA2 or FANCM. In a new collaboration project involving group of Prof. J.-L. Viovy (Institut Curie, Paris) we used electron microscopy to complement magnetic tweezers studies of RAD51-DNA complexes, in which the DNA was forced to take different twist values. Our study revealed that two different forms of RAD51-DNA complexes, the stretched and non-stretched form are convertible into each other without protein dissociation. This finding brings us closer to complete understanding of molecular mechanisms by which RAD51 protein mediates homologous pairing and DNA strand exchange during double-strand break repair.

Publications

Witz G, Dietler G, Stasiak A (2011) DNA knots and DNA supercoiling. Cell Cycle 1;10(9)

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Two major projects are underway in my laboratory:

**GENETICS AND CELLULAR BASIS OF SLEEP**

Based on available literature there is no doubt that many aspects of sleep are under a genetic control in both humans and animal models. These include not only the amount and the distribution of sleep but also very specific electroencephalographic (EEG) features of sleep and wakefulness. By using the inbred mouse as a genetic tool, we have been able to demonstrate that sleep as a quantitative trait is amenable to quantitative trait loci analysis (QTL). Although many genes with small effects might affect the amount and the distribution of sleep, some aspects such as the daily amount of paradoxical sleep may be under a major gene control. We have localized such a gene on the mouse chromosome 1 and are currently fine mapping the region to ultimately identify the responsible gene. We have been the first to report that a single gene may dramatically affect the quantitative sleep EEG. Genes regulating the EEG variant (theta) specific to paradoxical sleep, the contribution of slow waves to the sleep EEG, and a major gene involved in sleep need and recovery after sleep deprivation. More recently, we try to establish an in vitro model of sleep amenable to cellular and molecular analyses of sleep. Thalamocortical slices and primary cortical cultures are used in electrophysiology and molecular studies. Finally, we are interested in sleep and circadian rhythms and their molecular basis in social species such as ants.

**GENETICS OF NORMAL SLEEP AND SLEEP DISORDERS**

Little is known about molecular genetics of normal human sleep. We have initiated a large population based study (HypnoLaus) to investigate both normal and pathological sleep. 2000-3000 subjects from the Lausanne population are being recorded in the study. All subjects have been genotyped with hundred of thousands of genetic variants and gave also been investigated for metabolic, cardiovascular (CoLaus), and psychiatric (PsyCoLaus) disorders. This is the largest study ever combining sleep parameters with molecular and other biological variables.

Many sleep disorders run in families but their genetic bases are poorly understood. Our laboratory is specialized in the genetics of narcolepsy and sleepwalking. We perform family- and population-based studies using linkage, candidate gene, and genome-wide associations. We have localized the first familial susceptibility gene for narcolepsy and have reported the first genetic evidence in sleepwalking. More recently we have shown that specific HLA variants are causally involved in the pathophysiology of narcolepsy. Future plans include genome-wide association study in sleepwalking and exome sequencing in narcolepsy.

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**Mehdi Tafti**

Professor

**Genetics of sleep and sleep disorders**

Mehdi Tafti received his PhD from the University of Montpellier (France) in 1991 after completing his doctoral thesis on sleep regulation in human narcolepsy. He performed a postdoctoral fellowship with Dr. Mignot and Dr. Dement and was a Research Associate at the Department of Psychiatry and Biological Sciences at Stanford University. In 1995 he moved to the Department of Psychiatry in Geneva where he established the first laboratory dedicated to the molecular genetics of sleep and sleep disorders. He joined the Center for Integrative Genomics in September 2004 as an Associate Professor. Since November 2006, he is co-directing the Center for Investigation and Research in Sleep (CIG-CHUV). He was promoted full professor in 2011.
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Physiological genomics of energy homeostasis

PANCREATIC BETA-CELLS IN HEALTH AND TYPE 2 DIABETES

Glucose homeostasis is critically dependent on the capacity of the pancreatic beta-cells to secrete insulin according to the metabolic need of the organism. Maintaining glucose homeostasis over a lifetime requires adaptation of the secretion capacity of individual beta-cells as well as a regulation of their total number; impairment of these processes underlies the pathogenesis of type 2 diabetes.

We are continuing the investigation of the role of an autocrine loop that operates in beta-cells and that depends on IGF-2 secretion and IGF-1R activation. This autocrine loop is controlled by, and mediates the effect of the gluco-incretin hormone GLP-1 on beta-cell proliferation, protection against apoptosis, and increased glucose competence. Whereas GLP-1 increases this autocrine loop by enhancing IGF-1R expression, nutrients, in particular glucose and glutamine, increase the biosynthesis of IGF-2 through a translational mechanism that is rapidly followed by IGF-2 secretion via the regulated exocytotic pathway. This autocrine loop is therefore well designed to control beta-cell mass in response to nutrition, but also to insulin resistance. We are now testing the physiological role of this autocrine loop by studying mice with beta-cell-specific knockout of IGF-2, in particular its role in the beta-cell mass adaptation to insulin resistance conditions such as pregnancy.

As part of a European program, we are performing a Systems Biology investigation of beta-cell mass adaptation to metabolic stress. This involves the study of 6 different strains of mice fed two different diets for 4 different periods of time and the mice are extensively phenotyped for glucose homeostasis, islet transcriptomic, and islet and plasma lipidomic. Bioinformatic analysis (collaboration with the Swiss Institute of Bioinformatic) has now generated a new view of the functional modules underlying the adaptation, or failure of beta-cells to the metabolic stress. This new beta-cell functional map forms the basis for functional studies to identify novel regulatory mechanisms that control beta-cell function and sites of intervention for the treatment of diabetes.

BRAIN GLUCOSE SENSING AND CONTROL OF GLUCOSE HOMEOSTASIS

The brain critically depends on glucose as a source of metabolic energy and several areas, in particular the hypothalamus and brainstem, contain glucose sensitive neurons that control glucose and energy homeostasis. It is important to identify the cells involved in glucose sensing, the molecular mechanisms they use to sense glucose, and the circuits they form to control these homeostatic functions.

We are identifying glucose sensitive neurons that express the glucose transporter isoform Glut2, which is also required for glucose sensing by pancreatic beta-cells. Using mice that express a highly fluorescent protein in Glut2 neurons we have demonstrated that Glut2 neurons of the tractus solitarius (NTS) are activated by hypoglycaemia, through a glucose metabolism-dependent signalling pathway that controls a potassium conductance. These are GABAergic interneurons, which project to the dorsal motor nucleus of the vagus, suggesting a link between hypoglycaemia detection and control or parasympathetic nerve activity.

In parallel, we are investigating the physiology of mice with brain-specific Glut2 inactivation. We found that central Glut2 is required for the control by glucose of both the sympathetic and parasympathetic nerves. A major defect in these knockout mice is a defect in beta-cell mass expansion during the postnatal period, leading to reduced beta-cell mass in the adults. This leads to late onset of glucose intolerance due to defect in glucose-stimulated insulin secretion, a pathogenic mechanism that is precipitated by high fat diet feeding. Thus, we have identified a functional link between central glucose-dependent control of autonomic innervation and the long-term control of glucose homeostasis through a regulation of beta-cell mass in the perinatal period.

LIVER LIPID METABOLIC PATHWAYS AND LIVER FAILURE

We have previously linked the peroxisomal enzyme L-PBE with liver inflammation and steatosis. We have now characterized mice with genetic inactivation of this gene. These mice have no phenotype when fed a normal chow diet, but die of liver failure in 2-3 weeks when fed a coconut oil-, but not a lard-enriched diet. Lipidomic, transcriptomic, as well transcription reporter assays have revealed that the liver failure was caused by the loss of a mechanism that adapts the liver to medium chain fatty acid ingestion. This mechanism depends on lauric acid induction of microsomal omega-oxidation and the production of dicarboxylic fatty acids. These activate PPARalpha- and PPARdelta-dependent induction of all the beta- and omega-oxidation pathways to ensure fast and efficient degradation of medium chain fatty acids. However, whereas in normal conditions dicarboxylic fatty acids are degraded by L-PBE, the absence of this enzyme prevents this negative feedback mechanism leading to dicarboxylic fatty acids accumulation to toxic levels inducing liver failure.

