THE CENTER FOR INTEGRATIVE GENOMICS

REPORT 07-08

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de Génomique

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THE CENTER FOR INTEGRATIVE GENOMICS (CIG) AT A GLANCE

The Center for Integrative Genomics (CIG) is the newest department of the Faculty of Biology and Medicine of the University of Lausanne (UNIL). Its establishment was made possible as a result of the program "Sciences, Vie, Société", a tri-institutional program linking the Universities of Geneva and Lausanne and the Federal Institute of Technology in Lausanne (Ecole polytechnique fédérale de Lausanne – EPFL), which aimed to develop the life sciences as well as the humanities and social sciences in the Lémanic region.

The CIG has three main missions:

- The pursuit of a first rate research program in the biological sciences
- The development of an outstanding teaching program
- The development and support of core facilities offering cutting-edge technologies to the Lémanic research community and beyond

The research at the CIG centers on genome structure and function in a number of different experimental systems and relies on a large number of different techniques. It is performed by an international community of scientists, yet the character of the CIG is one of an integrated research center, where interactions among groups are numerous both in formal and informal settings.

Scientific Advisory Committee members

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THE SCIENTIFIC ADVISORY COMMITTEE (SAC)

The CIG Scientific Advisory Committee (SAC) is a consultative commission of external experts widely recognized for their contribution in the fields of activity of the CIG. Its principal responsibilities are:

- To advise on scientific objectives and priorities
- To evaluate the outcomes
- To propose means of improving outcomes and visibility
- To propose the acquisition of new technologies or the development of new research and educational activities or services

The members of the SAC visited the CIG in June 2007 and in June 2008. During these visits, they had discussions with the CIG Director, with each group leader, with the CIG students and postdoctoral fellows, and with members of the administrative and technical staff. They also met with the Dean of the Faculty of Biology and Medicine.

Their conclusions and recommendations, which were each time summarized in a report, led to considerable improvements for the CIG in aspects as diverse as policies for promotion proposals or the establishment of a cozy "coffee corner" on the CIG main floor. Their next visit is scheduled for 2010.

Message from the Director

We are indeed fortunate enough to be biologists in a time of remarkable advances in our field, the time of "omics".

Nouria Hernandez, CIG Director

The Center for Integrative Genomics was started in 2002 with the appointment of its founding Director, Walter Wahli. This was followed by a period of faculty recruitment as well as, starting in the Fall of 2004, the extensive remodeling of the building now known as the Génopode. These efforts culminated with the inauguration of the CIG in October 2005. Thus, the CIG will enter its fourth year as a fully functional department in its own quarters in the Fall of 2009. In the last two years, it has grown from thirteen to sixteen faculty members and is now at full steam! Together with this growth in the number of faculty members, the CIG has seen a steep increase in its research activities as measured, for example, by the amounts of external funds that have been raised. We have gone from about 35% of our UNIL budget in 2006 to close to 60% of this budget in 2008, and this number is likely to increase further in the next few years. Thus, the CIG is doing very well indeed and is well on its way to fulfilling its promise as a flagship research department of the University of Lausanne (UNIL).

Why put so much emphasis on research in universities, whose main function is, after all, the education of students? In fact, at the university level, research is intimately linked to teaching and vice-versa. On the one hand, the research carried out in our laboratories feeds directly into our courses and allows us to teach at the cutting-edge of current knowledge. On the other hand, in an academic environment a large part of the research is conducted by people in training; master- and graduate students, postdoctoral fellows, and even technician trainees! Without them, there would be little research indeed in universities! Teaching, and attracting the brightest students, is thus of paramount importance to maintain a high level of research, and vice-versa. The various CIG faculty members are now contributing to teaching at the Bachelor, Master, and PhD levels, but our next goal is the establishment of a flagship course or program that could be identified with the CIG. In thinking about such a program, it seems obvious that the role of the Center for Integrative Genomics should be to teach aspects of functional genomics, thus transmitting to the students the excitement of a biology revolution we are in the midst of experiencing.

We are indeed fortunate enough to be biologists in a time of remarkable advances in our field, the time of "omics". More than 800 microbial genomes have now been completely sequenced! For eukaryotes, the number of completely sequenced genomes is 23, with another 251 at the assembly stage and 256 still in progress. The tools to analyze these genomes are evolving at an ever accelerating speed. We can determine which genes are active when, when and where specific proteins are bound to the genome, how these proteins are modified, all of this on a genomic scale. Progress in the proteomics field allows the analysis of large mixture of proteins, indeed of the entire proteome of a cell under various circumstances. With such developments we can test the generality of mechanisms studied until now in only a few model systems. We can also use these large-scale data as a discovery tool, for example to compare the genomic landscapes of cells in different states. These developments also mean that an increasing number of large datasets produced for a specific published study are accessible to other researchers who can then use the same data to answer another question. This activity of data mining will become more and more important for the advancement of any research project as the number of searchable datasets increases.

The new biology, the "omics" biology has important implications for the teaching of biology, as it demands skills from researchers that were dispensable in the days of "good old" molecular biology. Indeed, whereas the human brain can easily deal with a few data points, it is another story when an experiment produces from thousands to millions of data points. Thus, the composition of research groups involved in large scale experiments is, ideally, a mix of "wet lab" researchers, who deal with real molecules, cells, tissues, or organisms, and the "dry lab" researchers, who deal with virtual molecules, datafiles and databanks, scripts, and algorithms. In this ideal situation again, researchers are familiar with both the "wet" and "dry" aspects of the research and capable of carrying out both, even if each specializes more in one aspect. The reality, however, is quite different. Most students studying molecular biology or biochemistry have little or no training in computational biology, even today. As a result, they lack the proficiency to analyze their own large-scale experiments as well as to take full advantage of published large datasets. In general, there is a lack of computational biologists in Switzerland, which will only become more severe in the next few years.

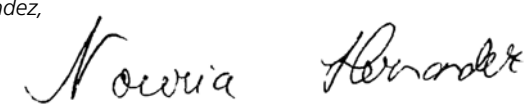
This is where I believe the CIG could make a unique contribution to teaching. Indeed, we have the privilege to be located in the same building as Vital-IT, the core facility of the Swiss Institute of Bioinformatics (SIB) dedicated to helping the biological sciences. Thanks to the concept of "embedded bioinformaticians" developed by Vital-IT Director Ioannis Xenarios and SIB Director Ron Appel, the bioinformaticians hired in "wet research groups" can be part of the SIB and thus have access to its considerable computing resources and its expertise.

Highlights of 2007-2008

Moreover, some of the CIG groups already combine both expertise. This seems, then, like a perfect environment to develop a PhD program centered not on a specific biology subject but on the concept that, at graduation, the new PhD student is fluent both in experimental "wet" research as well as in bioinformatics methods. According to taste and interests, the emphasis might be on one or the other, but both aspects will have been approached during the thesis.

Concretely, how could such a program be established? The program should be flexible enough to allow the participation of any laboratory, be it a uniquely computational laboratory, a uniquely "wet" experimentation laboratory, or a laboratory with both expertise. Depending on the expertise available in the chosen laboratory, a student might conceivably have a second thesis advisor who would be a collaborator on the project and might host the student for some period of time. In any case, by the time of graduation, the student would have performed a research project involving both pipetting as well as battling with a computer keyboard! The CIG is looking forward to materialize such an exciting program.

Nouria Hernandez,
CIG Director



LIFE AT THE CIG

R. Benton, S. Martin and A. Stasiak joined the CIG as group leaders

FUNDING

The CIG members attracted external research funds for about 11.5 millions CHF, among which

- an ERC Starting Independent Researcher Grant (R. Benton)
- a Career Development Award from Human Frontier Science Program (HFSP) (S. Martin)
- a Swiss National Science Foundation (SNSF) R'Equip grant for an Ultra High Throughput sequencing machine for the DAFL (N. Hernandez, with I. Sanders (UNIL), D. Trono (EPFL), S. Antonorakis (UNIGE))

FACULTY MEMBERS ACHIEVEMENTS

- B. Desvergne was promoted to Full Professor
- N. Hernandez was awarded the Cloëtta Prize 2007
- N. Hernandez was elected member of the European Molecular Biology Organization (EMBO)
- W. Herr was appointed vice-Dean for Biology at the Faculty of Biology and Medicine (FBM), UNIL
- W. Herr was elected member of the European Molecular Biology Organization (EMBO)
- H. Kaessmann was titularized and is now Associate Professor
- H. Kaessmann was awarded the Basic Life Science Research Award 2008, Faculty of Biology and Medicine (FBM), UNIL
- W. Wahli was awarded the Hartmann-Müller Foundation prize 2008
- W. Wahli was chosen as a member of the Swiss Science and Technology Council

RESEARCH

Richard Benton
Assistant Professor

Chemosensory perception in Drosophila: from genes to behaviour

Richard Benton received his PhD in 2003 from the University of Cambridge UK 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 Vosshall'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.

The overall goal of our research is to understand how sensory information in the environment is detected and processed in the brain to evoke an appropriate behavioural response. We focus on the olfactory and gustatory systems of the fruit fly, Drosophila melanogaster, a model genetic organism that displays a sophisticated repertoire of chemosensory-driven behaviours under the control of neural circuits that have similar anatomical and functional properties to those of mammals but with significantly reduced complexity. Our group takes a multidisciplinary approach to this problem, combining bioinformatics, genetics, molecular cell biology, electrophysiology, neuronal imaging and behavioural analysis. We aim to gain insights into both a fundamental problem of neuroscience - how genes and circuits control behaviour – and the evolutionary mechanisms operating in animal nervous systems. Our work also has potential direct application in the development of novel strategies to control the chemosensory-driven behaviours of pest insects.

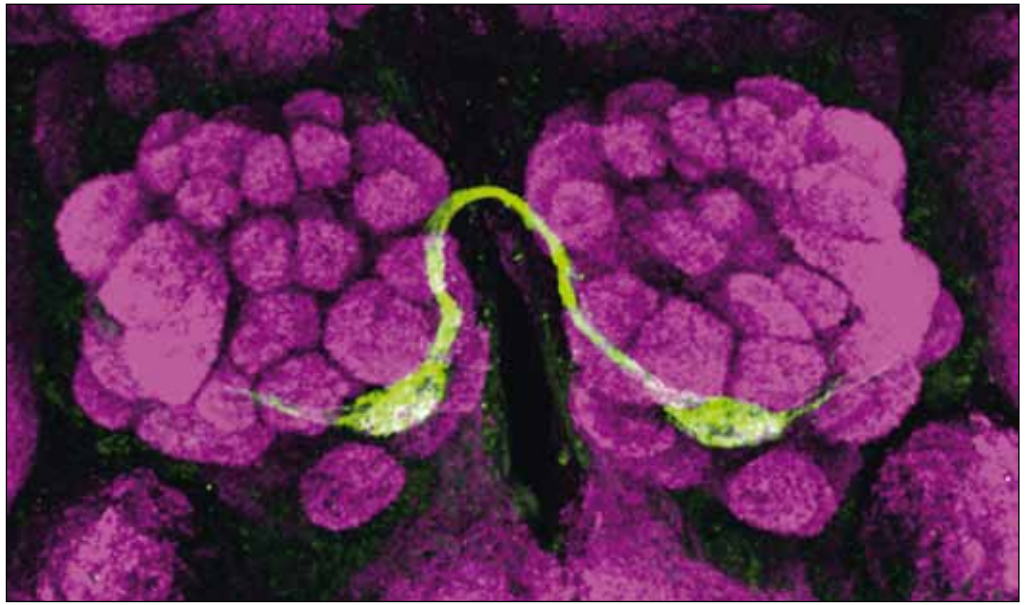
THE IONOTROPIC RECEPTORS: A NEW FAMILY OF CHEMOSENSORY RECEPTORS

We recently discovered a novel family of chemosensory genes, named the Ionotropic Receptors (IRs). These genes encode proteins that are structurally related to ionotropic glutamate receptors, a conserved class of ligand-gated ion channel best studied for their roles in synaptic transmission. IRs, however, have highly divergent ligand binding domains that lack glutamate-interacting residues. IR genes are expressed in specific combinatorials in neurons in the antenna - the major olfactory organ - that are distinct from those that express the well-characterised Odorant Receptors (ORs). IRs localise to the ciliated endings of olfactory sensory dendrites and expression of an IR in an ectopic neuron is sufficient to confer novel odour responses, providing evidence for a direct role in odour recognition. The IRs are therefore likely to define a previously unappreciated second "nose" in Drosophila. We are now using the IRs as a model system to study several aspects of the function and evolution of chemosensory circuits:

- How IRs transform ligand recognition into sensory neuron activity is unknown. We are combining structure-function analysis of IRs in vivo and in vitro to determine whether these receptors act as ion channels, the existence and functional specificity of different IR protein complexes and the molecular basis of IR ligand recognition.
- A key first step in understanding how information encoded by peripheral chemosensory neurons is represented centrally is to determine the neuroanatomical organisation of these circuits. We are generating genetic reagents in order to map the projections of IR-expressing neurons in the brain. These tools will also allow us to examine their physiological properties by optical imaging and to manipulate their activity to determine their role in mediating behaviour.
- Olfactory systems display remarkably rapid evolution, as organisms acquire and discard chemosensory receptors, neurons and responses with the ever-changing landscape of chemical stimuli in their environment. Insects provide an excellent opportunity to examine the genetic basis of these processes through the availability of the genome sequences of diverse insect species that have very different chemosensory sensitivities and preferences. Towards this, we have initiated bioinformatic and molecular analysis of the evolution of IR repertoires across insects.

FUNCTIONAL ANALYSIS OF A CD36 PROTEIN IN PHEROMONE DETECTION

We are also studying the function of a CD36 protein named SNMP, which we showed has an essential, and likely widespread, role in insect pheromone detection. CD36 transmembrane receptors are widely conserved in metazoans and implicated in diverse processes such as lipid transport, bacterial immune recognition, phagocytosis of apoptotic cells and fat taste perception. Their precise molecular role in any of these contexts is poorly understood. Our previous studies defined SNMP as one of the best characterised CD36 proteins in an in vivo biological process, in which we know the identity of both physiologically-relevant extracellular ligands (pheromones) and downstream effector pathways (OR-mediated neuronal activity). Thus, SNMP represents a powerful system to dissect the molecular function and specificity of this important class of proteins.



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Publications

RESEARCH ARTICLES

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Funding and Collaborations

FUNDING

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Swiss National Science Foundation (SNSF)
R'Equip Grant for a 2-photon microscope

Roche Research Foundation
PhD fellowship to R. Rytz

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Béatrice Desvergne
Professor

Networking activity of PPARs during development and in adult metabolic homeostasis

Béatrice Desvergne was trained as a MD. She initially specialized in Anesthesiology and Resuscitation, practiced medicine for a few years, and decided to move for fundamental research. She then carried out a post-doctoral stay from 1988 to 1992 at the National Institutes of Health in Bethesda, first as visiting fellow and then visiting associate in the National Institute of Diabetes and Digestive and Kidney Diseases. In 1992, she was appointed as Assistant Professor at the Institute of Animal Biology of the UNIL. After being appointed as Associate Professor, she was promoted as full Professor in 2008. She joined the Center for Integrative Genomics in 2003.