Bernard Thorens received his PhD from the University of Geneva for studies on the biosynthesis of immunoglobulins in pre-B lymphocytes. He then did a first postdoctoral fellowship in Geneva working on hematopoietic growth factors with Pierre Vassalli. In 1986 he moved to the Whitehead Institute for Biomedical Research in Cambridge (USA) for a postdoctoral fellowship in Harvey Lodish laboratory. In 1991 he came back to Switzerland to take a Career Development award from the SNSF and to establish his laboratory at the Department of Pharmacology and Toxicology at the UNIL. He then became Full Professor in the Physiology Department and joined the Center for Integrative Genomics in 2005.
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The multifaceted roles of PPARs and micronutrients in health and disease

Among nuclear receptors, peroxisome proliferator activated receptors (PPARs) are of special interest. Indeed, they are currently drug targets in a variety of human diseases, such as dyslipidemia and Type 2 diabetes, and they represent promising targets in various inflammatory processes (fibrosis, atherosclerosis, skin inflammation) as well as in cancer. The PPAR family consists of three isotypes encoded by three distinct genes, PPARalpha (NR1C1), PPARbeta/delta (NR1C2), and PPARdelta (NR1C3). PPARs exhibit a broad but isotype-specific tissue expression pattern, which can account for the variety of cellular functions they regulate. At the time they were identified, in the early 1990s, no endogenous ligand was known to activate them, but since then a number of lipid derivatives, mostly fatty acids, leukotrienes and prostaglandins, have been proposed to be endogenous ligands for PPARs. In addition, pharmaceutical companies have developed many high-affinity synthetic ligands that are selective for each PPAR isotype and have proven to be very useful for basic research.

In the past two years, we have analyzed diverse functions of PPAR-beta/delta using different experimental models. PPARbeta/delta protects against obesity by reducing dyslipidemia and insulin resistance via effects in muscle, adipose tissue, and liver. However, its function in pancreas remained ill defined. To gain insight into its hypothesized role in beta cell function, we specifically deleted PPARbeta/delta in the epithelial compartment of the mouse pancreas. Mutant animals presented increased numbers of islets and, more importantly, enhanced insulin secretion, causing hyperinsulinemia. Gene expression profiling of pancreatic beta cells indicated a broad repressive function of PPARbeta/delta affecting the vesicular and granular compartment as well as the actin cytoskeleton. Analyses of insulin release from isolated PPARbeta/delta-deficient islets revealed an accelerated second phase of glucose-stimulated insulin secretion. These effects in PPARbeta/delta-deficient islets correlated with increased filamentous actin (F-actin) disassembly and an elevation in protein kinase D activity that altered Golgi organization. Taken together, these results provide evidence for a repressive role for PPARbeta/delta in beta cell mass and insulin exocytosis, and shed a new light on PPARbeta/delta metabolic action.

PPARbeta/delta is also involved in tissue damage repair. Repeated and/or chronic liver injury exacerbates wound healing and tissue remodeling processes, leading to progressive fibrosis and, ultimately, end-stage cirrhosis. It is worth to note that chronic liver disease represents an important cause of mortality and morbidity. Our study focused on the role of GW501516-activated PPARbeta/delta in mouse liver fibrosis after long-term CCl4 induced injury. We found that GW501516 treatment enhanced the fibrotic response. Compared to the other experimental groups, CCl4/GW501516-treated wild type mice exhibited increased expression of various profibrotic and pro-inflammatory genes, such as those involved in extracellular matrix deposition and macrophage recruitment. Importantly, compared to healthy liver, hepatic fibrotic tissues from alcoholic patients showed increased expression of several PPAR target genes, including phosphoinositide-dependent kinase-1, transforming growth factor beta-1, and monocyte chemoattractant protein-1. GW501516 stimulated HSC proliferation that caused enhanced fibrotic and inflammatory responses, by increasing the phosphorylation of p38 and c-Jun N-terminal kinases through the phosphoinositide-3 kinase/protein kinase-C alpha/beta mixed lineage kinase-3 pathway. These results clarified the mechanism by which GW501516-activated PPARbeta/delta enhanced hepatic stellate cell proliferation, and may facilitate the development of therapeutic approaches to prevent the progression of liver fibrosis through antagonizing PPARbeta/delta.

In parallel to our work with PPAR, we have conducted studies on the role of micronutrient combinations on lipid metabolism. More than two billion people worldwide are deficient in key micronutrients. Single micronutrients have been used at high doses to prevent and treat dietary insufficiencies. Yet the impact of combinations of micronutrients in small doses aiming to improve lipid disorders and the corresponding metabolic pathways remains incompletely understood. The high morbidity associated with obesity warrants preventive measures. Strategies for weight gain prevention address socioenvironmental factors by promoting healthy nutrition and regular exercise. Unfortunately, there is little evidence for lasting effects of these interventions. Plasma lipid-lowering drugs are most commonly used to reduce obesity-related complications, but so far, no effective approach is available for prevention of both obesity and its cardiovascular complications. Thus, we investigated whether a combination of micronutrients would reduce fat accumulation and atherosclerosis in mice. We tested an original combination of specific micronutrients, which comprises several phyto-ingrediants and oils with beneficial effects on lipid metabolism. In fact, bioactive phytochemicals have been proposed for the prevention and treatment of diabetic complications and natural product libraries are a rich source of PPAR modulators in the treatment of cardiometabolic syndrome. We anticipated that when assembled in well-defined proportions, such ingredients combined to classic micronutrients would cooperate to produce effects at low concentrations. We showed that a micronutrient combination called Lipistase meets this expectation and reduces body weight gain, plasma lipids, hepatic steatosis, and atherosclerosis in mice deficient in low-density lipoprotein receptor (LDLrKO) or in apolipoprotein E (APOEKO), two common models for investigating adiposity or atherosclerosis, respectively.

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Walter Wahli studied biology at the University of Bern, where he completed a doctorate (PhD) in 1977 under the supervision of Rudolf Weber. He worked as a post-doc researcher at the Department of Embryology, Carnegie Institution of Washington in Baltimore (Igor Dawid), and was visiting associate at the National Cancer Institute, National Institutes of Health in Bethesda (1978-1980). He became Professor and Director of the Institute of Animal biology of the UNIL in 1980 and was Research Vice-rector for the UNIL from 1999 to 2003. He founded the CIG, which he directed from 2002 to 2005. In 2008, he became a member of the Swiss Science and Technology Council. He is an elected member of the European Molecular Biology Organization (EMBO) and the Swiss National Academy of Medical Sciences. Since 2012, he is also a member of the council of the Nestlé Foundation for the Study of Problems of Nutrition in the World. He became Visiting Professor at the Lee Kong Chian School of Medicine by Imperial College London and Nanyang Technological University Singapore in 2012.
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Infiltration of monocytes or macrophages is a common feature of inflammation and tumor angiogenesis, which is receiving increasing attention in an attempt to develop novel therapeutic strategies. The ability of tumoricidal macrophages to recognize and selectively destroy neoplastic cells has been demonstrated in a wide range of experimental systems while tumor-associated macrophages were also reported to promote tumor development, progression and metastasis. The functional heterogeneity of macrophages is likely to reflect their plasticity and adaptation to suit the microenvironment in which they reside made of a complex network of pro-angiogenic and pro-inflammatory mediators. In 2005, a unique population of highly pro-angiogenic monocytes expressing Tie-2 receptor tyrosine kinase has been identified in human and mice and designated TEM for Tie-2-expressing monocytes. In mouse model, TEM recruited to tumors accounted for all angiogenic activity of bone marrow-derived cells, and their ablation fully suppressed angiogenesis. We show that in breast cancer, TEM exposure to tumor microenvironment is required for the acquisition of their angiogenic activity and we identified critical tumor-derived factors synergistically promoting TEM proangiogenic and protumoral activities inpatient.