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) act as fatty acids sensors, responding to dietary as well as to endogenous challenges. Accordingly, they have an integrative role in controlling the expression of genes regulating the storage, mobilization, and/or utilization of lipids. Using various molecular, cellular, and animal approaches, our studies are aimed at understanding how PPARs are integrated in the main pathways that shape the organism during development on the one hand and maintain systemic homeostasis on the other hand.

We were among the first to generate PPAR mutant mice. Following a clinician-type of approach, our activities have been centered on revealing and understanding at the molecular levels the phenotypic expressions of PPAR mutations, taking them as leads to explore the physiopathological significance and novel therapeutic advances that PPARs carry.

Our studies during development show that both PPARβ and PPARγ are required for placenta development but each has specific activities: on the differentiation of trophoblast giant cells, via activation of the PI3K pathway and inhibition of Id2 for PPARβ, and on vascular development via controlling the expression of angiogenic factors for PPARγ. Further studies of the role of PPARβ and PPARγ in development were impeded by a partially and fully penetrant lethality of PPARβ-/- and PPARγ-/- embryos, respectively, at embryonic day 10.5. However, we have now generated fully viable mutant embryos and live pups, through an epiblastic selective PPAR deletion. It demonstrates that the cause of embryonic lethality in PPAR mutants is mainly due to the placental defects and gives us new tols for exploring the role of PPARγ in late development and in adult tissues.

In the adult animals, the gut is a very interesting organ, combining critical metabolic functions and a tightly regulated and highly active cell renewal capacity, from few adult stem cells to highly differentiated enterocytes, Paneth, Goblet, and enterodendocrine cells. In this tissue, we demonstrated that decrease of Indian Hedgehog via PPARβ ensures the final maturation of Paneth cell precursors whereas PPARγ is rather involved in controlling inflammation processes. We are now further exploring the importance of PPARs in response to challenges, either metabolic, infectious, or physical damages, with the purpose of bringing our mechanistic approaches in mouse models closer to human pathologies.

The role of PPARs as mediating the activity of some endocrine disruptors was an important focus of our recent activity. To understand how endocrine disruptors behave at the molecular levels in the living cells, we used a combination of Fluorescence Recovery After Photobleaching (FRAP), Fluorescence Correlation Spectroscopy (FCS) and Fluorescence Resonance Energy Transfer (FRET). We first demonstrated that PPARs readily heterodimerize with retinoid X receptor (RXR) and exhibit a ligand-induced reduction of mobility, probably due to enhanced interactions with cofactors and/or chromatin. We also demonstrated that coregulator recruitment (and not DNA binding) plays a crucial role in receptor mobility, suggesting that transcriptional complexes are formed prior to promoter binding. This allowed us to demonstrate that, in the living cells, the pollutant monoethylhexyl-phthalate (MEHP) directly binds to the ligand binding domain of PPAR and drives the recruitement of a specific subset of cofactors. We further analyzed the consequences in vivo of such activities and showed that MEHP protects mice from diet-induced obesity via a PPARα-dependent activation of hepatic fatty acid catabolism. This is accompanied by, and possibly due to, the up-regulation of the anti-obesity factor FGF21 hepatic expression. However, both effects are reversed in PPARα-humanized mice, underlining the importance of PPARα species-specific activities and questioning the impact of phthalates in human metabolic homeostasis.

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Publications

RESEARCH ARTICLES

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COMMENT

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*both authors contributed equally to this work.

**joint senior authors.

Funding and Collaborations

FUNDING

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Federation of European Biochemical Societies (FEBS)
Postdoctoral fellowship to L. Quignodon

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Christian Fankhauser
Associate Professor

The effects of light on plant growth and development

Christian Fankhauser received his PhD from the UNIL in 1994 after carrying out his thesis at Swiss Institute for Experimental Cancer Research (ISREC) in the laboratory of Dr. Viesturs Simanis. He performed postdoctoral studies with Dr. Marty Yanofsky at UCSD then with Dr. Joanne Chory at The Salk Institute for Biological Studies in San Diego. He became a Swiss National Science Foundation Assistant Professor at the Department of Molecular Biology of the University of Geneva in 2000. He joined the Center for Integrative Genomics in January 2005, where he was appointed Associate Professor.

Almost all our food, feed, fuel and fiber ultimately derives from plants. The growth of plants depends on photosynthesis, the process in which light energy is harnessed for the synthesis of high energy reduced 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. Given the central importance of light for growth, plants possess numerous photoreceptors enabling them to sense changes in the amount, quality (color), photoperiod and direction of light. The main goal of our research is to understand how light modulates plant growth and development in order to allow these sessile organisms to optimize their growth habit depending on the environmental conditions. We use the model plant Arabidopsis thaliana for our research.

Molecular genetic studies in Arabidopsis have identified four photoreceptor families that are present in all higher plants. There are three classes of blue light sensors: cryptochromes, phototropins and members of the Zeitlupe family. In addition plants sense red and far-red light with the phytochromes. In Arabidopsis these families are composed of three cryptochromes (cry1-cry3), two phototropins (phot1 and phot2), three Zeitlupe-like sensors and five phytochromes (phyA-phyE).

In our lab we concentrate our attention on phytochrome and phototropin-mediated signal transduction. Phytochromes are synthesized as Pr (R light absorbing); upon light excitation they are photo-transformed into Pfr (FR light absorbing), which is the active conformer. Light activation of the phytochromes triggers their accumulation in the nucleus where they mediate large changes in light-regulated gene expression. This activity is partly mediated by the conformation-specific interaction between Pfr phytochromes and a family of bHLH class transcription factors known as PIFs (Phytochrome Interacting Factor). Photon capture by these photoreceptors induces a suite of developmental responses including seed germination, seedling de-etiolation, regulation of tropic growth, shade avoidance and the control of flowering time. Some light responses are specifically induced by a single phytochrome (for example only phyA can trigger the de-etiolation response under a dense canopy), but there are many examples where integration of signals emanating from multiple photoreceptors is required. The phototropins are blue-light activated protein kinases composed of two light-sensing LOV domains and a carboxy-terminal protein kinase domain. By controlling phototropism, leaf positioning, chloroplast movements and opening of stomata the phototropins largely contribute to the optimization of photosynthesis. Interestingly the phototropic response is co-ordinately controlled by the phototropins and the phytochromes (in part indirectly by inhibiting the gravitropic response of the hypocotyl).

We combine molecular genetics, genome-wide expression studies, cell biology and biochemistry in Arabidopsis to address the following specific aims:

- Identify the molecular determinants leading to the specificity of phyA. Unlike other phytochromes, phyA can mediate light responses under conditions where the vast majority of the phytochrome is in its inactive Pr state. This correlates with the unique ability of phyA to accumulate in the nucleus in far-red light (mimicking light under a dense canopy).
- Determine the mechanisms by which the phytochromes control PIF-mediated growth responses. We mostly concentrate our attention on the role of PIF4 and PIF5 in the regulation of growth during the shade avoidance response.
- Uncover the mode of action of PKS (Phytochrome Kinase Substrate) proteins in the control hypocotyl growth orientation. Proper positioning of the stem is of central importance for the plant in order to optimize photosynthetic light capture. PKS proteins are involved both in phytochrome and phototropin signalling and may thus allow us to understand how these two photoreceptors co-ordinately control this growth response. Phototropism requires asymmetric growth of the shaded and lit sides of the hypocotyl. An important goal is to understand how this light response ultimately leads to asymmetric distribution of the plant hormone auxin, which is required for directional growth.

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RESEARCH ARTICLES

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Genetics and energetics of sleep homeostasis and circadian rhythms

Paul Franken received his PhD from the University of Groningen, The Netherlands, in 1993 for his work on sleep homeostasis and thermoregulation at the University of Zurich under the direction of Alexander A. Borbély. He was a postdoctoral fellow with H. Craig Heller at Stanford University, USA, where he studied the cellular mechanisms underlying circadian clock resetting. In 1996 he joined Mehdi Tafti at the University of Geneva where he used QTL analysis to map sleep and EEG traits in mice. He then moved back to Stanford in 2000 as a senior research scientist to establish an independent lab. At Stanford he continued to work on the genetics of sleep homeostasis and further focused on the molecular interactions between circadian rhythms, sleep homeostasis, and brain metabolism. He joined the CIG in 2005.

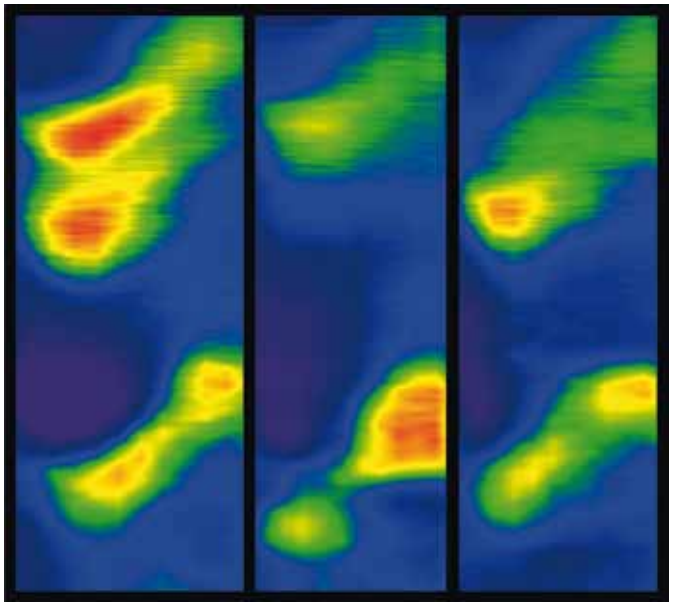
In the study of sleep two main regulatory processes have to be considered: a homeostatic process that is activated by and counters the effects of sleep loss and a circadian process that determines the time–of–day sleep preferably occurs. The fine–tuned interaction between the two permits us to stay awake 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.

QTL MAPPING

We use Quantitative Trait Loci (QTL) analysis as a forward genetics tool to map genomic regions that affect sleep. A first mouse reference population we used is a panel of recombinant inbred (RI) lines derived from the inbred strains C57BL/6J and DBA/2J referred to as BXD mice. 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 were successful at identifying the genes modifying two such traits thereby implicating novel signaling pathways involved in rhythmic brain activity. Ongoing work focuses on the Dps1 QTL on chromosome 13 that alters sleep homeostasis and for which Homer1 is a good candidate gene. In addition, we are now initiating two large scale projects to phenotype and map sleep traits in other mouse reference populations (i.e., CFW outbred mice and the 'Collaborative Cross' RI lines). To facilitate the phenotyping of large numbers of mice we helped develop and validate a novel non-invasive and high throughput method to measure sleep.

CLOCK GENES & SLEEP HOMEOSTASIS

Although the circadian and homeostatic processes are thought to operate independently, using reverse ('knock out') and molecular genetics (qPCR, micro-array) 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 investigate the mechanisms that link clock gene expression to the 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 using redox–sensitive GFP probes and developing in vivo imaging techniques to simultaneously monitor intracellular redox state and PER2 levels in freely moving mice. We 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) sequencing we aim to indentify which other NPAS2 target genes are differently regulated with sleep loss. Finally, using mathematical modeling we are now quantifying the complex relationship between changes in clock gene expression in the forebrain and the sleep-wake distribution in a similar way as we previously have quantified the relationship between the sleep-wake distribution and the EEG correlates of sleep need in mice. Model predictions are useful in helping to design relevant experiments to unravel these non-linear relationships.



Time course of the effects of a novel wake promoting drug on the EEG activity during wakefulness in three inbred strains of mice. Changes from baseline in EEG spectral profiles are plotted as a heat map, with colder (darker) colors indicating reduced EEG power density and warmer colors increased power density.

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Funding and Collaborations

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Nouria Hernandez performed her thesis research on mRNA splicing with Dr. Walter Keller at the University of Heidelberg in Germany and received her PhD in 1983. She did her postdoctoral studies with Dr. Alan M. Weiner at Yale University in New Haven, Connecticut, USA, working on 3' end formation of the U1 small nuclear RNA. She then joined Cold Spring Harbor Laboratory at Cold Spring Harbor, New York, in 1986 as an Assistant Professor. She became a Cold Spring Harbor Laboratory Professor in 1993 and joined the Howard Hughes Medical Institute as an Associate Investigator in 1994. She became a full Howard Hughes Medical Institute Investigator in 1999. In 2005, she joined the faculty of the UNIL as a Professor and as the Director of the Center for Integrative Genomics (CIG).

Mechanisms of basal and regulated RNA polymerase II and III transcription of ncRNA genes in mammalian cells

The task of transcribing the human genome is shared among three main RNA polymerases (RNAPs) known as RNAP-I, -II, and -III, as well as a newly identified single polypeptide RNAP-IV. RNAP-I transcribes the repeated 45S transcription unit, which gives rise to the 28S, 18S, and 5.8S ribosomal RNAs. RNAP-II transcribes the mRNA genes encoding proteins as well as most small nuclear RNA (snRNA) and microRNA genes. Thus, in contrast to RNAP-I, RNAP-II recognizes a large variety of promoter structures, reflecting the intricate regulation of its target genes in processes such as cell growth, proliferation, differentiation, and responses to various stresses. spRNAP-IV is thought to transcribe a few hundred mRNA-encoding genes. RNAP-III transcribes a collection of short genes encoding RNAs that are essential for cellular metabolism as well as some regulatory RNAs such as microRNAs.

We are interested in mechanisms of transcription regulation of genes producing transcripts that do not code for proteins, so-called non-coding RNA (ncRNA) genes. In particular we study the mechanisms that govern transcription of RNAP-II snRNA genes as well as transcription of RNAP-III genes, which according to current knowledge all give rise to ncRNAs. Both classes of genes are relatively understudied compared to classical RNAP-II mRNA-encoding genes, yet their regulation is of great importance for cell metabolism. Our recent focus has been in

i) the determination of the RNAP-III transcriptome in the human genome,

ii) the mechanisms of transcription activation of RNAP-III snRNA promoters, and

iii) the unexpected role of a subunit of the snRNA activating protein complex ($SNAP_c$), a transcription factor binding to the RNAP-II and RNAP-III core snRNA promoters.

TARGETS FOR BASAL TRANSCRIPTION FACTORS USED BY RNAP-II snRNA PROMOTERS AND RNAP-III PROMOTERS

In collaboration with Dr. H. Stunnenberg, Radboud University, we set out to characterize targets for $SNAP_c$ and RNAP-III in the human genome. We used an anti-TBP antibody we developed many years ago to select TBP-binding fragments and create a DNA array, which was then probed with DNA from chromatin immunoprecipitations performed with antibodies directed against various transcription factors including:

i) the RNAP-III transcription factors Brf1 and Bdp1;

ii) RNAP-III itself; and iii) the five $SNAP_c$ subunits. The results showed nearly perfect colocalization of Brf1, Bdp1, and RNAP-III on RNAP-III promoters, and good colocalization of the various $SNAP_c$ subunits on both RNAP-II and RNAP-III snRNA promoters. We are now extending this work to the entire genome using the ChIP-Seq methodology.