SIGNALING AXES CONTROLLING THE ANGIOGENIC ACTIVITY OF TEM IN BREAST CANCER

M.-A. Doucey, I. Xenarios (Vital-IT) and J.-F. Delaloye (CHUV)

We have observed that the tumor microenvironment plays a key role by shaping the phenotype and the function of TEM in breast cancer. Furthermore, we show that, in breast cancer, the role of the tumor microenvironment is twofold: firstly, it is involved in the commitment of myeloid precursors to angiogenic monocytes and secondly, it is necessary for the induction of the pro-angiogenic phenotype of TEM when they reach the tumor microenvironment. By interfacing experimental and modeling approaches, we identified the signaling axes controlling the angiogenic activity of TEM derived from breast tumor. These pathways represent therapeutic intervention points for anti-angiogenic therapies in breast cancer.
NANO-BIO-SENSORS FOR THE DETECTION OF SOLUBLE ANGIOGENIC PROTEINS IN BREAST TUMORS

M.-A. Doucey and S. Carrara (EPFL)

We show that TEM are plastic cells displaying a reversible functional state induced by specific tumor microenvironmental signals. To date, profiling inflammatory and angiogenic proteins in specific tumor zones remains a difficult task. To address this issue, we produced in collaboration with Dr. Sandro Carra (EPFL, Laboratory of Integrated Systems), a biosensor-based on the memristive effect in Schottky-barrier silicon nanowires functionalized with specific antibodies. This completely novel memristive detection mode senses VEGF at very high sensitivity in the femtomolar range. The memristive conductivity into the wire is supported by interactions at the nanoscale between the molecular charges trapped by the bio-layer and the ambipolar carriers. Our current work is focused on the detection of VEGF in breast tumor extracts using these nanowire-based sensors.

RPPA (REVERSE PHASE PROTEIN ARRAY) AT CIG/PAF

M. Quadroni (CIG) and M.-A. Doucey

For a period of two years from summer 2011, 20% of my working time is dedicated to the set up and implementation of a RPPA platform at the PAF/CIG (Protein Analysis Facility at the CIG) in collaboration with Dr. M. Quadroni (Head of the PAF). The platform represents a valuable tool to explore signaling pathways in limited amounts of cells or patient tissue specimen and will be part of the service activities offered by the PAF.

Group members 2011-2012

PROJECT LEADER
Marie-Agnès Doucey

TECHNICIANS
Sylvian Bron
Eveline Faes
Pierre-Olivier Regamey

SCIENTIFIC COLLABORATORS
Luc Henry
Ziad Julier

Publications


Funding

Swiss National Science Foundation (SNSF)

- Project grant
- Interdisciplinary project (with J.F. Delaloye (UNIL))
The Molecular Modeling group develops and employs molecular modeling techniques such as homology modeling, molecular dynamics, protein-protein and protein-ligand docking, in silico drug design and free energy simulations. The group focuses on the computer-aided rational design of proteins or small molecule inhibitors for the research and treatment of human diseases, mostly in the field of oncology.

The group has developed several web services and databases for computer-aided rational drug design and molecular modeling. SwissDock (www.swissdock.ch) is a free docking web service to predict the molecular interactions that may occur between a target protein and a small molecule. The web interface of SwissDock aims at lowering the technical barrier of docking software, and generalizing the use of docking tools beyond the traditional molecular modeling community. Other tools include SwissParam (http://www.swissparam.ch) which provides topology and parameters for the molecular modeling of small organic molecules, SwissSidechain (http://www.swisssidechain.ch) that gathers information about hundreds of commercially available non-natural sidechains for peptide design, the SwissBioisostere database (http://www.swissbioisostere.ch) which collects more than 5 millions bioisosteric replacements for lead optimization, and SwissADME (http://www.swissadme.ch) which estimates physico-chemical properties of small molecules in relation with their pharmacokinetic, pharmaco-dynamic and druglikeness characteristics. We have employed these tools to design new inhibitors of Indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme involved in the immune escape mechanisms used by cancer cells, and obtained compounds with affinities in the nanomolar range in enzymatic and cellular assays. The most interesting compound demonstrated a significant activity in mouse model after oral administration, without detectable toxicity.

The molecular modeling group is also active in the field of protein engineering. It has developed several methods based on free energy simulation techniques to estimate the role played by protein residues in their activity and structural stability. Using these techniques, the group has been able to engineer T-cell receptors targeting several melanoma-related antigen (NY-ESO1 and MelanA) with affinities up to 160 times higher than the wild type receptor. In collaboration with the group of Dr. Nathalie Rufer, it has been demonstrated that T-cells expressing these new receptors exhibit an increased ability to kill cancer cells. A mouse model is currently being setup, opening the way to clinical trials.

The Molecular Modeling Group is operating the Protein Modeling Facility (PMF), whose objective is to provide researchers with access to state of the art molecular modeling and protein structure prediction techniques, for the interpretation and design of relevant experiences. The PMF has collaborated in tens of research projects, with groups of the Lausanne and Geneva Universities, the CHUV, the EPFL and private companies.
Publications


Funding

Swiss Institute of Bioinformatics
Swiss National Science Foundation
Ludwig Institute for Cancer Research
Oncosuisse
Swiss National Science Foundation (SNSF)
EMBO
Solidar-Immun Foundation
Keith Hashman received his PhD in biochemistry from the California Institute of Technology in 1990 working in the laboratory of Carl Parker on the isolation and characterization of eukaryotic transcription factors. Following postdoctoral fellowships with Walter Schaffner at the University of Zurich and Dennis Ballinger at the Sloan-Kettering Cancer Center, in 1993 he joined Myriad Genetics Inc. where he worked first as a Senior Scientist and later as the Director of Central Nervous System Disease Research. In 1997 he moved to the Department of Immunology & Oncology of the Spanish National Biotechnology Center in Madrid as the Head of the Functional Genomics Unit. He has been the coordinator of the Lausanne Genomic Technologies Facility since November of 2002.

Genomic Technologies Facility (GTF)

DESCRIPTION OF SERVICES

The primary goal of the Lausanne Genomic Technologies Facility (GTF) is to provide the user community with access to state-of-the-art technologies used to detect and measure quantitative and qualitative variations in nucleic acids. The principal technology platforms supported by the GTF during the period 2011-2012 are:

• Illumina HiSeq, Pacific Biosciences RS and Ion Torrent Personal Genome Machine high throughput DNA sequencing instruments
• Affymetrix GeneChip oligonucleotide arrays for the analysis of mRNA and DNA
• Agilent oligonucleotide arrays for the analysis of small non-coding RNA
• Applied Biosystems 7900HT Sequence Detection System for quantitative real-time PCR analyses
• Liquid handling robots for the preparation of high throughput sequencing libraries and qPCR reaction plates

In most cases, the GTF performs all of the steps of the experiment, beginning with nucleic acids provided by the user. The facility also allows users to carry out their own experiments in its laboratories by providing training and supervision in all aspects of the molecular biology and instrument manipulations associated with its technology platforms as well as providing access to support equipment and bench space. A key aspect of the GTF service platform is the bioinformatics support and consultation service it provides at the stages of experimental design, data collection and storage, image analysis and, when appropriate, higher level data analysis. Additionally, the facility maintains a close collaboration with Vital-IT Project of the SIB/Swiss Institute of Bioinformatics in the area of data management and storage. Finally, the GTF is active in a range of educational activities focusing on genomic technologies and applications. These activities include undergraduate and graduate level course lectures, organizing technology-focused seminars and workshops as well as assisting in the planning and organization of the Lausanne Genomics Days Symposium, a 2 day event in which invited scientists present on recent developments in genomic research in molecular biology, medicine, ecology and evolution.