ACTIVATION OF RNAP-III TYPE 3 PROMOTERS AND RNAP-II snRNA PROMOTERS

Our studies on the mechanisms of transcription activation have been centered on the role of the zinc finger protein Staf in activating transcription from the RNAP-III U6 promoter. We found that Staf can bind to preassembled chromatin templates and activate transcription in vitro, suggesting that it recruits activities that modify the chromatin. Indeed, purification of Staf-associated proteins and their identification by multi-dimensional protein identification technology (MudPIT) revealed a number of proteins linked to chromatin remodeling and histone modification, among them the chromodomain-helicase-DNA binding protein 8 (CHD8). We showed that CHD8 binds to histone H3 di- and tri- methylated on lysine 4, resides on the human U6 promoter as well as on the mRNA IRF3 promoter in vivo, and is involved in efficient transcription from both these promoters. This suggests that RNAP-III transcription requires chromatin remodeling and uses some of the same factors used for chromatin remodeling at RNAP-II promoters.

AN UNEXPECTED FUNCTION FOR A SUBUNIT OF $SNAP_c$

The unexpected role of a $SNAP_c$ subunit was discovered during a routine examination of $SNAP_c$ localization. We found that the SNAP45 subunit localizes to centrosomes during parts of mitosis, as well as to the spindle midzone during anaphase and the mid-body during telophase. Consistent with localization to these mitotic structures, both down- and up-regulation of SNAP45 led to a G2/M arrest with cells displaying abnormal mitotic structures. In contrast, down-regulation of SNAP190, another $SNAP_c$ subunit, led to an accumulation of cells with a G0/G1 DNA content. Thus, SNAP45 seems to play two roles in the cell, one as a subunit of the transcription factor $SNAP_c$, and another as a factor required for proper mitotic progression.

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Mitotic functions for SNAP45, a subunit of the small nuclear RNA-activating protein complex SNAPc. J Biol Chem 283:14845-14856

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REVIEW

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Michels AA, Bensaude O (2008)
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Regulation of cell proliferation

Winship Herr received his PhD from Harvard University in 1982 for studies on recombinant retroviruses in leukemogenic mice with Walter Gilbert. After postdoctoral studies with Frederick Sanger in Cambridge England and Joe Sambrook at Cold Spring Harbor Laboratory, he joined the Cold Spring Harbor Laboratory faculty in 1984. There he served as assistant director of the Laboratory from 1994-2002 and from 1998-2004 was the founding dean of the Watson School of Biological Sciences, a doctoral degree-granting school. He arrived at the CIG in September 2004. Professor Herr was elected member of the European Molecular Biology Organization (EMBO) in 2008.

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.

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 site-specific DNA-binding proteins and recruits histone-modifying activities [e.g., Sin3 histone deacetylase and mixed-lineage leukemia (MLL) family of histone methyltransferases] for repression and activation of transcription. After synthesis, HCF-1 is cleaved into two subunits by an unusual process of proteolytic maturation. These two subunits remain associated but regulate different phases of the human cell cycle: The N-terminal subunit permits cells to progress into S phase for genome replication and the C-terminal subunit is required for proper segregation of the replicated genome into the two daughter cells in M phase.

Our recent studies in human cells have revealed important links between HCF-1 and the E2F family of cell cycle regulators. E2F transcriptional regulators control human-cell proliferation by repressing and activating the transcription of genes required for cell-cycle progression, particularly the S phase. E2F proteins repress transcription in association with retinoblastoma pocket proteins but less has been known about how they activate transcription. We have shown that human HCF-1 associates with both activator (E2F 1 and E2F3a) and repressor (E2F4) E2F proteins, properties that are conserved among their respective homologs in insect cells. Human HCF-1–E2F interactions are versatile: Their associations and binding to E2F-responsive promoters vary through the cell cycle, and HCF-1 displays co-activator properties when bound to the E2F1 activator and co-repressor properties when bound to the E2F4 repressor. During the G1-to-S phase transition, HCF-1 recruits the MLL and Set-1 histone H3 lysine 4 methyltransferases to E2F responsive promoters, and induces histone methylation and transcriptional activation. These results suggest that HCF-1 induces cell-cycle-specific transcriptional activation by E2F proteins to promote cell proliferation.

As indicated above, HCF-1 function is conserved in animals. We take advantage of this property to perform genetic, genomic, biochemical, bioinformatic, and molecular studies in diverse organisms including the C. elegans worm and Drosophila fruit fly. Our recent studies have benefited from such inter-species studies in flies and worms. For example, in flies, we have learned about mechanisms of HCF-1 proteolytic maturation. We have demonstrated that the Drosophila MLL and HCF-1 homologs, called Trithorax and dHCF, are both cleaved by Drosophila Taspase1 — Taspase1 being the protease in human cells previously shown to cleave MLL proteins. Although highly related, the human and Drosophila Taspase1 proteins display cognate species specificity: Thus, human Taspase1 preferentially cleaves human MLL and Drosophila Taspase1 preferentially cleaves the fly Trithorax protein, consistent with co-evolution of Taspase1 and Trithorax-related proteins.

In contrast, HCF proteins display even greater species-specific divergence in processing. Thus, dHCF is cleaved by the Drosophila Taspase1 but human and mouse HCF-1 maturation does not involve mammalian Taspase1. Instead, an in vitro HCF-1 cleavage assay shows that vertebrate HCF-1 proteins are cleaved by a novel proteolytic activity. Thus, from insects to humans, HCF proteins have conserved the aspect of proteolytic maturation but evolved different mechanisms to achieve it.

Using worms, we have investigated the role of HCF proteins in animal development by characterizing the effects of loss of the HCF-1 homolog in C. elegans, called Ce HCF-1. Two large worm hcf-1 deletion mutants are viable but display reduced fertility. Loss of Ce HCF-1 protein at lower temperatures (e.g., 12°C) leads to a high incidence of embryonic lethality and early embryonic mitotic and cytokinetic defects reminiscent of mammalian cell-division defects upon loss of mammalian HCF-1 function. Even when viable, however, at normal temperature, mutant embryos display reduced levels of phospho-histone H3 serine 10 (H3S10P), a modification implicated in both transcriptional and mitotic regulation. Mammalian cells with defective HCF-1 also display defects in mitotic H3S10P status. These results suggest that HCF-1 proteins possess conserved roles in the regulation of cell division and mitotic histone modification.

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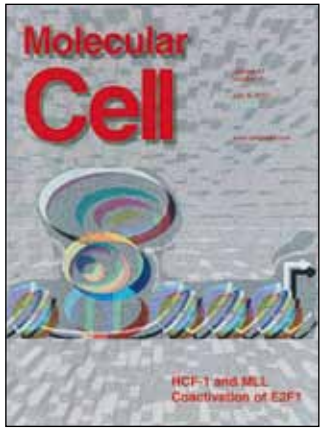

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Independent Basic Research Grant

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European Molecular Biology Organization (EMBO)
Long term fellowship to S. Tyagi

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Mammalian evolutionary genomics

Henrik Kaessmann received his PhD in 2001 from the University of Leipzig after working on the genetic diversity of humans and the great apes in the laboratory of Dr. S. Pääbo at the University of Munich and subsequently at the MPI for Evolutionary Anthropology, Leipzig. He obtained his postdoctoral training with Dr. Wen-Hsiung Li in the Dpt of Ecology and Evolution at the University of Chicago, where he worked on the origin of human genes and gene structures. In 2003 he joined the CIG as an Assistant Professor. He was appointed Associate Professor (with tenure) in 2007. Since 2005, he has been an EMBO Young Investigator. He was awarded the Basic Life Science Award by the Faculty of Biology and Medicine, UNIL in 2008 for his outstanding contributions to Basic Life Sciences research at the UNIL.

The research of my group has focused on the origin and evolution of new genes that emerged from duplicate gene copies in primates and other mammals. We have been particularly interested in the origin of new genes by retroposition (also termed retroduplication), a mechanism that creates intronless duplicate gene copies in new genomic positions through the reverse transcription of mRNAs from parental source genes.

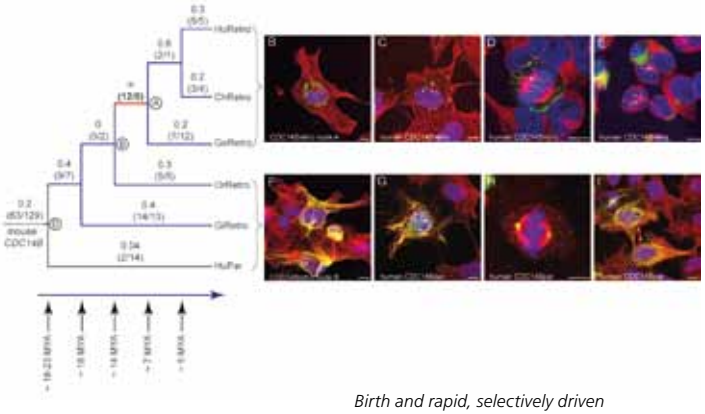
In the past two years, we have uncovered a novel mechanism underlying the emergence of new gene functions through a unique combination of evolutionary analyses and genomics/cell biology experiments. We found that proteins encoded by newly emerged genes can obtain new functional roles during evolution through changes of their localization in the cell, a process that we termed subcellular adaptation.

We also followed up on our original work pertaining to the out–of–X movement of genes. In this study, we established the reason for the excess of new retrogenes originating from X–linked parental genes: autosomal retrogenes substitute for the silencing of their X–linked parents during the transcriptional silencing of sex chromosomes during meiosis. Moreover, by dating the onset of the out–of–X movement, we established that our sex chromosomes originated late in the common ancestor of placental mammals and marsupials – rather than in the ancestor common to all mammals – and are thus much younger than previously thought.

In the framework of another line of research, we completed a major study performed in collaboration with the group of Prof. Alexandre Reymond pertaining to copy number variation (CNV) of genes within a species/population due to the duplication or deletion of genes. In this study, we established (using the mouse as a model) that CNV shapes tissue transcriptomes in various ways. We showed that the expression of genes both within and in the vicinity of CNV regions are affected by copy number changes. The extent of CNV-induced expression change depends on the spatial expression pattern of genes. For example, genes expressed in the brain are less affected by copy number changes, presumably due to more efficient regulatory feedback loops. Together with the observation that brain-expressed genes are underrepresented in CNV region, our results suggest strong selective constraint on gene expression changes in the brain.

In parallel to these lines of research, my group has pursued other projects regarding the origin of mammal–specific phenotypes. For example, we performed a study regarding the evolutionary origin of key features of mammals – lactation and placentation – and the associated loss of egg yolk nourishment of the young. We found that egg yolk genes were progressively lost in mammals due to the emergence of alternative nourishment resources for the young: lactation (we found that key milk genes – caseins – emerged in the common ancestor of all mammals) and the placenta.

Finally, in collaboration with Dr. Amalio Telenti (Institute of Microbiology, and University Hospital (CHUV), Lausanne), we completed several projects pertaining to the evolution of antiviral restriction in primates.



Birth and rapid, selectively driven subcellular adaptation of a hominoid-specific CDC 14B protein.

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Brawand D, *Wahli W, *Kaessmann H (2008)
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Molecular mechanisms of cell polarization

Sophie Martin earned her Diploma in 1999 from the UNIL for her study of chromatin organization in the laboratory of Dr Susan Gasser at the Swiss Institute for Experimental Cancer Research (ISREC). She then joined the group of Dr Daniel St Johnston at the Wellcome/CR UK Gurdon Institute to study the molecular mechanisms of cell polarization and mRNA localization using Drosophila as model system and received her PhD in 2003 from the University of Cambridge. She obtained postdoctoral training in the laboratory of Dr Fred Chang at Columbia University in New York, studying cell polarization and the cytoskeleton in the fission yeast. She joined the CIG as a Swiss National Science Foundation Professor in September 2007.

Polarity is crucial for cell function both during development and in differentiated cells. Cell polarity underlies the asymmetric division of stem cells to generate cell diversity and the function of differentiated cells, such as neurons, epithelial or immune cells. In proliferating cells, cell polarization is tightly linked with cell cycle controls. Indeed, loss of cell polarity has been associated not only with diseases affecting specific tissues or organs, but also with cancer, where it may contribute to uncontrolled proliferation. Thus understanding how a cell acquires and maintains polarity is a fundamental question in cell biology.

Our research aims to address how a cell acquires and maintains cell polarity and how this process is linked with cell proliferation. We use the fission yeast, Schizosaccharomyces pombe, as model system because it affords powerful genetic, biochemical and live-cell imaging tools. Fission yeast has a very small genome, encoding about 5000 genes, two thirds of which show direct homology with mammalian genes. This organism has been successfully used over the last 30 years to unravel fundamental mechanisms of cell proliferation and morphogenesis. We focus on three major areas of research:

MICROTUBULE-DEPENDENT CELL POLARIZATION

The cytoskeleton – microtubules and actin filaments – is essential for cell polarization. In rod-shaped fission yeast cells, microtubules are organized in a dynamic network aligned with the length of the cell and serve to transport polarity determinants towards the extremities of the cell. Microtubules provide positional information for growth at cell extremities and cells with anomalies in their microtubule network grow at ectopic locations. The actin cytoskeleton is organized at the cell extremities and essential for polarized growth. We had previously demonstrated that a microtubule-associated protein, tea4p, binds an actin nucleator of the formin family, for3p, thereby directly linking positional information provided by microtubules to actin assembly. We have now generated point mutations in tea4p to investigate its mode of localization and regulation. Our ongoing investigations suggest that tea4p may integrate phosphorylation and de-phosphorylation events to control cell polarization.

FORMIN-DEPENDENT CELL POLARIZATION

Formins are key actin organizers that nucleate linear actin filaments. Formins are essential for cell polarization in vegetative cells as they assemble a polarized network of actin cables that allows the delivery of myosin-driven cargoes to sites of polarized cell growth. These cargoes include membrane material and cell wall remodeling components essential for polarized cell growth. Yeast cells also show prominent polarization during the mating process, when two cells of opposite mating type extend cellular projections towards each other. We are currently investigating formin regulation during polarized cell growth.

CONNECTIONS BETWEEN POLARIZATION AND PROLIFERATION

Cell polarization is intimately linked to cell cycle changes. For instance, it has been proposed that loss of cell polarity influences cell proliferation and contributes to tumour formation. We have focused our investigations on a well-studied regulator of cell morphogenesis, the DYRK kinase pom1p, and uncovered a novel function for pom1p as an inhibitor of cell cycle progression. Pom1p forms gradients from cell ends. As cells grow in length during interphase, the pom1p gradients get further apart, lowering the concentration of pom1p at the cell middle in longer cells. We found that pom1p negatively regulates the SAD kinase cdr2p, a cell cycle activator itself localized at the cell equator throughout interphase. Our data suggest a model in which overlap between pom1p and cdr2p at the middle of short cells leads to mitotic delay while pom1p levels are no longer sufficient at the middle of long cells to inhibit cdr2p, thus allowing entry into mitosis. Gradients of pom1p thus provide a novel cell-intrinsic measure of cell length to ensure that sufficient length is attained before division. The high conservation of cell cycle regulators and cell polarization mechanisms across evolution suggests that lessons learned from yeast will be applicable to mammalian cells.