EXPANDING THE GTF SERVICE BASE

The period 2011-2012 saw a continued expansion of the GTF’s service base, in particular by increasing and improving its high throughput DNA sequencing platform. The facility’s 2 Illumina Genome Analyzer II instruments were replaced in 2011 with an Illumina HiSeq 2000. Furthermore, in 2012 the GTF added 2 two new sequencing instruments to its sequencing platform: the Pacific Biosciences RS (financed in part by the Loterie Romande through the Fondation pour la Recherche en Médecine Génétique) and the Ion Torrent Personal Genome Machine. The facility also saw increased use of its array-based mRNA expression profiling, quantitative real-time PCR and miRNA analysis platforms. Finally, at the end of 2012, the GTF is preparing to install an Illumina HiSeq 2500 as well as a Nanostring nCounter.
Chaignat E, Yahya-Graison A, Henrichsen CN, Chrast J, Schütz F, Pradervand S, Reymond A (2011) Copy number variation modifies expression time
As a core facility, the GTF receives acknowledgements but not authorship on publications containing results obtained from regular services. Authorships reflect extensive collaborations beyond regular services.
Manfredo Quadroni
Maître d’Enseignement et de Recherche

Protein Analysis Facility (PAF)

Analysis of cells at the protein level directly targets the main players in cellular processes and gives access to events that cannot be studied by genomics and transcriptomics. Proteomics techniques have evolved considerably in the last decade and are now sufficiently mature to analyze complex systems and cellular pathways in detail. In addition to determine protein abundance levels and their changes, it is possible to study protein complexes and post-translational modifications. The PAF supports the UNIL research community in all tasks in this field, utilizing both protein and peptide-level separation techniques coupled with mass spectrometry as an analytical tool.

IMPROVED OFFER OF SERVICES

To satisfy the demand, and thanks to the purchase in 2010 of new instrumentation, the facility has reoriented its focus further towards large scale proteomics analyses. There has been a growth in the number of quantitative proteomics analyses performed, mainly using the SILAC (Stable Isotope Labeling with Amino Acids in Culture) workflow. Using this technology we were able to routinely quantitate about 4000-5000 proteins in cell lines or in some cases mouse tissues. For samples that cannot be metabolically labeled, we have introduced the iTRAQ workflow, which allows the quantitation of up to 8 samples in one experiment. The transition to large scale quantitative proteomics also required setting up some essential pipelines for data processing, statistical evaluation and data interpretation. This process is still ongoing and should result in an extended support to users in this often neglected part of the experimental process. Finally, the PAF is evaluating an antibody-based platform of Reversed-Phase Protein Arrays (RPPA) for targeted protein quantitation. The RPPA technology could be important – among other things – to bridge the gap between fundamental and applied (clinical and translational) research.

INDEPENDENT R&D PROJECTS

In a project funded by the Swiss National Research Foundation, we have developed a metabolic labeling strategy aimed at determining, on a proteome scale and for two biological conditions, protein synthesis and degradation rates. The approach, which we termed pulse-chase SILAC, should help to shed light on the mechanisms underlying changes in cellular protein concentrations in response to various stimuli. To test the strategy we have studied in a human cell line the inhibition of the molecular chaperone Hsp90 by geldanamycin, a drug which causes, simultaneously, a stress response and the depletion of Hsp90-dependent proteins. The system proved to be adequate as a proof of concept and also yielded biologically relevant insights into the mechanisms of cellular response to stress (articles submitted). In parallel to this project, we have continued studies on post-translational modifications (Waridel et al, 2012).

COLLABORATIVE PROTEOMICS STUDIES

We collaborated with the group of D. Moradpour (IMUL, Lausanne) to identify the intracellular substrates of the Hepatitis C Virus NS3-4A protease. To achieve this, we developed an approach based on isotope labeling and protein separation based on molecular weight (SDS-PAGE), to quantify protein mass shifts induced by a specific biological condition – in this case the inducible expression of the protease. At least two confirmed substrates of NS3-4A have been determined and validated. We have continued our collaboration with the group of P. Moreillon, aimed at the characterization of the surface proteome of Staphylococcus aureus, with focus on monitoring the expression of adhesion-mediating proteins which play a role in pathogenesis (Ythier et al, 2012). We also continued our collaboration with Dr. M. Molinari at the Institute for Research in Biomedicine in Bellinzona, centered on the study of ER-resident components of the protein folding quality control machinery.

Manfredo Quadroni received his PhD in Biochemistry at the Swiss Federal Institute of Technology Zurich (ETHZ) in 1996 working with E.Carafoli and P.James on protein analysis techniques applied to calcium signaling molecules. He completed his first postdoctoral training at the University of British Columbia, Canada, in the group of Prof. J. Schrader, with focus on the proteomics analysis of cell signaling complexes in immunology. His second postdoctoral training brought him back at ETH Zurich (1998–2000) to work on development of methods for proteome analysis. He was then Maître assistant at the Institute of Biochemistry of the University of Lausanne between 2000 and 2003. He joined the CIG in March 2003 as Maître d’Enseignement et de Recherche (MER) to coordinate the PAF facility.


Swiss National Science Foundation (SNSF) Project Grant

Collaborations

W. Herr
UNIL, Lausanne, Switzerland
D. Moradpour
IMUL, CHUV, Lausanne
M. Molinari
Institute for Research in Biomedicine, Bellinzona, Switzerland
P. Moreillon
UNIL, Lausanne, Switzerland
The Mouse Metabolic Evaluation Facility (MEF)
The Mouse Metabolic Evaluation Facility (MEF) was created in 2006 as the result of a joint financial and structural effort of the Center for Integrative Genomics in the Faculty of Biology and Medicine (FBM) of the UNIL, the University Hospital (CHUV), Lausanne and the NCCR Frontiers in Genetics. The MEF is located in the Génopode.

The mission of the MEF is to provide the Lausanne and Swiss research community with a wide repertoire of state-of-the-art, standardized investigative techniques to analyze the metabolic status of mice models of complex human disorders.

Given the high level of complexity of most techniques, the MEF provides services to the researchers. The MEF also provides teaching for those who want to introduce specific techniques into their own laboratories. In order to broaden the scope of phenotyping tests, the MEF aims also at developing new investigation techniques in partnership with laboratories at the UNIL, the CHUV and the EPFL, Lausanne, Switzerland.

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www.unil.ch/cig/page41381_fr.html

The Center for Investigation and Research in Sleep (CIRS)
Sleep disorders are very prevalent, and represent an "emerging worldwide epidemic". However, despite an impressive progress during the last 3 decades, biological and molecular bases of most sleep disorders remain unknown. Consequently, almost all available treatments for sleep disorders are symptomatic and not evidence-based. Given their variety and impact on different biological systems (respiration, metabolism, motor control, cognition), a multidisciplinary approach is needed, not only for understanding the pathophysiology but also for diagnosis and treatment of sleep disorders.

Thus, in collaboration with basic scientist in sleep, we have established the Center for Investigation and Research in Sleep (CIRS). This joint venture between the CIG and the centre Hospitalier Universitaire (CHUV) provides a state-of-the-art infrastructure to conduct high level basic and clinical research and to offer to the community the highest standard for diagnosis and treatment of sleep disorders.

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The Bioinformatics Core Facility (BCF)

The BCF provides a consulting service on biostatistics matters, on a mandate from (and partially funded by) the SIB and the Swiss Confederation. This service is aimed at all people active in life sciences in Switzerland. It includes training and teaching, consulting, data analysis, and research collaboration, with a focus on high-throughput technologies in genomics or proteomics.

HEAD
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The Cellular Imaging Facility (CIF)

The Cellular Imaging Facility (CIF) was created in 2003 to assist researchers with imaging needs ranging from wide-field fluorescence and transmission optical microscopy, confocal microscopy, time-lapse and ion imaging, to digital image processing and analysis. In 2005, the CIF has extended its activities on the Dorigny campus, and in 2009 on the Epalinges campus.

The CIF is organized around three complementary activities:

- Service activities: Investigators of the Faculty of Biology and Medicine and associated institutions are offered access to a panel of state-of-the-art imaging equipment and techniques.
- Training: The CIF shares and diffuses the practical and theoretical know-how on these approaches through teaching and training. A series of lectures on cellular imaging are being given yearly. Practical training on the instruments are provided in the form of short “hands-on” courses, even individual, throughout the year, and workshops on various aspects of imaging organized for pre- and post-graduate students.
- Research: Technological Development. A consortium of investigators affiliated with the CIF develop and implement most advanced optical and imaging technologies. This unit has an open and dynamic interface with the service, so that emerging technological developments are implemented and rendered accessible to more users of the CIF.

The CIF existence is the result of a joint financial and structural effort of the Faculty for Biology and Medicine of the UNIL and the University Hospital (Hospices/CHUV). The hosting institutes have also brought a major contribution by offering room, infrastructure, logistics, administrative, and technical support.

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TECHNICAL MANAGERS
Yannick Kemp (Bugnon)
Arnaud Paradis (Dorigny)
Florence Morgenthaler (Epalinges)

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Vital-IT

Vital-IT is a bioinformatics competence center that supports and collaborates with life scientists in Switzerland and beyond. The multidisciplinary team provides expertise, training and maintains a high-performance computing (HPC) and storage infrastructure, so as to help develop, maintain and extend life science and medical research. Vital-IT stems from the vision of the University of Lausanne (UNIL), the University of Geneva (UNIGE), the École Polytechnique Fédérée de Lausanne (EPFL), University of Berne (UNIBE), University of Fribourg (UNIFR), and of the SIB Swiss Institutes of Bioinformatics to create a scientific and technological center of competence in bioinformatics by teaming up with several industrial partners.

The Vital-IT group in Lausanne and the Swiss-Prot group in Geneva provide a unique service to the community. Vital-IT provides algorithms, computing and storage whereas the Swiss-Prot group provides biological knowledge (UniProtKB/Swiss-Prot, PROSITE, etc.).

MISSION
- To support research groups in biology and medicine
- To maintain and develop algorithms in life science
- To teach and liaise with embedded bioinformaticians
- (education in algorithm development and use of high performance computing environment)
- To keep active research inside Vital-IT, mainly through collaborations with partners
- To operate high productivity computational and storage resources

VISION AND MAJOR ACTIVITIES
With the advent of next generation technologies for sequencing, proteomics and large scale imaging, biology and medicine have entered the data intensive era. Vital-IT serves as:

- a service that brings together, with its partners and funding institutions, solution to collect, analyze and solve this century’s biological and medical problems.
- a model to create a complementary infrastructure to small-scale computing clusters and supercomputers. Its role is to liaise and work tightly with high-performance and supercomputing infrastructures in Switzerland and beyond and to provide the right expertise to bring forward compute and data intensive projects.
- a broker that brings about meetings and partnership opportunities with SMEs and startups, and helps shape some of their products.

DIRECTOR
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A central mission of the CIG is education. The members of the CIG, whether research group leaders or members of core facilities, give courses at the Bachelor, Master and PhD levels at the UNIL and other organizations. Doctoral students and postdoctoral fellows actively participate in teaching activities, in particular for what concerns laboratory courses. The CIG is further heavily involved in the organization of teaching: Winship Herr and Liliane Michalik are the Director and vice-director of the UNIL School of Biology, Christian Fankhauser heads the master “Molecular Life Sciences” (MLS), Keith Harshman the doctoral program “Integrated Experimental and Computational Biology” (IECB), and Nouria Hernandez the CUSO (Academic Conference of Western Switzerland) doctoral program StarOomics.

The CIG hosts a large number of PhD students and post-doctoral fellows pursuing research projects in individual laboratories. CIG PhD students have, in addition to their PhD advisor, an “academic mentor”, who can offer a complementary support in areas such as the development of career plans. However, another important role of the academic mentor is to give advice in case of any conflicts that may arise with the PhD advisor.

Beyond formal courses, research is learnt through interactions and collaborations with colleagues. To favor formal and informal exchanges, the CIG organizes numerous internal and external seminars and symposia as well as an annual retreat.

Last but not least, a number of educational activities are directed towards non-biologists and towards the public at large.

Courses and lectures given by CIG Faculty members at the UNIL

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<th>Richard BENTON</th>
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DOING A PhD OR POSTDOC AT THE CIG

Education and support to graduate students and post-doctoral fellows is a central concern of the CIG. All PhD students at the Center belong to the doctoral school of the UNIL Faculty of Biology and Medicine (FBM), which determines the program and sets the rules of PhD studies.

To ensure that students are well prepared for the challenges of modern biology, which relies more and more on computational techniques for the analysis of large sets of data, the CIG established in 2010 a new thematic doctoral program within the FBM doctoral school, titled “Integrated Experimental and Computational Biology” (IECB). The program, established with the help of the Swiss Institute of Bioinformatics, aims at attracting the best international students to the UNIL and offering them training in experimental as well as computational techniques. Students within this program can also apply to the “Fund for Research and Education in Genetics” for funding to participate in an international conference or course. The Center was also instrumental in setting up the StarOmics program, an interinstitutional program funded by the “conference universitaire de Suisse occidentale (CUSO), which offers a wide range of courses to doctoral students.

Graduate students at the CIG benefit from a mentoring program. Through this program, each student is coupled with a mentor, in general a faculty member working in a different field than the one pursued by the graduate student. This mentor is available for scientific or non-scientific discussions and advice. The students and postdoctoral fellows also organize their own seminars, which gives them the opportunity to present and discuss their work with all CIG members and to train their presentation skills. In addition, the CIG offers to the assistants the possibility to organize and attend workshops and courses to help them increase their employability after their training at the CIG and to develop the “soft skills” a necessity for a successful career in research or in another field.

Opportunities to learn about different research topics and technologies are numerous, for example during the annual CIG retreat, which is attended not only by the CIG groups but also by all other research groups in the Génopode building, or the annual CIG symposium, which is organized every year by different CIG faculty members on a topic of interest to CIG scientists. The CIG seminar series brings every week leading scientists from all over the world, who present their work in a formal seminar and then spend time discussing with interested students and post-doctoral fellows.

Doctoral program

The CIG has organized a support program, in which each PhD student selects a member of the CIG Faculty as an academic mentor.

This mentor provides support and advice during the PhD studies, and can act as a reference later. In principle, the academic mentor works on a different topic than the one pursued by the PhD student, as this helps to provide different points of view and broadens horizons and connections.

The academic mentoring program is one arm of a two-tier mentoring scheme, in which students receive guidance from both a research mentor and academic mentor. The research mentor is the thesis advisor. The academic mentor is an interested, and impartial, faculty member chosen to provide diversity in the student’s education.

THE IECB DOCTORAL PROGRAM

The thematic doctoral program “Integrated Experimental and Computational Biology”, which started towards the end of 2010 under the leadership of Keith Harshman, developed well in 2011 and in 2012 became very successful, with now seventeen participating students. The program aims at providing doctoral students with an education not only in experimental biology but also in computer programming and computational data analysis, such that they will be ready to face a job market that requires more and more of these types of skills. One exciting development was the funding provided by the Fund for Research and Education in Genetics, which provides each IECB student with the opportunity to attend one international course or one international conference during the course of his/her PhD thesis.

THE DOCTORAL PROGRAM STAROMICS

StarOmics is a doctoral program of the Universities of Lausanne, Bern, Fribourg, Geneva and Neuchâtel. It is coordinated by Nouria Hernandez and Laurent Falquet (SIB). It covers quantitative aspects of modern biology as well as novel biological strategies and reasoning and aims at building a new generation of scientists who will be at ease with the new challenges put by Genomics, Transcriptomics, Proteomics, Metabolomics, Connectomics and all other large scale data generating technologies.