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RESEARCH ARTICLE

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Funding and Collaborations

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Roche Research Foundation
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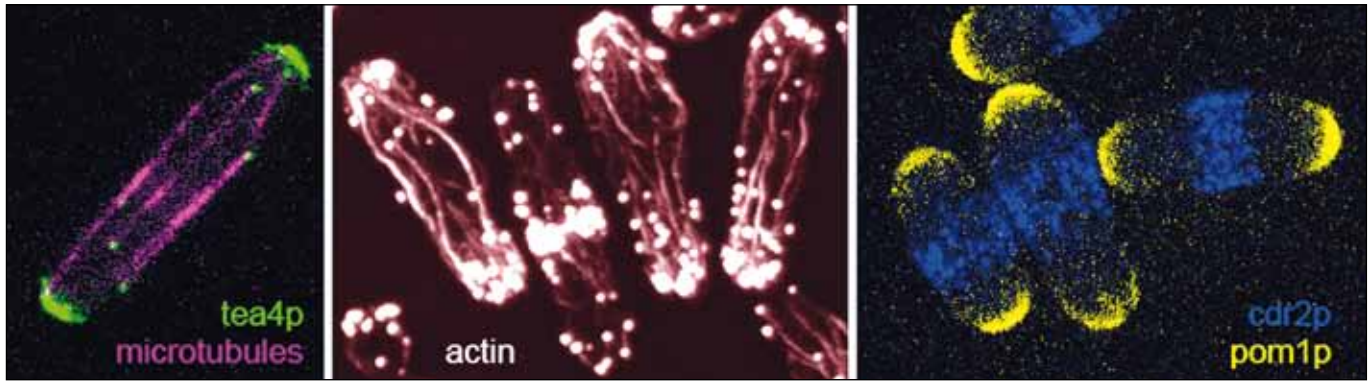


Liliane Michalik
Maître d'Enseignement et de Recherche

Transcriptional control of tissue repair and angiogenesis

Liliane Michalik received her PhD from the University Louis Pasteur of Strasbourg in 1993, for work on microtubule-associated proteins in the group of Jean-François Launay, INSERM. In 1994, she joined the group of Walter Wahli at UNIL for her post-doctoral training, during which she initiated a research project aimed at elucidating the roles of the nuclear hormone receptors PPARs in skin homeostasis and repair. Between 1996 and 2002, she persued her research in the same field as Maître Assistant, then Maître d'Enseignement et de Recherche at UNIL. She arrived at the Center for Integrative Genomics in 2003 as Maître d'Enseignement et de Recherche, and is MER-privat docent since 2008.

The vasculature is required to ensure blood and nutrient supply to the developing organs in the embryo, for organ and body growth after birth, and for organ repair in the adult. Because of this key functions, the vasculature and the heart are the first organ systems to be functional in vertebrate development. The nuclear hormone receptors PPARs were initially identified as regulators of energy metabolism and inflammation. Interestingly, they were recently reported as modulators of blood vessel formation, although the mechanisms remain unclear. We are interested in the functions of PPARs in the development of blood vessels during embryogenesis, adult skin repair and skin tumor growth.

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. Healing of cutaneous wounds proceeds via a well-tuned pattern of events that include inflammation, re-epithelialization, and matrix and tissue remodeling. We have observed that inflammatory molecules released immediately after the injury increase the expression of PPARbeta and trigger the production of endogenous PPARbeta ligands. Once expressed at high levels and activated, PPARbeta activates a major cellular survival pathway, which protects keratinocytes from death at the site of injury. Re-epithelialization depends on directional sensing and migration of keratinocytes, two processes that are impaired in PPARbeta-null mice. We found that the activation of PPARbeta amplifies a cellular internal signal, involving localized increase in the PIP3/PIP2 ratio, which is required for cellular directional sensing and activation of several effectors involved in cell polarization and pseudopodia extension. These processes are impaired in PPARbeta-null keratinocytes due to a reduced activity of the PI3K/Akt1 signaling cascade and its effectors involved in actin cytoskeleton plasticity and integrin recycling. Consistently, early wound biopsies of PPARbeta-null mice reveal delayed and uncoordinated migratory fronts at the wound edge demonstrating a defect in directional sensing and migration in vivo. In addition to re-epithelialization of the epidermis, these cell functions and molecular mechanisms are also involved in the development of tumors and in angiogenesis. We currently explore the roles of PPARs as transcriptional regulators of

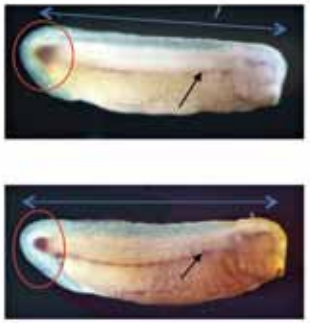
i) blood vessels formation during embryogenesis in the Xenopus tadpole and the mouse embryo,

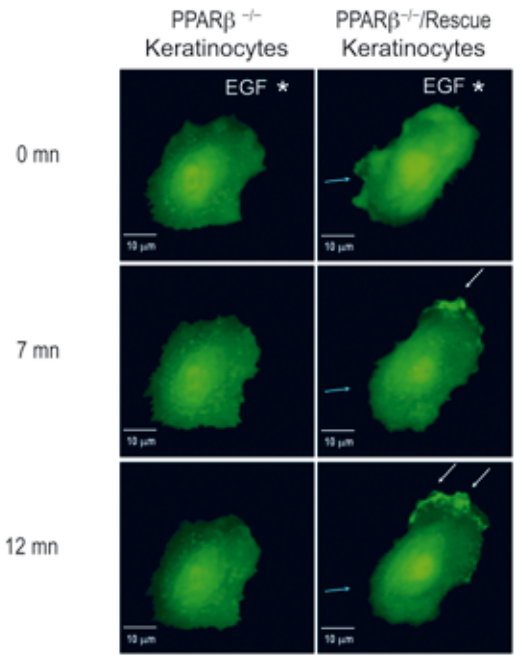
ii) angiogenesis during skin repair

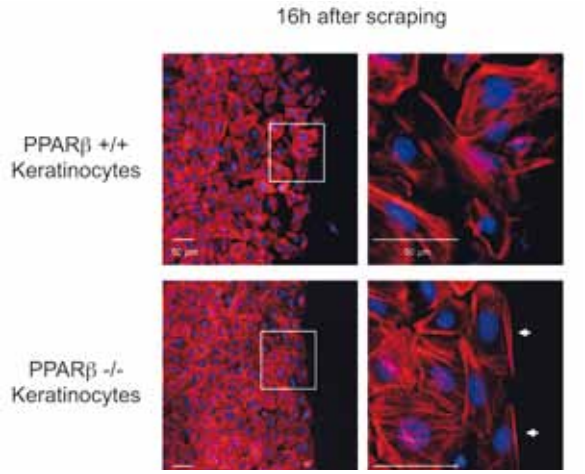
iii) UVB-induced skin tumor growth.

Mouse embryos

***Xenopus laevis* tadpoles**







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Rodriguez-Calvo R, Serrano L, Coll T, Moullan N, Sanchez RM, Merlos M, Palomer X, Laguna JC, Michalik L, Wahli W, Vazquez-Carrera M (2008) Activation of peroxisome proliferator-activated receptor beta/delta inhibits lipopolysaccharide-induced cytokine production in adipocytes by lowering nuclear factor-kappaB activity via extracellular signal-related kinase 1/2. Diabetes 57:2149-2157

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BOOK CHAPTER

Michalik L, Wahli W (2008) Tissue repair and cancer control through PPARs and their coregulators. In: Nuclear Receptors Co-regulators and Human Disease. Edited by Kumar BOMaR. World Scientific Publishing, London Singapore; 409-440

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Genome structure and expression

COPY NUMBER VARIANT

A fundamental question in current biomedical research is to establish a link between genomic variation and phenotypic differences, which encompasses both the seemingly neutral polymorphic variation, as well as the pathological variation that causes or predisposes to disease. In addition to the millions of individual base-pair changes that distinguish any two unrelated copies of our genome, recent reports have described large numbers of copy number variable regions (CNVs). Much effort has been put into the identification and mapping of these regions in humans and a number of model organisms, but a comprehensive understanding of their phenotypic effects is only beginning to emerge.

To assess the functional impact of CNVs at the genome-wide scale we have undertaken a large-scale CNV study using the mouse as a model organism. We have generated an extensive map of CNV in wild mice and classical inbred strains. Copy number variable regions cover ~11% of their autosomal genome. Genome-wide expression data from different major organs not only reveal that expression levels of genes within CNVs tend to correlate with copy number changes, but also that CNVs influence the expression of genes in their vicinity - an effect that extends up to half a megabase. Notably, genes within CNVs show lower expression levels and more specific spatial expression patterns than genes mapping elsewhere in the genome. Furthermore, our analyses reveal differential constraint on copy number changes of genes expressed in different tissues. In particular, dosage alterations of brain-expressed genes are less frequent than those of other genes and are buffered by tighter transcriptional regulation. Thus, we provide initial evidence that CNVs shape tissue transcriptomes on a global scale and thus represent a substantial source for within-species phenotypic variation.

MECHANISMS AT PLAY

The functional impact of modifying the copy number of a given copy number variation remains unstudied at a genome-wide scale. Such a global assessment is achievable nowadays using the mouse as a model organism. Mouse models of the Smith-Magenis (SMS) and Potocki-Lupski (PTLS) syndromes carry a deletion at band MMU11B2 (strain Df(11)17)/+) and its reciprocal duplication (Dp(11)17/+), respectively. These heterozygous mice show phenotypic features similar to those identified in human SMS and PTLS patients. These models and their normal littermates (+/+) allow to study the influence of one, two and three copies of the same CNV in an otherwise identical genomic background. A fourth strain (Dp(11)17/Df(11)17) obtained by mating the Dp(11)17/+ and Df(11)17/+ animals allows to generate mice with two copies of that same CNV in cis, while they are in trans in +/+ animals.

Preliminary studies of the hippocampus transcriptome of PTLS models and normal littermates showed that a highly significant propensity of the most differentially expressed transcripts are mapping to the engineered SMS/PTLS interval. Interestingly, a statistically significant overrepresentation of the genes mapping to the flanks of the engineered interval was also found in the top-ranked differentially expressed genes, confirming the results described above. But how may changes in copy number of CNV regions alter the expression of genes in their vicinity? Different CNV-induced mechanisms that include the physical dissociation of the transcription unit from its cis-acting regulators, modification of transcriptional control through alteration of chromatin structure, and modification of the positioning of chromatin within the nucleus and/or within a chromosome territory of a genomic region might play a role, both individually or in combination. Copy number changes might also influence gene expression through perturbation of transcript structure.

BALANCED REARRANGEMENT

A third type of variation comprises the balanced chromosomal rearrangements, such as reciprocal translocations and inversions, which elicit no gain or loss of genetic material. Balanced rearrangements occur in approximately 1 in 500 individuals in the general population and recent studies have identified hundreds of polymorphic inversions. We will study the effect of balanced chromosomal rearrangements on gene expression by comparing the transcriptomes of cell lines from control and t(11;22)(q23;q11) individuals. This translocation between chromosomes 11 and 22 is the only recurrent constitutional non-Robertsonian translocation in humans.

Alexandre Reymond carried out his thesis in the laboratory of Dr. Viesturs Simanis at the Swiss Institute for Experimental Cancer Research (ISREC) and received his PhD from the UNIL in 1993. After completion of his postdoctoral training with Dr Roger Brent in the Department of Molecular Biology, Massachusetts General Hospital and in the Department of Genetics, Harvard Medical School in Boston, he moved to the Telethon Institute of Genetics and Medicine (TIGEM) in Milan in 1998 to lead a research group. He joined in 2000 the Department of Genetic Medicine and Development, University of Geneva Medical School. He moved to the Center for Integrative Genomics in October 2004 and became an Associate Professor in February 2009.

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Functional transitions of DNA structure

Andrzej Stasiak received his PhD in 1981 from the Institute of Biochemistry and Biophysics of Polish Academy of Sciences in Warsaw. From 1981 to 1989 he was a postdoctoral fellow and research associate in the laboratory of Theodor Koller at Institute for Cell Biology, ETHZ, Zurich, Switzerland. In 1989 he joined the Laboratory of Ultrastructuaral Analysis directed by Jacques Dubochet at the UNIL. In 2007 he joined the Center for Integrative Genomics as Maître d'Enseignement et de Recherche (MER).

Our group is interested in two main subjects:

1. Topology and biophysics of DNA and of polymers in general,
2. Mechanism of action of proteins involved in DNA recombination and DNA repair.

In the field of DNA topology one of central questions pursued in many laboratories is how DNA topoisomerases keep the level of DNA knotting much below the level that would have resulted from random intersegmental passages. One of the considered hypothetical mechanisms proposed that topoisomerases may act preferentially at DNA-DNA juxtapositions where two independent DNA regions are interhooked with each other. We have tested this mechanism by numerical simulations and demonstrated that selection of interhooked juxtapositions could indeed provide a mechanism assuring that steady state knotting level within living cells is orders of magnitude lower than this that would heave resulted from random intersegmental passages. For more details, see: Burnier Y., Weber C., Flammini A. & Stasiak A. Local selection rules that can determine specific pathways of DNA unknotting by type II DNA topoisomerases. NAR, 35: 5223 – 5231, 2007.

Continuing our efforts directed toward understanding how DNA topoisomerases avoid DNA knotting in bacterial cells we investigated the effect of DNA supercoiling on DNA knotting and have revealed that supercoiling provides the free energy gradient that opposes DNA knotting. Burnier, Y., Dorier, J. & Stasiak, A. DNA supercoiling inhibits DNA knotting. NAR, 36: 4956-4963, 2008.

Consideration of DNA knots and DNA topoisomerases provided a motivation for the development of a software that could be used to find out which pairs of DNA knots can be converted into each other by one intersegmental passage mediated by type II DNA topisomerases or that could tell for example how many topo II mediated passages are needed to convert a given knot into another one. The software development project was done with external collaborators (Isabel Darcy, USA and Rob Scharein, Canada). To make our software broadly known and accessible to interested biologists we have described it in a paper: Darcy I., Scharein R. & Stasiak A. 3D visualization software to analyse topological outcomes of topoisomerase reactions. NAR, 36, 3515-3521, 2008.

The effects of knotting on statistical mechanics of cyclic polymers is currently an active field of research. In a collaboration project involving several laboratories we have used numerical simulation approach to understand how the scaling behaviour of global curvature and global torsion depends on the knot type of the polymer chains with increasing length. For more details, see: Total curvature and total torsion of knotted polymers. Macromolecules, 40, 3860-3867, 2007.

Another collaboration project in the field of biophysics of polymers concerned investigation of basic shapes adopted by cylindrical tubes that locally attract each other. We observed that most of known biological structures can be reproduced and explained using this very simple tube model. See: Structural motifs of biomolecules. PNAS, 104, 17283-17286, 2007.

The second leading subject of our research proposal concerned investigation of mechanism of action of various proteins involved in the process of DNA recombination and DNA repair.