Website: http://biologie.cuso.ch/staromics/welcome/

The mentoring program

THE ROLE OF THE MENTORING PROGRAM AND OF ACADEMIC MENTORS

- To provide graduate students with the unique experience of having close contact with a senior member of the scientific community
- To provide graduate students with a faculty member whose primary concern is their academic development
- To provide graduate students with a letter of reference
- To act as a conduit

Website: http://www.unil.ch/cig/page62072.html

PhD theses obtained at the CIG (2011-2012)

David BRAWAND
Group Kaessmann
Stéphane DORSAZ
Group Tafti
He FU
Group Desvergne
Matthew HALL
Group Desvergne
Patricia HORNITSCHECK
Group Fankhauser
Cédric HOWALD
Group Reymond
Philine JULIEN
Group Kaessmann
Raphael RYTZ
Group Benton
Audrey SAMBEAT
Group Thorens
Magali SOUMILLON
Group Kaessmann
Saajit THOTTATHIL OOMMEN
Group Desvergne
Marta WAWRZYNIAK
Group Liliane
Ralf WIMMER
Group Franken
Robert WITWICKI
Group Reymond
Génopode

CIG SEMINARS
PROGRAM SPRING 2012
12:15 – Génopode, Dorigny – Auditorium B

Monday January 16, 2012
Andrea Superti-Furga,
CIG, University of Lausanne, Switzerland
«Genetics of human skeletal development and growth»
Host: Winship Herr

Monday January 23, 2012
Wolf Reik,
CIG, University of Lausanne, Switzerland
«PANs stand at the crossroads of metabolism, tissue repair and cancer»
Host: Alexandre Reymond

Monday January 16, 2012
Dirk Schübeler,
Friedrich Miescher Institute, Basel, Switzerland
«DNA sequence determinants of the epigenome»
Host: Alexandre Reymond

Monday February 13, 2012
Dirk Schübeler,
Friedrich Miescher Institute, Basel, Switzerland
«DNA sequence determinants of the epigenome»
Host: Alexandre Reymond

Monday March 12, 2012
Edward M. Marcotte,
University of Texas at Austin, USA
«Steps towards a modular theory of disease: Insights from proteomics into cellular evolution and surprising disease models»
Host: Isamet Xenarios

Monday March 19, 2012
Charles Weissmann,
The Scripps Institute, Jupiter, USA
«Evolution of primate»
Host: Nouria Hernandez

Monday March 26, 2012
Brian Charlesworth,
The University of Edinburgh, UK
«The effects of genetic recombination on molecular evolution and variation»
Host: Henrik Kaessmann

Monday April 16, 2012
Eran Segal,
Weizmann Institute of Science, Rehovot, Israel
«Cracking the regulatory code using thousands of designed promoter sequences»
Host: Alexandre Reymond

Monday April 23, 2012
Nancy Kleckner,
Harvard University, Cambridge, USA
«How do bacteria organize and segregate their chromosomes?»
Host: Andrzej Stasiak

Monday April 16, 2012
Dirk Schübeler,
Friedrich Miescher Institute, Basel, Switzerland
«DNA sequence determinants of the epigenome»
Host: Alexandre Reymond

Monday May 14, 2012
Julius Brennecke,
Harvard University, Cambridge, USA
«How do bacteria organize and segregate their chromosomes?»
Host: Andrej Sliski

Monday May 21, 2012
James Kapur,
Nestlé Institute of Health Sciences, Lausanne, Switzerland
«Developing research strategies for personalized nutrition, medicine, and health care»
Host: Walter Wahli

Monday May 28, 2012
Marc Bühler,
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
«Shaping the epigenome with help of non-coding RNAs»
Host: David Gatfield

Monday August 27, 2012
Marc Bühler,
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
«Shaping the epigenome with help of non-coding RNAs»
Host: David Gatfield

Monday November 19, 2012
Duncan Walt, CIG, University of Lausanne, Switzerland
«Transcriptional regulatory evolution in mammals»
Host: Henrik Kaessmann

Monday November 26, 2012
Hernán López-Schier,
Helmholtz Zentrum München, Germany
«Assembly & homeostasis of synaptic specificity in a mechanosensory organ»
Host: Richard Benton

Monday December 10, 2012
Sabine Werner,
EPFL, Lausanne, Switzerland
«Cytoskeletale Ausrichtung der Sekretion von menschlichen Zellen in Wirtszelle»
Hosts: Nouria Hernandez & Liliane Michalk

Monday December 17, 2012
Kai Johnsson,
EPFL, Lausanne, Switzerland
«Spying on drugs and metabolites in living cells»
Host: Christian Fankhauser

CIG SEMINARS
PROGRAM FALL 2012
12:15 – Génopode, Dorigny – Auditorium B

Monday August 27, 2012
Marc Bühler,
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
«Shaping the epigenome with help of non-coding RNAs»
Host: David Gatfield

Monday October 29, 2012
Nouria Hernandez,
CIG, University of Lausanne, Switzerland
«Pol II or III? A tale of two RNA polymerases»
Host: Alexandre Reymond

Monday November 19, 2012
Duncan Walt, CIG, University of Lausanne, Switzerland
«Transcriptional regulatory evolution in mammals»
Host: Henrik Kaessmann

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Hosts: Nouria Hernandez & Liliane Michalk

Monday December 17, 2012
Kai Johnsson,
EPFL, Lausanne, Switzerland
«Spying on drugs and metabolites in living cells»
Host: Christian Fankhauser
CIG Symposium 2011: Genetics of behavior

ORGANIZERS
L. Keller
C. Sandi
M. Tafti

Christian LÜSCHER
University of Geneva, Switzerland
Probing drug-evoked synaptic plasticity to identify vulnerability genes for addiction

Trudy MACKAY
N.C. State University, Raleigh, USA
Complex genetic architecture of drosophila behaviors

Andreas MEYER-LINDENBERG
Central Institute of Mental Health, Mannheim, Germany
Genetic and environmental risk mechanisms for schizophrenia

Andreas PAPASSOTIROPOULOS
University of Basel, Switzerland
Genetics of human memory: understanding complexity

SELECTED TALKS
William BROWN
University of East London, UK
Genomic imprinting and language evolution

Valérie HINARD
UNIL, Lausanne, Switzerland
Electrophysiological and metabolic correlates of an in vitro model of sleep

Romain LIBBRECHT
UNIL, Lausanne, Switzerland
Complex genetic influences on division of labor in social insects

Pavan RAMDYA
UNIL, Lausanne, Switzerland
An algorithm for odor avoidance in drosophila melanogaster

Christine LÜSCHER
University of Geneva, Switzerland
Probing drug-evoked synaptic plasticity to identify vulnerability genes for addiction

Trudy MACKAY
N.C. State University, Raleigh, USA
Complex genetic architecture of drosophila behaviors

Andreas MEYER-LINDENBERG
Central Institute of Mental Health, Mannheim, Germany
Genetic and environmental risk mechanisms for schizophrenia

Andreas PAPASSOTIROPOULOS
University of Basel, Switzerland
Genetics of human memory: understanding complexity

Alcino SILVA
University of California, Los Angeles, USA
Reversing neurodevelopmental disorders in adults

Larry YOUNG
Emory University School of Medicine, Atlanta, USA
Oxytocin, vasopressin and the neurogenetics of social relationships
CIG symposium 2012:  
Transcription, from development to nutrigenomics

PRESENTATION OF THE 2012 GUENIN PRIZE

Julie VIENNE  
Brandeis University, USA  
The effects of gamma-hydroxybutyrate, baclofen and GABAB receptors on brain activity and sleep in mice and humans

SELECTED TALKS

Frederica GILARDI  
UNIL, Lausanne, Switzerland  
Dynamics of SREBP1-DNA binding in mouse liver

Sébastien HERZIG  
University of Geneva, Switzerland  
Identification and functional expression of the mitochondrial pyruvate carrier

Sylvie CHAPPUIS  
University of Fribourg, Switzerland  
The mouse clock protein PER2 is involved in non-shivering thermogenesis

Jerome FEIGE  
Novartis  
The myostatin / ActRIIB pathway represses brown adipogenesis and thermogenesis

Sander KERSTEN  
Wageningen University, Netherlands  
Nutrigenomics of fatty acid sensing: role of Angpt14