In a collaboration project with the group of Prof. A. Constantinou (UNIL) aimed to understand the action and function of FANCM protein. This human protein is required for DNA repair after various DNA damages including DNA crosslinking. Patients with defective FANCM gene suffer from Fanconi anaemia. Our electron microscopy images revealed that FANCM protein preferentially binds to point of strand exchange in Holliday junctions. These images complemented biochemical analysis performed in the laboratory of A. Constantinou and strongly indicated that the FANCM protein promotes branch migration by specific interaction with the strand exchange region in Holliday junctions. For more details, see: FANCM can promote branch migration of Holliday junctions and regression of replication forks. Molecular Cell, 29, 141-148, 2008.

Continuing our productive collaboration with the group of J.-Y. Masson (Canada) we participated in two projects intended to understand functions of proteins that stimulate and participate in Dmc1 and Rad51-mediated DNA recombination and DNA repair. For more details, see: Fission yeast and mouse Hop2-Mnd1 stimulate Dmc1 and Rad51 recombinases. NAR, 35, 2719-2733, 2007 and A glycine-arginine domain in control of the human MRE11 DNA repair protein. Mol. Cell. Biol., 28, 3058-3069, 2008.

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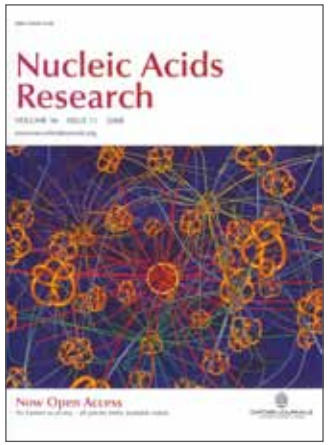

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Genetics of sleep and the sleep EEG

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. An EEG variant specific to paradoxical sleep (slow theta frequency) has been identified as the most heritable phenotype in inbred mice and subsequent mapping and functional studies identified Acads (acyl Coenzyme A dehydrogenase for short chain fatty acids) as the underlying gene. More recently, we have shown that the slow wave activity during sleep is also affected by a single gene (Rarb) involved in the vitamin A signaling pathway. We are now concentrating our research efforts on the genetic dissection of sleep need. Sleep need is homeostatically regulated (loss of sleep leads to compensatory processes, which are responsible for deeper recovery sleep). A gene for sleep need has been mapped on the mouse chromosome 13. Gene expression profiling after sleep deprivation to investigate the molecular correlates of prolonged wakefulness, identified Homer1a on chromosome 13 as the best molecular marker of sleep need. Finally, we are interested in sleep and circadian rhythms and their molecular basis in social species such as ants.

GENETIC S OF SLEEP DISORDERS

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 also initiated a new Center for Investigation and Research in Sleep (CIRS) in collaboration with the Department of Medicine of the University Hospital (CHUV), Lausanne, where we plan to conduct sleep research in normal subjects and patients with sleep disorders. We have localized the first familial susceptibility gene for narcolepsy and have reported the first genetic evidence in sleepwalking. Future plans include genetics of normal sleep in twins, families, and the general population.

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.

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Molecular and physiological analysis of energy homeostasis in health and disease

Bernard Thorens received his PhD from the University of Geneva for studies on the biosynthesis of immunogluobulins 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 fellowhisp 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. Since 2002 he is Professor on Physiology and joined the Center for Integrative Genomics in 2005.

Glucose homeostasis and development of type 2 diabetes are critically dependent on the capacity of the insulin secreting beta-cells of the pancreas to secrete insulin according to the metabolic need of the organism. This secretory capacity depends on both the number and secretion capacity of the differentiated beta-cells.

One of our research projects aimed at identying novel genes that regulate beta-cell proliferation, secretion capacity and apoptosis. To this end we are evaluating the mode of action on beta-cells of the gluco-incretin hormones GLP-1 and GIP, which are known to stimulate beta-cell precursor differentiation and proliferation of mature beta-cells, as well as to protect these cells against apoptosis. Our ongoing work was initiated by performing transcript profiling of islets from mice with genetic inactivation of the GLP-1 and GIP receptors, and which showed decreased secretion capacity and increased susceptibility to apoptosis. The function of these genes is investigated by overexpression or down-expression (siRNA) studies in beta-cell lines, primary beta cells and in transgenic mice, followed by functional analysis of proliferation, apoptosis, insulin secretion, as well as whole body glucose homeostasis.

Glucose homeostasis, feeding behavior and energy expenditure are under the control of the hypothalamus, where neuronal circuits integrate internal signals, informing on food absorption and metabolic energy storage, and send new signal to regulate energy homeostasis.

In a second line of investigation we thus aim at identifying, at the cellular and molecular levels, the mechanisms by which glucose is sensed by neurons, and how these sensing neurons regulate the function of the hypothalamic neuronal circuits controlling glucose and energy homeostasis. These studies are based on the analysis of gene knockout mice, which show loss of central glucose sensing and, as a consequence, deregulated control of feeding and energy expenditure. These studies are being pursued by genetically marking the glucose sensing cells to identify them and characterize the neuronal circuits they form to control the melanocortin pathway, a key hypothalamic neuronal circuit controlling glucose and energy homeostasis. We are also generating mice with tissue and cell-specific knockout of a glucose transporter to inactivate these glucose sensors and evaluate their role in specific anatomical sites. These investigations involve the use of molecular biology techniques, immunohistochemistry, and integrated physiological analysis of control or genetically modified mice.

In a third line of investigation, we seek to identify the metaboplic pathways in liver that are associated with susceptibility or resistance to diet-induced steatosis using comparative transcriptomic and lipidodomic analysis of liver from different strains of mice. We have previously provided evidence that resistance to steatosis development was associated with increased expression of enzymes controlling peroxisomal beta-oxidation and microsomal fatty acid elongation; lipidomic analysis has demonstrated that many lipid species were differently produced in association with resistance to steatosis development. We are testing the role of these lipids in controlling insulin resistance and the proinflammatory state of the resistant mice. These studies are being pursued by combined transcriptomic, lipidomic and physiological analysis of mice with knockout of some of the identified genes. These studies will investigate the functional role of specific lipid species in controlling gene expression and the proinflammatory state, which is tightly associated with development of metabolic diseases.

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The multifaceted roles of PPARs

Walter Wahli received his PhD from the University of Bern. He was a postdoc at the Carnegie Institution of Washington in Baltimore, and a visiting associate at the National Cancer Institute, NIH, Bethesda. He became Professor and Director of the Institute of Animal Biology of the UNIL in 1980 and was Vice-rector. He founded the CIG, which he directed until 2005. He has been a member of the SNSF's research council and presided over the Biology and Medicine Division. He became a member of the Swiss Science and Technology Council in 2008. He is an elected member of the EMBO and of the Institut Jurassien des Sciences, des Lettres et des Arts. Since 2007, he is an elected individual member of the Swiss National Academy of Medical Sciences. He received the Otto-Naegeli Prize (2002), the European Federation of Lipid Research Award (2002) and the Hartmann Müller Prize (2008).

The three Peroxisome Proliferator-Activated Receptors (PPARs) are nuclear receptors that act as lipid sensors to modulate gene expression. They are implicated in major metabolic and inflammatory regulations with far-reaching medical consequences, and in important mechanisms controlling cellular fate. PPARs exhibit a broad but isotype-specific tissue expression pattern, which can account for the variety of cellular functions they regulate. This diversity of functions is also reflected by the broad range of ligands that can be accommodated within their ligand binding pocket. These ligands are naturally occurring lipids, which include diverse fatty acids, leukotrienes and prostaglandins. Recently, his group has analyzed functions of the three PPAR isotypes, PPARbeta (also called PPARdelta) in wound-healing, muscle energy metabolism and early development of Xenopus, PPARgamma in adipogenesis, and PPARalpha in liver sexual dimorphism.

Healing of cutaneous wounds proceeds via a pattern of events including inflammation, re-epithelialization, and tissue remodeling. We have shown that the inflammation that immediately follows injury increases the expression of PPARbeta and triggers the production of endogenous PPARbeta ligands. PPARbeta then activates a major cellular survival pathway, which protects keratinocytes from death at the site of injury. We have also demonstrated that transforming growth factor beta (TGFbeta1) down regulates the action of inflammation-induced PPARbeta, thereby participating in the coordination of re-epithelialization. This latter event depends on directional sensing and migration of keratinocytes. We found that the activation of PPARbeta amplifies intracellular signals required for cellular directional sensing, cell polarization and pseudopodia extension. These processes are delayed and reduced in PPARbeta-null keratinocytes. Consistently, early wound biopsies of PPARbeta-null mice reveal uncoordinated migratory fronts at the wound edge demonstrating a defect in directional sensing. Together, these observations reveal the molecular mechanisms by which PPARbeta and its ligands contribute to wound closure. In addition, PPARbeta contributes to the homeostatic control of keratinocyte proliferation and differentiation mediated via its regulation, in dermal fibroblasts, of IL-1 signaling.

We have undertaken an in depth analysis of the role of PPARs in Xenopus laevis development. Down regulation of PPARbeta has dramatic effects on both gastrulation and early organogenesis. PPARbeta controls gastrulation movements. At the molecular level, it regulates the Nodal pathway by controlling the transcription of the 6 Nodal ligands (Xenopus nodal related genes 1-6; Xnr 1-6). Interestingly, PPARbeta behaves as a positive regulator of Xnr genes immediately prior to gastrulation but functions as a repressor during gastrulation. All together, our data pinpoint PPARbeta as a key factor in early embryo patterning.

PPARgamma is involved in adipocyte differentiation and insulin sensitivity. Synthetic ligands, the thiazolidinediones (TZD), are used as insulin sensitizers in the treatment of type 2 diabetes. PPARgamma serves as an essential regulator of adipocyte differentiation and lipid storage, and is required for maintenance and survival of mature adult adipocytes. Deregulations of its functions are thought to account for diseases such as obesity and diabetes. We found recently that deletion of one PPARgamma allele not only affects lipid synthesis, pentose phosphate shunt, lipolysis, and glycerol export, but also, more surprisingly, networks of genes involved in IR/IGF-1 signaling, cellular integrity, detoxification, and inflammation/immunity. These results unveil novel roles of PPARgamma in the adipose tissue and underscore the multifaceted action of this receptor in the fine-tuned functioning of this major tissue in the healthy and diseased organism.

Most metabolic studies are conducted in male animals and, consequently, the molecular mechanism controlling gender-specific pathways has been neglected. Our recent work showed that PPARalpha has broad female-dependent repressive actions on hepatic genes involved in steroid metabolism and inflammation. Using the steroid oxysterol hydroxylase gene Cyp7b1 as a model, we elucidated the molecular mechanism of this PPARalpha-dependent repression. Physiologically, this repression confers protection against estrogen-induced intrahepatic cholestasis, suggesting a novel therapy against the most common hepatic disease during pregnancy.

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(continued on next page)

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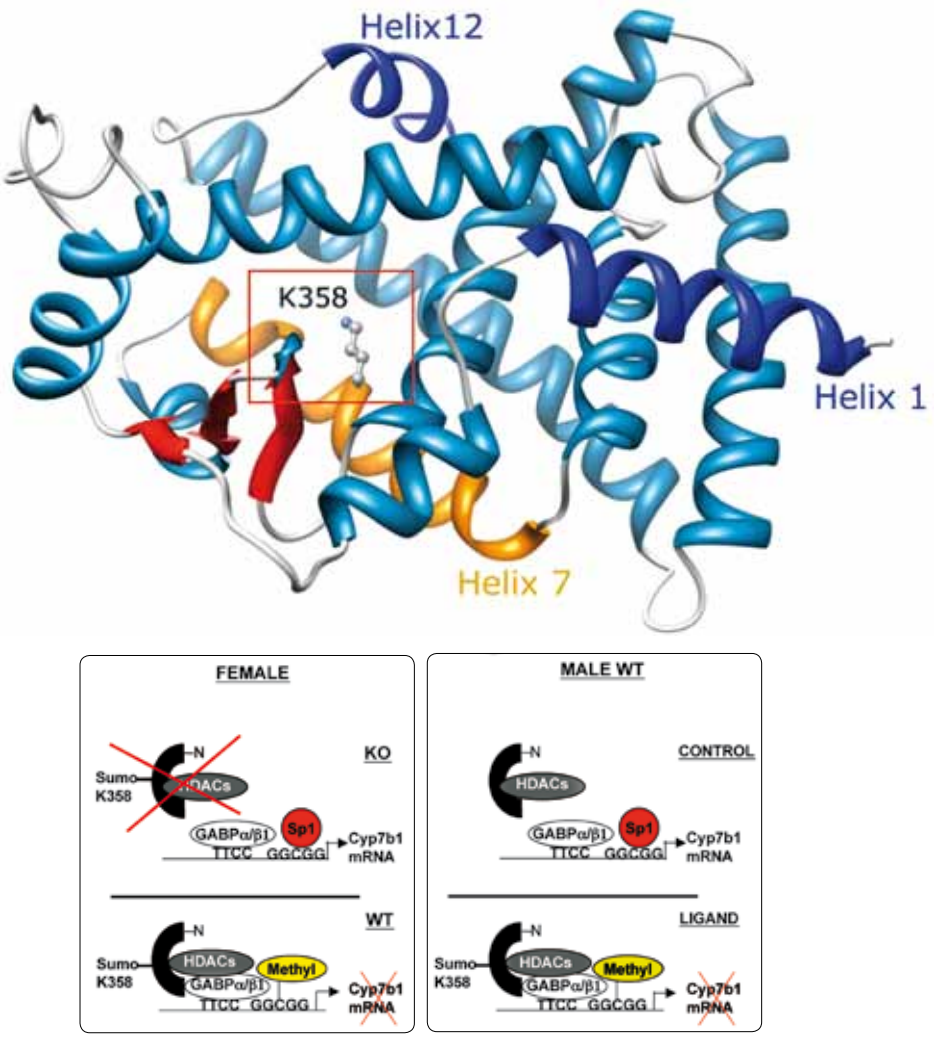

Sex-specific sumoylation of PPARα regulates DNA methylation-dependent gene repression.
The molecular mechanism of gender-specific repression of the steroid hydroxylase Cyp7b1 gene by PPARα involves sumoylation of Lysine 358 in the ligand-binding domain of PPARα. This post-translational modification is essential for the interaction of PPARα with the GA-binding protein alpha (GABPα) bound to the target promoter. Histone deacetylase (HDAC) is then recruited and, in addition, histones and adjacent Sp1-binding site are methylated. These events result in the loss of Sp1 binding to the Cyp7b1 promoter and thus, down-regulation of its activity.

OTHER RESEARCH GROUPS AT THE GÉNOPODE

The CIG is located in the UNIL building called Génopode. This building also shelters the direction of the Swiss Institute of Bioinformatics (SIB) and some groups belonging to that Institute, as well as to the Ludwig Institute for Cancer Research (LICR) and the UNIL/CHUV CePO (Multidisciplinary Oncology Center).

These groups contribute greatly to the dynamism of the CIG and of the Génopode by extending further the interactions and integration of different views, technologies and fields in research.

Marie-Agnès Doucey
Chargée de recherche

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Understanding signalling pathways controlling inflammatory cell functions

Inflammatory cells and pro-inflammatory cytokines are central in immune protection and in cancer progression. The identification of key signaling proteins controlling the function of inflammatory cells are of paramount significance in the design of immune protection and cancer therapies.