ORGANIZERS

B. Desvergne  
L. Michalik  
B. Thorens

Pierre CHAMBON  
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Strasbourg, France  
Molecular dissection of the signaling curcuitry underlying the control of intestinal epithelial cells (IEC) homeostasis by the gut Microbiota

Steven KLIewER  
University of Texas  
Southwestern Medical Center, Dallas, USA  
Regulation of metabolism by PPAR-FGF21 pathways: from feast to famine

Robert ROEDER  
The Rockefeller University, New York, USA  
Transcriptional regulatory mechanisms in animal cells

Johan AUWERX  
EPFL, Lausanne, Switzerland  
Protein homeostasis in the control of mitochondrial function and aging

Allan BALMAIN  
UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA  
Genetic approaches to analysis of the complex roles of inflammation in cancer

Ueli SCHIBLER  
University of Geneva, Switzerland  
The daily rhythms of genes, cells and organs

John GURDON  
The Gurdon Institute, University of Cambridge, UK  
The transcriptional characteristics of a Xenopus oocyte

Igor DAWID  
National institute of child health and human development, Bethesda, USA  
Genetic and environmental risk mechanisms for schizophrenia

Walter GEHRING  
Biozentrum, University of Basel, Switzerland  
The evolution of vision

Denis DUBOULE  
University of Geneva and EPFL, Switzerland  
Regulatory archipelagos

Henrik KAessmann  
UNIL, Lausanne, Switzerland  
The evolution of mammalian tissue transcriptomes

Walter WAHLI  
UNIL, Lausanne, Switzerland  
Transcription, from development to nutrigenomics

Registration by May 14, 2012

Center for Integrative Genomics (CIG)  
University of Lausanne  
1015 Lausanne  
Switzerland
CIG AND THE PUBLIC

The CIG being a university department, its first teaching duties are to students and other members of the academic staff. However, in a world where the development of knowledge and technology in the biological sciences concerns each and everyone, the CIG considers it part of its mission to establish a link with the public at large and to communicate with non-scientists.

The CIG is particularly active in communication with children and teenagers, tomorrow’s voting citizen and maybe tomorrow’s researchers. The Center organizes every year visits within the framework of the “Passeport Vacances”, a program that organizes activities for children during their holidays. It also welcomes children visiting with their schoolteachers.

During the UNIL open doors (les Mystères de l’UNIL) and other occasions anyone can come to the Center, visit the laboratories and discuss with the scientists.

These activities are not only an opportunity to inform the public about the research done at the CIG, but also a chance to interact with non-scientists and discuss different research-related issues raised in today’s society. For the scientists, and in particular for the PhD students and postdoctoral fellows, it is an opportunity to talk with the general public about their work and to get experience in describing science to non-scientists, whether it be children, teenagers or adults.

Communication with the public can also take the form of features in the media. CIG members and their research have been commented on the radio, TV and in the written press.

For its activities directed at the public, the CIG collaborates with the public laboratory of the UNIL, L’Eprouvette, which is part of the UNIL Interface Science and Society, and with UNICOM (the UNIL communication services).

The CIG is very fortunate to have the support of “Fund for Research and Education in Genetics”, which allows it to host the “John Grace Lectures”. A chance for the public to hear world renowned scientists present their research. The John Grace Lecture was given in 2011 by Professor Ralph Greenspan (San Diego USA) and in 2012 by Professor John Gurdon (Cambridge UK).

Moreover, the Fund organizes the “women in science lecture and luncheon” series, whose first edition took place on October 11th, 2012, at the Montreux Palace, featuring CIG Director Nouria Hernandez as the inaugural speaker. The lecture, titled “The genomic era in biology: impact on knowledge and health” was enjoyed by a full house. This lecture series aims at getting the local community interested in the activities of both the CIG and the Eprouvette.
Activities proposed for the public (non-exhaustive)

“L’ADN fait son cinema”
L. Michalik
A conference on the realities of genetics and modern biology based on extracts from movies such as “Jurassic Park”, “Spiderman” etc.

“L’horloge interne”
F. LaSpada, et al., Lab. P. Franken
An activity explaining the study of the influence of the circadian rhythms on the life of human beings and vertebrates in general

“Analyses d’ADN”
GTF
A visit of the Genomic Technology Facility and an explanation on genomics

“Les yeux des plantes”
L. Vuillet, S. Lorrain, et al. Lab C. Fankhauser
A visit of the Fankhauser lab and explanation on the perception light by plants

“La perception des odeurs par les mouches”
Lab R. Benton
A visit of the Benton lab and an explanation on how odors are perceived

“L’enquête du Professeur Erudix”
L. Michalik et al.
An enquiry on a “laugh epidemic” introducing children to basic analysis in the laboratory

“La tactique du tic-tac”
lab. D. Gatfield, P. Franken and M. Tafti
An explanation of circadian rhythms

Academic courses for non biologists

Interdisciplinarity is particularly favored at the UNIL. A program, Science2, has been developed with the ambition to reinforce the dialogue between the different academic branches, thus to bring science to the square.

The members of the CIG participate actively in the program. Within the program, Liliane Michalik organizes the course «genes to human being», to which participate A. Reymond and C. Fankhauser, as well as colleagues from other departments and from the UNIL public laboratory L’Eprouvette.

see also: http://www.unil.ch/sciencesaucarre
The CIG activities and dynamism result not only from the work of the group leaders and faculty members, but also in a large part from the contributions of people in training: master and graduate students, as well as postdoctoral fellows. Laboratory technicians and members of the technical and administrative staff are also key to research. The CIG is currently composed of more than 200 members originating from 34 different countries.

In order to function the CIG also relies on its central services.

**Central services**

- **Chief operating officer**: Nicole Vouilloz
- **Administration**: Corinne Dentan, Anne Donaldson, Fabienne Sauvain
- **IT service**: Fanny Gex, Corinne Hängeli, Edgar Scherwey
- **Washing facility**: Suresh Balsiger, Joan Justiniano
- **Stock, maintenance and ordering**: Marlyne Berger, Noura Egger
- **Phenotyping facility**: Catherine Moret
- **Genotyping facility**: Armelle Bauduret, Marianne Carrard, Katharina Hausherr
- **Sequencing facility**: Marina Pronina
- **Workshop**: Gilles Boss
- **Apprentices**: Anouk Berger, Jérôme Blanc, Daniel Catalano, Nathalie Fares

**CIG members in 2011-2012**

- **Laboratory Technician**: Jérôme Soyer
- **PhD Student**: Laure Allenbach
- **Post-doctoral Fellow**: Ali Afza
- **Master Student**: Jacques Anken
- **Visiting Student**: Bulkar Arpat
- **Laboratory Technician**: Cagri Avo
- **Technical Helper**: Pierre Bady
- **Laboratory Technician**: Julie Baker
- **Visiting Professor**: Suresh Balsiger
- **PhD Student**: Andreas Gschwend
- **Post-doctoral Fellow**: Michael Baurachet
- **Laboratory Technician**: Davide Basco
- **Post-doctoral Fellow**: Armelle Bauduret
- **Laboratory Technician**: Emmanuel Beaudoin
- **Bioinformatician**: Rati Bell
- **PHD Student**: Fabrizio Benedetti
- **Post-doctoral Fellow**: Richard Berridge
- **Laboratory Technician**: Katharina Hausherr
- **Facilities Manager**: Stocks, Maintenance and Ordering
- **Laboratory Technician**: Gaëlle Berthoud
- **Master Student**: Tanja Bhuyan
- **PhD Student**: Adem Bilic
- **PhD Student**: Jérôme Blanc
- **Apprentice**: Karolina Bokowska
- **Laboratory Technician**: Marta Bombardo
- **PhD Student**: Nicolas Bonhoure
- **PhD Student**: Naomi Borel
- **PhD Student**: Gilles Boss
- **Lab Technician**: David Bravand
- **PhD Student**: Sylvan Bron
- **Laboratory Technician**: Frédéric Brun
- **PhD Student**: Diane Buczynski
- **Post-doctoral Fellow**: Géraldine Buttet
- **Technical Help**: Donatella Canella
- **Post-doctoral Fellow**: Danielle Canepa
- **Post-doctoral Fellow**: Francesca Carelli
- **PhD Student**: Marianne Carrard
- **Laboratory Technician**: Cristina Casals
- **Post-doctoral Fellow**: Daniel Catalano
- **Apprentice**: Animal Keeper
- **Group Leader**: Jacqueline Chrait
- **Laboratory Technician**: Daniela Cisterna
- **Administrative Collaborator**: Catherine Clement
- **Master Student**: Natasia Cleve
- **Post-doctoral Fellow**: Francesco Cozzolino
- **PhD Student**: Cristiano Consalvi
- **Post-doctoral Fellow**: Floriane Consales
- **Laboratory Technician**: Nathalie Constantin
- **Research Assistant**: Diego Claudio Cortez
- **Post-doctoral Fellow**: Pascal Cousin
- **Laboratory Technician**: Annick Crevoisier
- **Administrative Collaborator**: Vincent Croset
- **PhD Student**: Stéphane Cruchet
- **Laboratory Technician**: Thomas Curie
- **Post-doctoral Fellow**: Anabela Da Costa
- **Laboratory Technician**: Maria De Matos
- **Laboratory Technician**: Mieke De Wit
- **Post-doctoral Fellow**: Gwendoline Deguercou
- **PhD Student**: Maude Delacombez
- **Laboratory Technician**: Jose Manuel Delpepiaine
- **Master Student**: Emile Demaray
- **Post-doctoral Fellow**: Corinne Dentan
- **Administrative Collaborator**: Brigitte Desvergne
- **Group Leader**: Gérard Didelet
- **Post-doctoral Fellow**: Shanaz Diessier
- **PhD Student**: Jun Ding
- **Post-doctoral Fellow**: Jean-Gaël Dierens
- **Master Student**: Wanda Dolci
- **Laboratory Technician**: Anne Donaldson
- **Administrative Collaborator**: Julien Donier
- **Bioinformatician**: Tino Dorbusch
- **Post-doctoral Fellow**: Stéphane Dory
- **PhD Student**: Alexandre Doucey
- **Group Leader**: Ngoc-Hien Du
- **PhD Student**: Melanie Dupasquier
- **Laboratory Technician**: Kalina Duszka
- **Post-doctoral Fellow**: Ilenia D’Errico
- **Post-doctoral Fellow**: Noura Egger
- **Stocks, Maintenance and Ordering**: Yann Emmenegger
- **Laboratory Technician**: Eveline Eas
- **Laboratory Technician**: Minnaertham Fanahkhan
- **Group Leader**: Nathalie Ferreira
- **PhD Student**: Iris Finci
- **PhD Student**: Paul Franken
- **Group Leader**: Christiane Freymond
- **Stocks, Maintenance and Ordering**: Laure Froidevaux
- **Laboratory Technician**: He Fu
- **PhD Student**: Teresa Galera
- **Summer Student**: Marceal Galemme
- **Visiting Student**: David Gatfield
- **Group Leader**: Fanny Gex
- **IT Technician**: Nele Gheldof
- **Post-doctoral Fellow**: Giuliana Giannuzzi
- **Post-doctoral Fellow**: Federica Gillard
- **Post-doctoral Fellow**: Greta Giordano
- **Attendant**: Post-doctoral Fellow: Carolina Gómez
- **Diaz Post-doctoral Fellow**: Patrick Gouait
- **Chief Animal Keeper**: Erwan Gouranton
- **Post-doctoral Fellow**: Anupama Goyal
- **Post-doctoral Fellow**: Andreas Gschwend
- **Post-doctoral Fellow**: Alain Gueniot
- **Animal Keeper**: Oscar Guerra
- **Trainee**: Katerina Guschanski
- **Post-doctoral Fellow**: Kyle Gustafson
- **Post-doctoral Fellow**: Otto Hagenbüchle
- **Core Facility Coordinator**: Corinne Hangélé
- **IT Technician**: Louise Harewood
- **Post-doctoral Fellow**: Keith Hargrave
- **Core Facility Director**: Katharina Hausherr
- **Laboratory Technician**: Eija Heikila
- **Post-doctoral Fellow**: Céline Hernandez
- **Bioinformatician**: Daniel Hernandez
- **Technical Help**: Nouria Hernandez
- **CIG Director**: Winship Herr
- **Group Leader**: Valérie Hinard
- **Post-doctoral Fellow**: Hitomi Sanno
- **Post-doctoral Fellow**: Hyun Hori
- **Post-doctoral Fellow**: Charlotte Horn
- **Post-doctoral Fellow**: Patricia Hornitschek
- **Thielan PhD Student**: Cédric Hovald
- **PhD Student**: José Luis Huaman Larios
- **Animal Keeper**: Nicole James
- **Faresse PhD Student**: Annesoe Faustock
- **Post-doctoral Fellow**: Peggy Janich
- **Post-doctoral Fellow**: Sonia Jimenez
- **Laboratory Technician**: Philippe Julien
- **PhD Student**: Fabienne Junod Fontollet
- **Animal Keeper**: Joan Justiniano
- **Washing Facility**: Suresh Balsiger
- **Joan Justiniano**
- **Stock, maintenance and ordering**: Marlyne Berger
- **Noura Egger**
- **Christian Freymond**
- **Animal facility**: Patrick Gouait
- **Alain Guéniot**
- **José Luis Huaman Larios**
- **Fabienne Junod Fontollet**
- **Senda-N’ton Mafuala-Manua**
- **Brigitte Notari**
- **José Luís Huaman Larios**
- **Annemieke Lammers**
- **Laboratory Technician**: Alexandre Laverrière-Loss
- **PhD Student**: Adria Le Bauf
- **Post-doctoral Fellow**: Cristina Leon
- **Master Student**: Sha Li
- **PhD Student**: Lu Angeles
- **Lecturer**: Marc Lieut
- **Apprentice Laboratory Technician**: Maria Nicla
- **PhD Student**: Loviglio
- **PhD Student**: Johanna
- **Master Student**: Philippe
- **L’Hôte Laboratory Technician**: Séverine Lorrain
- **Research Assistant**: Senda Nton Mafuala-Manua
- **Animal Keeper**: Géraldine Mang
- **PhD Student**: Katrin Männik
- **Post-doctoral Fellow**: Ray Marin
- **Florez**
- **Post-doctoral Fellow**: Neila Mele
- **Technical Help**: Salima Metre
- **Laboratory Technician**: Andreas Metschke
- **Invited Professor**: Julien Meunier
- **Post-doctoral Fellow**: Patrick Meylan
- **PhD Student**: Liliane Michalik
- **Group Leader**: Joëlle Michaud
- **Schütz Post-doctoral Fellow**: Annemieke
- **Michels Post-doctoral Fellow**: Eugenia Migliavacca
- **Voeffray Bioinformatician**: Cyril Mikhail
- **PhD Student**: Shilpi Mincho
- **Post-doctoral Fellow**: Owen Modie
- **PhD Student**: Alexandre Montagnier
- **Post-doctoral Fellow**: Josselin Moosbrugger
- **Master Student**: Gabriel
- **Moquet-Torcy Post-doctoral Fellow**: Hélène Motlaz
- **Laboratory Technician**: Catherine Moret
- **Laboratory Technician**: Linda Müller
- **Master Student**: Audrey Naïdi
- **Post-doctoral Fellow**: Pipat
- **Nutimak Post-doctoral Fellow**: Anamaria Nescul
- **Post-doctoral Fellow**: Guy Niederhäusern
- **Laboratory Technician**: Brigitte Notari
- **Animal Keeper**: Andrea Orioli
- **Post-doctoral Fellow**: Alexandra Paillusson
- **Laboratory Technician**: Arnaud Paradis
- **Laboratory Technician**: Mariangiovanna Parente
- **Visiting Student**: Jihye Park