In spite of the critical role of memory T cells in immune protection and cancer progression, the biochemical mechanisms controlling the diverse functional outcomes of human central and effector memory T cell responses remain poorly understood. We implemented reverse phase protein arrays to profile T cell receptor signalling components in human CD8 and CD4 memory T cells populations isolated ex vivo and we identified c-Cbl as a critical regulator of the functional heterogeneity of memory CD4 T cells.

Recently a distinct lineage of Tie-2/tek-expressing monocytes has been identified in peripheral blood of mouse and humans and shown to be recruited to tumor and to comprise a functionally distinct myeloid lineage of paracrine inducers of angiogenesis and tumor growth. These monocytes may represent a valuable marker for cancer diagnostic and a promising target of novel anti-cancer therapies. However, the mechanisms promoting TEM recruitment at tumor sites, and the molecular basis of their pro-tumor and pro-angiogenic activities have not been identified yet. Our current research aims to evaluate the diagnostic value of TEM in breast cancer (in collaboration with Professor J.-F. Delaloye, University Hospital (CHUV), Lausanne) and to gain insight into the signalling pathways and the molecular mechanisms controlling their functions by interfacing computational and experimental approaches (in collaboration with Dr. Ioannis Xenarios, Vital-IT). Finally, to characterization the soluble factors that mobilize angiogenic monocytes to the tumor, we are currently constructing a biosensor based on functionalized silicon nanowires for the label-free detection of pro-inflammatory and angiogenic factors in breast tumor extracts (in collaboration with Dr. Hourlier, CNRS, Lille, France).

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Ronet C, Voigt H, Himmelrich H, Doucey M-A, Breton M, Hauyon-Latorre Y, Tacchini-Cottier F, Bron C, Louis J, Launois P L (2008)
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Cancer genomics

The research interests of the group focus on two major themes:

- the evolution and variability of the genes encoding cancer-testis antigens
- the development of in silico techniques for the efficient analysis of novel high-throughput genomics data.

CT genes are normally expressed only in immuno-privileged cells of the germ line, but re-expressed in a variable proportion of cancers. Most of the human genes with a strict CT expression pattern are localized on the X chromosome, and are members of families that have undergone recent expansion in the primate lineage. One focus of our research is to trace the evolutionary history of CT-X genes. To this end, we are establishing a comprehensive catalogue of CT-X genes in the human genome, which is a challenging task because many of them occur in regions with segmental duplications that have not been assembled correctly or contain gaps. This work has led us to identify new CT-X families and to produce more detailed genomic maps of known families. We are also looking for CT homologues in the ever increasing collection of available genomes, with the goal of tracing the emergence and evolution of each family, and therefore inferring possible function. Finally, we are studying copy number variations (CNV) of CT-X genes, both at the genetic (inter-individual differences) and the somatic (cancer-specific) levels.

On the methodological side, we have developed tools for the efficient utilization of short reads generated by "next-generation" sequencing machines. The "Rolexa" algorithm makes it possible to interpret and map a significantly larger proportion of individual reads from Solexa/Illumina sequencers than the manufacturer's proprietary software. The "fetchGWI" software implements a very efficient method for matching large collections of short sequences to genome-size databases, facilitating SNP inference. We have also evaluated methodologies for extracting reliable CNV information from genome-wide hybridization data in very large cohorts.

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Molecular modeling, in silico drug design and protein engineering for the development of cancer therapies

The Molecular Modeling group studies mechanisms of molecular recognition, in particular protein-protein or protein-small ligand interactions. The group develops and employs molecular modeling techniques such as homology modeling, molecular dynamics, protein-ligand docking, structure-based fragment-based drug design and free energy simulations. Most efforts are concentrated on the development of new small molecule inhibitors of important targets for cancer therapy, as well as the design of optimized peptides vaccines or T Cell Receptor (TCR) sequences for cancer immunotherapy.

In silico structure-based ligand design is becoming a very attractive alternative to high throughput in vitro methods. We have developed the EADock docking program, which uses a very accurate and universal scoring function to provide a good description of molecular interactions from small fragments up to complete ligands. An efficient conformational search engine has been designed based on an evolutionary algorithm. We are currently using a fragment-based approach to design specific inhibitors of important cancer targets for which several micro and nano-molar compounds have been obtained lately.

Specific cellular immune responses are based on the recognition by cytotoxic T lymphocytes of immunogenic peptides presented in the context of the class I Major Histocompatibility Complex (MHC). TCR sequence modifications designed to improve recognition of a given p-MHC complex represent a very attractive approach since these modified sequences can be incorporated in the patient's lymphocytes using viral vectors and used in an adoptive transfer setting. We have developed several free energy calculation methods not only to dissect TCR-p-MHC interactions, but also to interpret the effect of a mutation and guide peptide and/or TCR modifications. Several mutations proposed by the in silico approach have recently been shown to improve TCR affinity as well as tumor cell killing by transfected lymphocytes in vitro.

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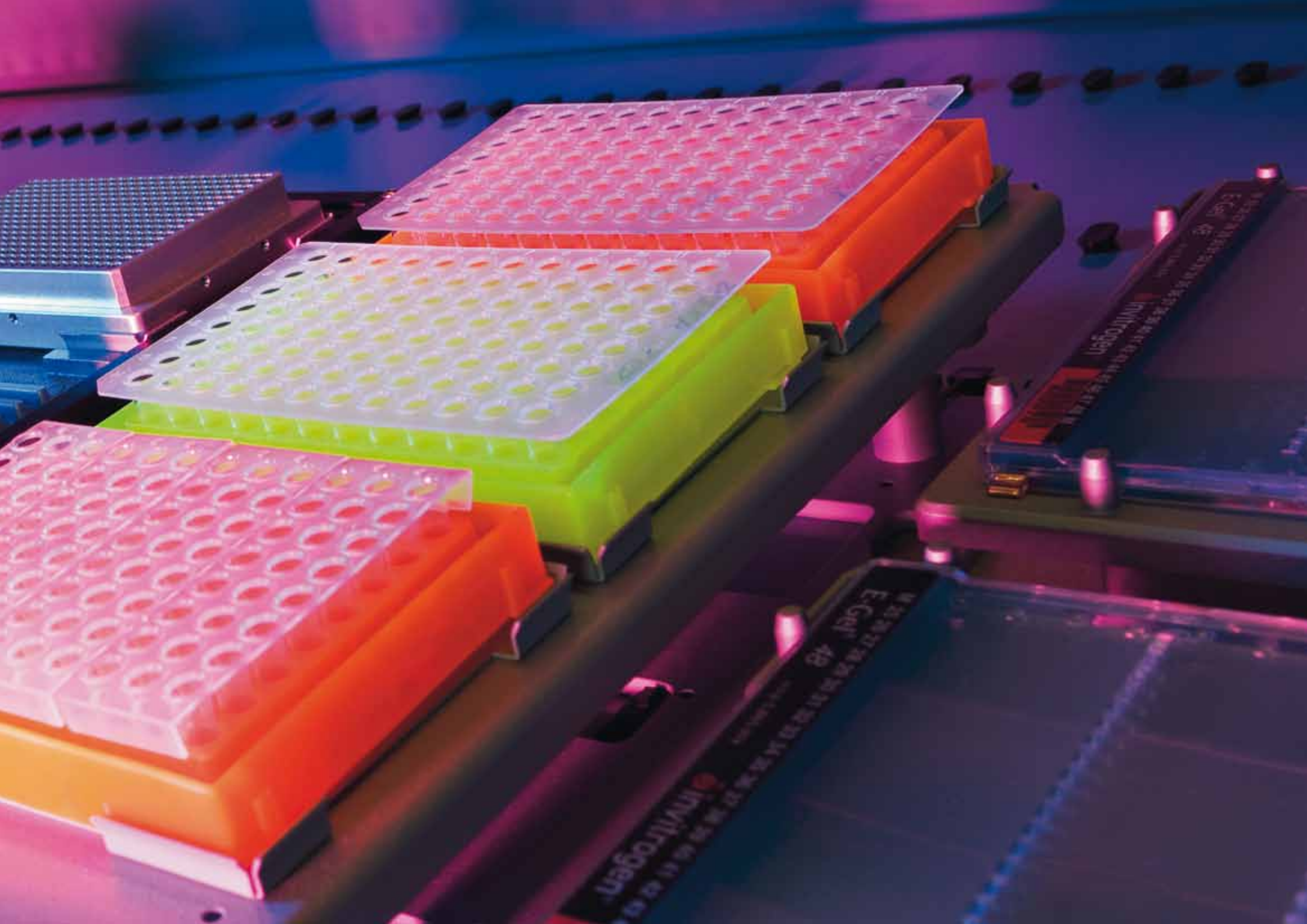
InvitroGen
E-Gel 48

Keith Harshman
Maître d'Enseignement et de Recherche

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 post doctoral 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 DNA Array Facility since November of 2002.

Lausanne DNA Array Facility (DAFL)

The goal of the Lausanne DNA Array Facility (DAFL) is to provide the user community with access to the state-of-the-art technologies used to measure quantitative and qualitative variations in nucleic acids. The principal technology platforms supported by the DAFL to achieve this goal are:

- The Illumina Genome Analyzer II and the 454 Genome Sequencer FLX ultra high throughput DNA sequencing instruments
- Affymetrix GeneChip oligonucleotide arrays for the analysis of mRNA and DNA
- Illumina BeadChip oligonucleotide arrays for the analysis of mRNA
- Agilent oligonucleotide arrays for the analysis of small non-coding RNA
- the Applied Biosystems 7900HT Sequence Detection System for as quantitative real-time PCR analyses
- sample handling robots for the production of custom spotted DNA and protein arrays

The DAFL provides users with training and supervision in all aspects of the molecular biology and instrument manipulations associated its technology platforms. In many cases, the DAFL will perform all of the steps of the experiment, beginning with nucleic acids provided by the user. A key aspect of the DAFL 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. The facility allows users to carry out their experiments in its laboratories by providing equipment and bench space. Furthermore, the DAFL maintains computer workstations and software with which users can analyze their data.

EDUCATIONAL ACTIVITIES

The DAFL is also active as an educational resource for the community. Its principal activities have been in organizing a yearly week-long microarray use and application course under the auspices of the Schweizerische Kommission fuer Molekularbiologie (SKMB) and the IIIème Cycle Romand en Sciences Biologiques. Additionally, the DAFL assists in the planning and organization of the Lausanne Genomics Days Symposium, a 2 day event in which invited scientist present on recent developments in genomic research in molecular biology, medicine, ecology and evolution.

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Brembilla NC, Weber J, Rimoldi D, Pradervand S, Schutz F, Pantaleo G, Ruegg C, Quadroni M, Harshman K, Doucey MA (2008)
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ACKNOWLEDGEMENTS IN PUBLICATIONS

As a core facility, the DAFL receives ackowledgement but not authorship on publications containing results obtained from regular services. Authorships reflect extensive collaborations beyond regular services.

Within the years 2007 and 2008, the DAFL was ackowledged in at more than 30 publications in the following journals:

- Aging Cell
- BMC Bioinformatics
- Breast Cancer Res
- Cancer Res
- Cell
- Cell Stem Cell
- Curr Biol
- Dev Cell
- Plant Cell
- Genome Biol
- Genome Res
- Hepatology
- Hum Mol Genet
- J Bacteriol
- J Biol Chem
- Lancet Oncol
- Mol Cell Biol
- Mol Cell Neurosci
- Nature
- Nature Medicine
- Plant Cell
- PLoS Genet
- Proc Natl Acad Sci U S A
- PLoS ONE

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 expression levels, it is nowadays 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

In 2007-2008 the PAF has expanded its offer to include support for analysis of phosphorylation in complex samples (phosphoproteomics) as well as SILAC (Stable Isotope Labeling with Amino Acids in Culture) experiments for quantitative proteomics. We have in addition improved the sensitivity of our analyses as well as the quality of data analysis and experiment reporting provided to users. Our service of shotgun protein identification aimed at discovering protein-protein interactions has grown in popularity – the number of analysed samples has doubled over previous years.

INDEPENDENT TECHNOLOGY DEVELOPMENT PROJECTS

We have pursued our development of methods for metabolic labeling of cells to specifically identify in complex mixtures such as whole cell extracts the proteins that were synthesized at high rates during a given time. We have applied variants of these labeling protocols to study changes in protein turnover in cells infected by Herpes Simplex virus. We found several molecules display changes, the functional importance of which is under investigation. As a second application we have devised a strategy to explore the pool of proteins secreted by human cell lines (the "secretome") under regular culture conditions. The presence of a vast excess of bovine serum proteins makes the analysis of these samples particularly challenging. The experience we accumulated with stable isotope labeling with amino acids has resulted, among other things, in the development of a novel method of relative protein quantification. This new technique (termed ISIS) is based on labeling with isobaric amino acid analogs which give rise to distinct reporter ion fragments in tandem MS spectra.

COLLABORATIVE STUDIES ON FUNCTIONALLY RELATED SETS OF PROTEINS

We have continued collaboration with the group of M. Peter (ETHZ, Zurich, Switzerland) focused on the study of protein complexes formed by the E3 Ubiquitin ligases Cullin-3 and Cullin-4A. We were able to show specific association of Cul-3 with a family of Kelch domain-containing proteins (KLH-9, -13, -21 and others), while Cul-4A recruited WD40-domain containing proteins instead. All these molecules are believed to be recruiting subunits which determine the set of substrates ubiquitinated by each E3 ligase complex. The Cul-3-KLH9-KHL13 complex was later shown to play a key role in mitosis. Another collaboration with the group of C. Ruegg (Multidisciplinary Oncology Center (CePO), Lausanne) has led us to determine a set of cell surface proteins which localize in lipid rafts and are candidate markers of metastatic melanoma. In the context of a third collaborative effort with the group of M. Monod (Dermatology, University Hospital (CHUV), Lausanne, Lausanne) we were able to complete the first comprehensive identification of the proteins secreted by the two skin infecting fungi Trychophyton rubrum and Trychophyton violaceum. This fraction is highly enriched in proteases, which play a role in the invasion of the skin layers, but surprisingly was found to contain numerous other hydrolases such as lipases and glycosidases whose role in pathogenesis remains largely unknown.

Manfredo Quadroni got his PhD in Biochemistry at the ETHZ, Zurich, Switzerland 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 ETHZ, Zurich, Switzerland (1998–2000) to work on development of methods for proteome analysis. He was then Maître assistant at the Institute of Biochemistry of the UNIL between 2000 and 2003. He joined the CIG in March 2003 as Maître d'Enseignement et de Recherche (MER) to coordinate the PAF facility.

Group members

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COORDINATOR AT THE GENOPODE

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BIOINFORMATICIANS

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Céline Hernandez

TECHNICIANS

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PHD STUDENT

Mara Colzani

Publications

Brembilla NC, Cohen-Salmon I, Weber J, Ruegg C, Quadroni M, Harshman K, Doucey MA (2009)
Profiling of T-cell receptor signaling complex assembly in human CD4 T-lymphocytes using RP protein arrays. Proteomics 9:299-309

Baruthio F, Quadroni M, Ruegg C, Mariotti A (2008)
Proteomic analysis of membrane rafts of melanoma cells identifies protein patterns characteristic of the tumor progression stage. Proteomics 8:4733-4747

Brembilla NC, Weber J, Rimoldi D, Pradervand S, Schutz F, Pantaleo G, Ruegg C, Quadroni M, Harshman K, Doucey MA (2008)
c-Cbl expression levels regulate the functional responses of human central and effector memory CD4 T cells. Blood 112:652-660

Colzani M, Schutz F, Potts A, Waridel P, Quadroni M (2008)
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Da Cruz S, Parone PA, Gonzalo P, Bienvenut WV, Tondera D, Jourdain A, Quadroni M, Martinou JC (2008)
SLP-2 interacts with prohibitins in the mitochondrial inner membrane and contributes to their stability. Biochim Biophys Acta 1783:904-911

Giddey K, Favre B, Quadroni M, Monod M (2007)
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Giddey K, Monod M, Barblan J, Potts A, Waridel P, Zaugg C, Quadroni M (2007)
Comprehensive analysis of proteins secreted by Trichophyton rubrum and Trichophyton violaceum under in vitro conditions. J Proteome Res 6:3081-3092

Grill B, Bienvenut WV, Brown HM, Ackley BD, Quadroni M, Jin Y (2007)
C. elegans RPM-1 regulates axon termination and synaptogenesis through the Rab GEF GLO-4 and the Rab GTPase GLO-1. Neuron 55:587-601

Sumara I, Quadroni M, Frei C, Olma MH, Sumara G, Ricci R, Peter M (2007)
A Cul3-based E3 ligase removes Aurora B from mitotic chromosomes, regulating mitotic progression and completion of cytokinesis in human cells. Dev Cell 12:887-900

Tinel A, Janssens S, Lippens S, Cuenin S, Logette E, Jaccard B, Quadroni M, Tschopp J (2007)
Autoproteolysis of PIDD marks the bifurcation between pro-death caspase-2 and pro-survival NF-kappaB pathway. Embo J 26:197-208

Funding and Collaborations

FUNDING

Swiss National Science Foundation (SNSF)
Independent Basic Research Grant

COLLABORATIONS

J.–J. Diaz and A. Greco
INSERM, Lyon, France

M. Peter
ETHZ, Zurich, Switzerland

C. Ruegg
University Hospital (CHUV) and UNIL, Lausanne, Switzerland

M. Monod
University Hospital (CHUV) and UNIL, Lausanne, Switzerland

ACKNOWLEDGEMENTS IN PUBLICATIONS

As a core facility, the PAF receives ackowledgement but not authorship on publications containing results obtained from regular services. Authorships reflect extensive collaborations beyond regular services.

Within the years 2007 and 2008, the PAF was ackowledged for example in publications in the following journals:

- Brain Res Bull
- Circ Res
- Mol Biol Cell
- Proteomics
- Vox Sang

CORE FACILITIES ASSOCIATED WITH THE CIG

In addition to the DNA array facility (DAFL) and the protein analysis facility (PAF), a number of other core facilities are associated with the CIG, either because they are located in the Génopode and/or because they are directed by CIG members. Such facilities contribute greatly to the dissemination of novel techniques and know-how, to the highly interactive atmosphere of the CIG, and thus to the quality and creativity of the research at the CIG and beyond.

The Bioinformatics Core Facility (BCF)

The Bioinformatics Core Facility (BCF) is a research and service group, member of the Swiss Institute of Bioformatics (SIB), located within the Génopode. The BCF offers consulting, data analysis support, training and research collaborations. Our core competences and activities reside in the interface between biomedical sciences, statistics and computation, particularly in the application of high-throughput omics technologies in biochemical, translational and clinical research, such as the study of gene-gene and gene-phenotype associations and biomarker development. Main activities:

- Data Analysis Support and Biostatistics Consulting: We provide basic bioinformatic and data analytic support at all stages of high-throughput studies, from design to data acquisition, analysis, and interpretation. The consulting service is run on a mandate from - and partially funded by - the SIB and the Swiss Confederation.
- Training: We train researchers in the application of basic methods of data analysis and interpretation through course and workshop offerings.
- Research and Collaborations: We can provide collaborative data analysis and method implementation for projects requiring advanced or innovative approaches to academic and industrial partners.

The emergence of "omics" science presented challenges for integrating multiple modes of assays (DNA, RNA, proteins) and heterogeneous, independent datasets (multi-center cohorts in clinical studies). We develop solutions for data curation and management, application of rigorous statistical methods and implementation of effective and efficient computational methods.

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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. Since the end of 2005, the CIF has extended its activities on the Dorigny 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 . In parallel to service activities, a consortium of investigators affiliated with the CIF will develop and implement most advanced optical and imaging technologies. This unit will have an open and dynamic interface with the service, so that emerging technological developments will be 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 (FBM) of the UNIL and the University Hospital (CHUV), Lausanne. The hosting institutes have also brought a major contribution by offering room, infrastructure, logistics, administrative, and technical support.

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TECHNICAL MANAGER AT THE CIG

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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 clinicians specialist in sleep disorders, we have established the Center for Investigation and Research in Sleep (CIRS). This joint venture between the CIG and the University Hospital (CHUV), Lausanne, is providing 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.

DIRECTORS

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www.unil.ch/cig/page42710_fr.html

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.

The MEF is an integral part of the CHUV-FBM CardioMet Research Center that gathers three coordinated investigative units, namely the MEF, the Rodent Cardiovascular Phenotyping Center (coordinated by Prof. T. Pedrazzini, at the FBM) and the Clinical Investigation Center (coordinated by Prof. F. Pralong at CHUV). Cardiomet aims at fostering joint projects in clinical and basic research, in the Cardiovascular and Metabolic fields.

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COORDINATOR

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Vital-IT

Vital-IT is an innovative life science informatics initiative providing computational resources, consultancy and training to connect fundamental and applied research. It is a collaboration between the Swiss Institute of Bioinformatics (SIB), the UNIL and University of Geneva, the Ludwig Institute for Cancer Research (LICR), the EPFL, Lausanne, and industrial partners. These partners form an alliance of unrivalled expertise in the processing and analysis of biological information. Using their complementary competencies, they provide fundamental science and leading edge technology for the construction of a world-class high-perfomance computing platform, and the expertise to allow it to be exploited effectively for solution of both scientific and commercial problems.

Vital-IT provides infrastructure and computational expertise to support research conducted primarily by its partners, and develops hardware and software solutions to allow research results to be turned into products. Additionally, the group serves as an interface between academic research and the commercial world. The main activities undertaken by Vital-IT are:

- Providing an HPC environment to support the research work of its partners, in areas ranging from sequence analysis through molecular modelling, genomics, proteomics and image analysis
- Developing specialist software engineering techniques for parallelization, optimization and validation of complex algorithms.
- Development activities to turn concepts derived from research into robust software solutions.
- Consulting and educational activities geared towards the computational needs of companies in the life sciences.
- Acting as an agent for new collaborations with industry and in future, including potential spin-off of new companies in the field of life-science informatics.

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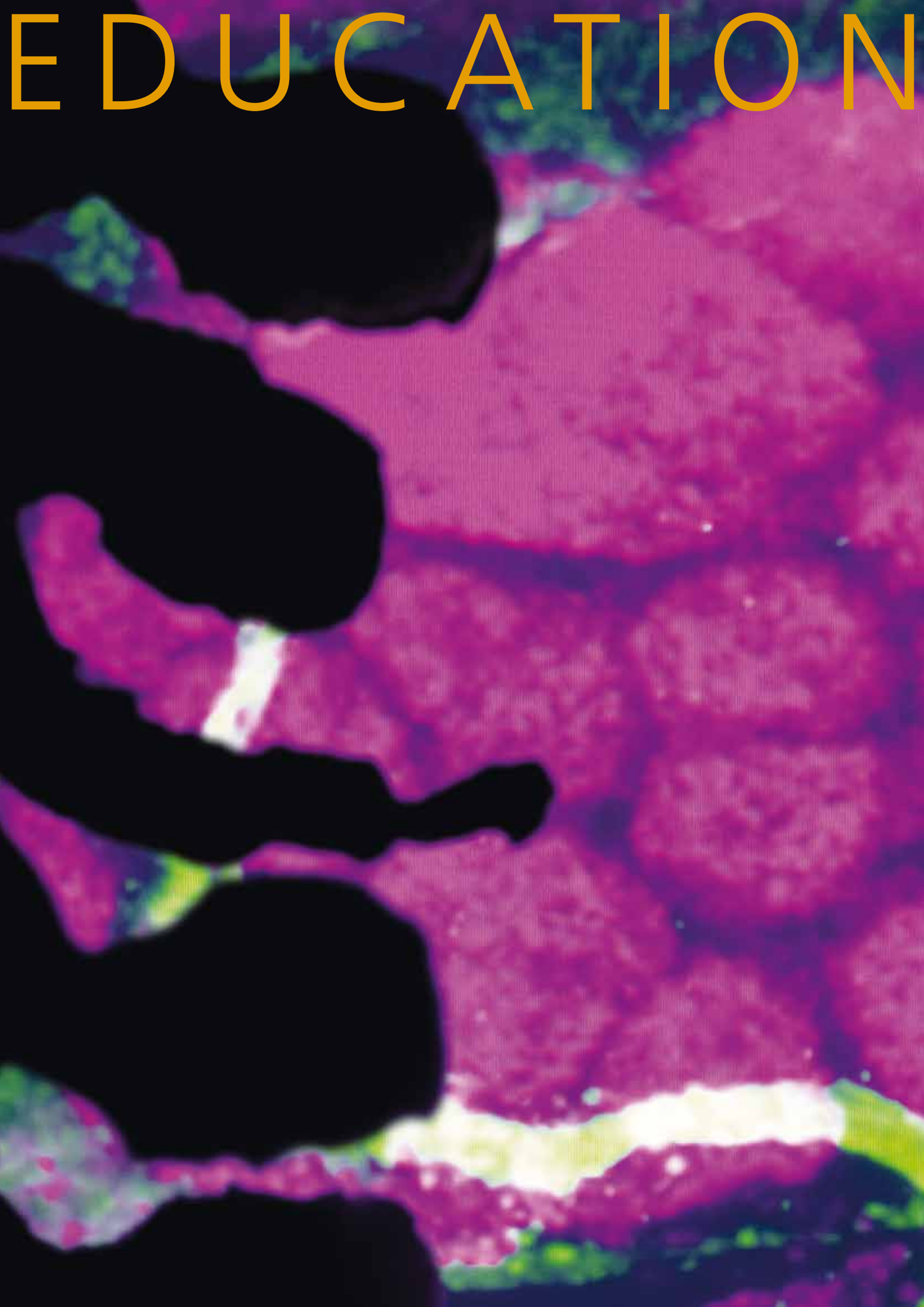
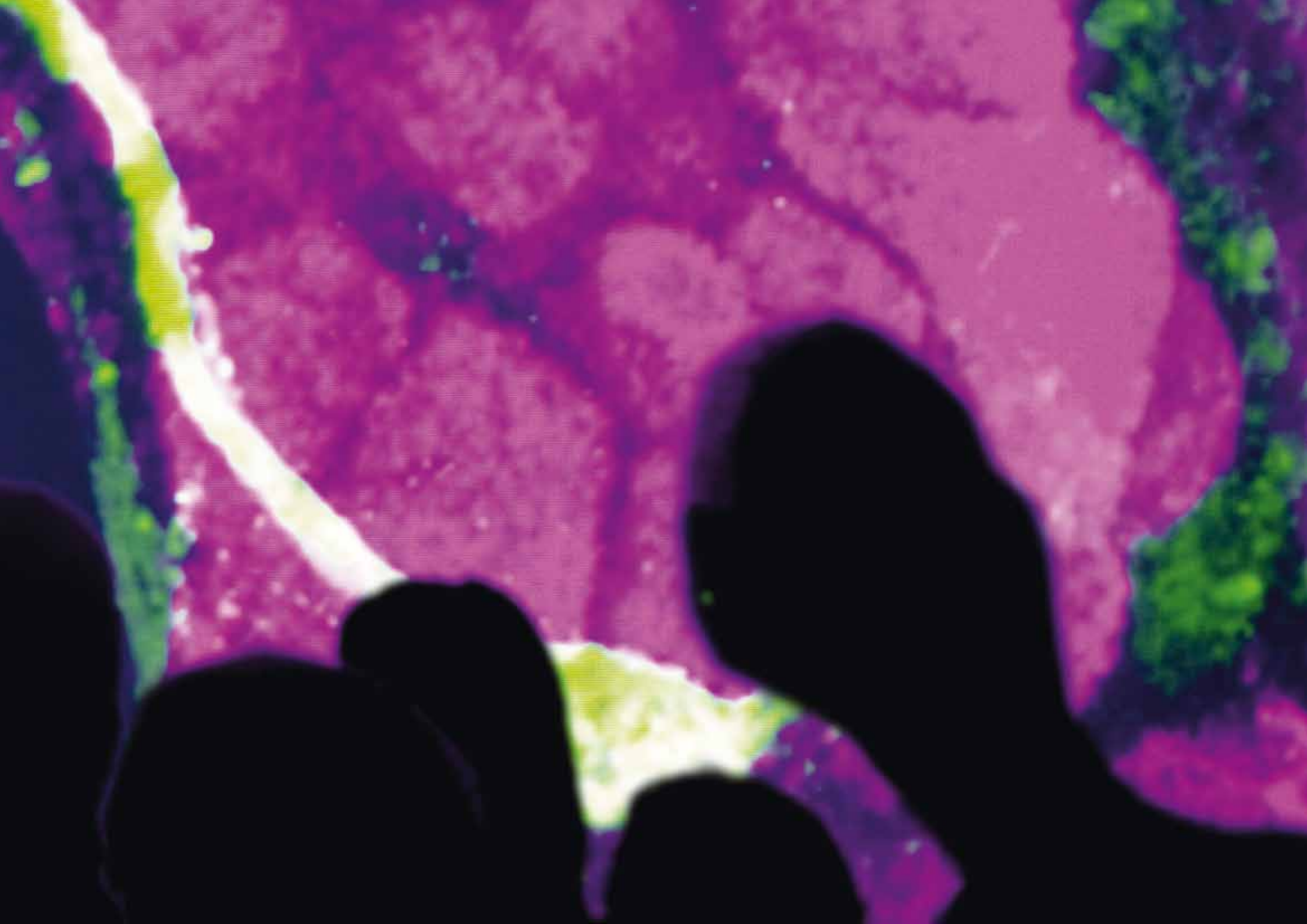
EDUCATION





EDUCATION AT THE CIG

A central mission of the CIG is education. The members of the CIG, whether research group leaders, research assistants or members of core facilites, give courses at the Bachelor, Master and PhD levels at the UNIL and at other organizations. The CIG is also active in the organization of undergraduate studies, for example with the involvment of C. Fankhauser in the organization of the UNIL Master GBE (Genomics and Experimental Biology), see www.unil.ch/enseignement/page28113_en.html.

CIG research groups comprise researchers at every stage of their training, including not only post-doctoral fellows and PhD students, but also students working toward their master degree in Biology. Moreover, during the summer, the CIG hosts pre-graduate students through a summer research program run by the EPFL School of Life Sciences in collaboration with the CIG (see http://ssv.epfl.ch/page64103.html). Postdoctoral fellows and graduate students, who spend several years doing research at the CIG, benefit from a mentoring program (see p. 52).

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

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

Courses and lectures given by CIG members

Courses at the UNIL

BACHELOR LEVEL

Béatrice DESVERGNE
Génétique avancée
Biologie et société
Biologie animale et génétique I
Biologie animales et génétique II

Béatrice DESVERGNE
co-instructor:
Nicolas ROTMAN
(maître-assistant)
Génétique avancée
Biologie animale et génétique II

Béatrice DESVERGNE
Liliane MICHALIK
Walter WAHLI
co-instructor:
Nicolas ROTMAN
(maître-assistant)
Biologie cellulaire animale

Nouria HERNANDEZ
Walter WAHLI
Transcription et maturation de l'ARN

Nouria HERNANDEZ
co-instructor:
Erwann VIEU
(maître-assistant)
Travaux pratiques structurés

Winship HERR
From genotype to phenotype and phenotype to genotype

Henrik KAESSMANN
Introduction to molecular evolution
Molecular evolution

Liliane MICHALIK
Biologie cellulaire animale
Embryologie

Alexandre REYMOND
BCM: du génome au phénome
Statistiques pour biologistes

Andrzej STASIAK
Mechanism of DNA recombination

Mehdi TAFTI
BCM – du phénome au génome

MASTER LEVEL

Béatrice DESVERGNE
Régulation transcriptionnelle du métabolisme

Christian FANKHAUSER
Structure des génomes des végétaux
Effets de l'environnement sur le développement

Christian FANKHAUSER
Johann Weber
Cartographie, séquençage et structure des génomes

Paul FRANKEN
Keith HARSHMAN
Mehdi TAFTI
Johann WEBER
Génomique protéomique et génétique quantitative

Winship HERR
Virologie

Henrik KAESSMANN
Alexandre REYMOND
Evolutionary and comparative genomics

Liliane MICHALIK
Embryologie

Manfredo QUADRONI
Alexandra POTTS
Jachen BARBLAN
Proteomics: introduction

Bernard THORENS
PPP métabolisme

Walter WAHLI
Chapitres choisis de développement
Récepteurs nucléaires et régulation génétique

PhD LEVEL

Christian FANKHAUSER
Paul FRANKEN
Circadian clocks

Winship HERR
Reasoning and logic in genetics and molecular and cellular biology

Alexandre REYMOND
Mapping transcription start sites

Bernard THORENS
Introduction endocrinologie 2.1
Métabolisme glucidique 2.4

Courses at other organizations

Paul FRANKEN
Genetics of sleep (PhD level)
Regulation of sleep (PhD level)
European Marie Curie Teaching courses

Otto HAGENBÜCHLE
Methods for transcriptome analysis (Master level)
EPFL, Lausanne, Switzerland

Otto HAGENBÜCHLE
Keith HARSHMAN
Johann WEBER
RNA expression profiling using DNA microarrays
(Master/ PhD level)
3e Cycle Romand en Sciences Biologiques

Nouria HERNANDEZ
Biologie moléculaire II
(Bachelor level)
EPFL, Lausanne, Switzerland
Exercice de biologie
(Bachelor level)
EPFL, Lausanne, Switzerland

Liliane MICHALIK
PPARs: skin repair and cancer
(PhD level)
NCCR Frontiers in Genetics

Manfredo QUADRONI
FT-ICR mass spectrometry
(Master level)
University of Geneva

Alexandre REYMOND
The human genome project
(Bachelor level)
University of Geneva
Functional genomics (PhD level),
EPFL, Lausanne, Switzerland

Mehdi TAFTI
Neurobiologie des états de vigilance (Master level)
University of Geneva

Bernard THORENS
Integration by the brain of peripheral signals to control energy homeostasis
(PhD level)
NCCR Frontiers in Genetics

Walter WAHLI
Thiazolidinediones et autres approches médicamenteuse
(Bachelor level)
University of Geneva

Walter WAHLI
co-instructor:
Nicolas ROTMAN
(maître-assistant)
Récepteurs nucléaires
(PhD level)
NCCR Frontiers in Genetics

Undergraduate students

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Group Herr

Jovan MIRCETIC
Group Hernandez

Cylia ROCHAT
Group Martin

Ana TUFEGJZIC
Group Herr

Vanja VUKOJEVIC
Group Fankhauser

Fang WANG
Group Fankhauser

Zhou ZHOU
Group Martin

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Group Michalik

Michaël BARUCHET
Group Michalik
Group Wahli

Claire BERTELLI
Group Hernandez

Vincent CROSET
Group Benton

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Cynthia DAYER
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Sebastien DEL RIZZO
Group Tafti

Pieric DORIOT
Group Wahli

Diego GONZALES
Group Herr

Henrietta HROBOVY CRAUSAZ
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Group Wahli

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Frédéric LAURENT
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Group Franken

Deborah WIDMER
Group Benton

Gilles WILLEMIN
Group Thorens

DOING A PhD AT THE CIG

Education and support to graduate students is a central concern of the CIG. All PhD students at the Center are part of the doctoral school of the UNIL Faculty of Biology and Medicine (FBM), which determines the program and regulations of PhD studies.

In addition, the CIG set up a mentoring program to support and advise graduate students. Through the program, each student is coupled to a mentor, in general a faculty member working in a different field than the one pursued by the graduate student, who is available for scientific or non-scientific discussions and advice.

Opportunities to learn about different research topics and technologies are numerous, for example during the annual CIG retreat, which is attended not only by all CIG groups but also by all other research groups in the Génopode, 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 external leading scientists from all over the world, who give their presentation and then spend time discussing with interested students and post-doctoral fellows.

The CIG is proud to support the activities of the "CIG Association of Scientists" CAOS, which groups students, post-doctoral fellows, and technicians. In particular, the "Careers for Biologists Seminars" feature speakers with a biology training and a career outside of the university environment. They come to share with the audience the steps that led them to their present position and their professional experience.

The number of PhD students has considerably increased with the development of the Center over the past few years and is now more than 40, with students from many different nationalities and backgrounds. On the other hand, we have seen the first graduations, as the students who started their PhD research when the CIG was being set up completed their thesis projects.

see also www.unil.ch/cig/page62067.html

The mentoring 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 an 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 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

see also: www.unil.ch/cig/page62072.html

PhD theses

Silvia ANGHEL
Group Wahli
PPARgamma and adipose tissue functions (2007)

Subah HASAN
Group Tafti
Comment garder le cerveau éveillé? Pharmacogénomique et effets du vieillissement sur la régulation veille-sommeil chez la souris cosanguine (2008)

Charlotte HENRICHSEN
Group Reymond
Structure et fonction du génome: de l'homme à la souris (2008)

Stéphanie MARET
Group Tafti
La dissection génétique des oscillations lentes du cerveau durant le sommeil chez la souris (2007)

Ana MARQUES
Group Kaessmann
The role of gene duplication in the origin and evolution of new biological functions (2008)

Nicolas VINCKENBOSCH
Group Kaessmann
Understanding mutational and selective processes that govern gene duplication in mammals (2008)

Prizes awarded to CIG students and postdoctoral fellows

Jérôme FEIGE
Group Desvergne
Prix d'Excellence du jeune chercheur 2007 of the Faculty of Biology and Medicine (FBM), UNIL

Yaël GROSJEAN
Group Benton
Poster prize at the D.Day 2008, UNIL, awarded by the Société Vaudoise des Sciences Naturelles

Chitose KAMI
Group Fankhauser
Best poster 2008 at the 25th Annual Missouri Plant Biology Symposium

Stéphanie MARET
Groups Franken and Tafti
Sponsors Award (2008) for Outstanding Basic Sleep Research, awarded by the Société Suisse de Recherche sur le Sommeil, de Médecine du Sommeil et de Chronobiologie

Stéphanie MARET
Groups Franken and Tafti
Prix Guenin 2008

Ana MARQUES
Group Kaessmann
Prize of the Faculty of Biology and Medicine (FBM), UNIL, for her PhD thesis (2008)

Marianne RENAUD
Group Hernandez
Prize of the Faculty of Biology and Medicine (FBM), UNIL, for her Master's thesis (2008)

PhD students

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Group Herr

Silvia ANGHEL
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Rati BELL
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Group Kaessmann

Jean-Marc BRUNNER
Group Desvergne

Francesca CAPOTOSTI
Group Herr

Evelyne CHAIGNAT
Group Reymond

Mara COLZANI
Group Quadroni – PAF

Marion CORNU
Group Thorens

Dimitry DEBRIEUX
Group Fankhauser

Matthieu DE CARBONNEL
Group Fankhauser

Davide DEMURTAS
Group Stasiak

Stéphane DORSAZ
Group Tafti

Ilhem ELKOCHAIRI
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Matthew HALL
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Philippe JULIEN
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Sonia KLINGER
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Kyriakos KOKKORIS
Group Martin

Francesco LA SPADA
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Alexandra LAVERRIÈRE
Group Thorens

Nicolas LEUENBERGER
Group Wahli

Stéphanie MARET
Group Tafti

Ana MARQUES
Group Kaessmann

Nell MARTY
Group Thorens

Honey MODI
Group Thorens

Virginie PHILIPPE
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Lukasz POTRZEBOWSKI
Group Kaessmann

Cédric HOWALD
Group Reymond

Yann RAVUSSIN
Group Thorens

Jaime Humberto REINA
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Marianne RENAUD
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Raphaël RYTZ
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Audrey SAMBEAT
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Magali SOUMILLON
Group Kaessmann

Raphaël TERRIER
Group Michalik

Sajit THOTTATHIL OOMMENT
Group Desvergne

Julie VIENNE
Group Tafti

Nicolas VINCKENBOSCH
Group Kaessmann

Marta WAWRZYNIAK
Group Michalik

Robert WITWICKI
Group Reymond

The CIG Association of Scientists (CAOS)

CAOS, or CIG Association of Scientists, is an association founded by the PhD students and postodctoral fellows of the CIG, which any CIG member may join. The association has three main aims:

SCIENCE

Among the scientific activities of the CAOS are:

- the organization of regular CIG junior scientists meetings, during which students and postdoctoral fellows present and discuss their work with their peers.
- the organization of a yearly conference (the Lausanne Life Science Festival) with leading scientists from Switzerland and abroad

FUTURE

With the aim of helping the CIG junior scientists to plan their career in academic fields or in industry after they obtain their PhD, the association organizes:

- Career for Biologists Seminars: these monthly seminars give the opportunity to students to discover different career possibilities for PhDs
- workshops to help students to develop particular skills, for example, write their CV
- Some occasional events such as the participation to the EPFL Job Forum

SOCIAL

Informal meetings are an important tool for junior scientists to build bonds, which will remain important thourough their career. CAOS thus organizes social, cultural and throughout events which are open to all CIG personnel including students, postdocs, professors, and technical and administrative staff.

see also: http://www3.unil.ch/wpmu/caos/scientific/

Careers for biologists seminars

Jérôme BILLOTTE
Strategos and Amethis
Lausanne, Switzerland

Emilie BRICAUD
Roche Diagnostics
Rotkreuz, Switzerland

Andreas FÜRHOLZ
Nestlé Research Center
Lausanne, Switzerland

Rolf MARTI
Swiss Cancer League
Bern, Switzerland

Luca ROSSI
Philip Morris International R&D
Neuchâtel, Switzerland

Magdalena SKIPPER
Nature Reviews Genetics
London, UK

SEMINARS AND SYMPOSIA

The integrative nature of the CIG, with its different research fields, model organisms and technologies, as well as its location among other first rate research institutions, make it an ideal place to hear and learn about different fields of research.

Interactions with external scientists is of central importance. The CIG organizes a series of weekly seminars (the CIG seminar series) and co-organizes together with other departments of the FBM the "BIG" (Biology and Integrative Genomics) seminars. In addition, many ad hoc seminars are organized independently by CIG faculty members. In 2008, the CIG organized a special series of seminars to select a new Swiss National Science Foundation (SNSF) "professeur boursier" candidate for the Department.

The CIG symposium, organized yearly by CIG faculty members (see page 58), offers the possibility to explore a particular field during the course of one and half day, during which invited leading scientists in that particular field present their work. CIG members are also involved in the co-organization of numerous other symposia, conferences, and advanced courses (see p. 59).

CIG seminars

Geneviève ALMOUZNI
Curie Institute, Paris, France
Chromatin assembly factors, histone H3 variants and the cell cycle

Wendy BICKMORE
MRC Human Genetics Unit, Edinburgh, UK
Nuclear reorganisation, chromatin decondensation, and the regulation of gene expression during differentiation and development

Cathrin BRISKEN
ISREC/EPFL, NCCR Molecular Oncology, Lausanne, Switzerland
Genetic dissection of signalingpathways in breast development and breast cancer

Gerhard CHRISTOFORI
University of Basel, Switzerland
Distinct mechanisms of tumor invasion and metastasis

Manolis DERMITZAKIS
The Wellcome Trust Sanger Institute, Cambridge, UK
Causes and patterns of regulatory variation in the human genome

Barry DICKSON
University of Vienna, Austria
Wired for sex: genetic and neutral control of Drosophila mating behaviour

Gian Paolo DOTTO
UNIL, Lausanne, Switzerland
Notch signaling: a key node in the control system network of keratinocyte stem cell potential and carcinogenesis

Laurent DURET
Université Claude Bernard Lyon 1, Villeurbanne, France
The mystery of intron splicing

Russell G. FOSTER
Imperial College London, UK
Light, clocks and sleep: the signalling pathways of photosensitive retinal ganglion cells

Tom GINGERAS
Affymetrix Inc, Santa Clara, USA
Transcriptional landscape of the human genome: interlaced model for genome organization

Pierre GONCZY
ISREC/ EPFL, Lausanne, Switzerland
Mechanisms of centrosome duplication in C. elegans and beyond

Rolf GRUETTER
EPFL, Lausanne, Switzerland
Perspectives on functional genomics with functional, molecular and metabolic imaging

Ingrid GRUMMT
German Cancer Research Center, Heidelberg, Germany
Non-coding RNA and chromatin remodeling: Intergenic transcripts regulate the epigenetic state of rRNA genes

Ernst HAFEN
ETHZ, Zurich, Switzerland
Genetics of growth control in Drosophila

Thanos HALAZONETIS
University of Geneva, Switzerland
DNA damage checkpoints and cancer

Michael HALL
University of Basel, Switzerland
TOR signaling and control of cell growth in yeast and mammals

Christine HARTMANN
IMP, Vienna, Austria
Skeletal lineage decision – a matter of beta-catenin

Elisa IZAURRALDE
Max Planck-Institute for Developmental Biology, Tübingen, Germany
How do miRNAs silence gene expression?

Daniela KAUFER
University of California, Berkeley, USA
Stress as a model for brain plasticity

Brigitte KIEFFER
University Louis Pasteur, Illkirch, France
Opioid receptors, pain and addiction: genetic approaches

Steve KOWALCZYKOWSKI
University of California, Davis, USA
Visualization and analysis of protein-DNA complexes at the single-molecule Level

Wilhelm KREK
ETHZ, Zurich, Switzerland
The von Hippel Lindau tumor suppressor: a central controller of energy metabolism and tissue growth

Cris KUHLEMEIER
University of Bern, Switzerland
Mathematical modeling of phyllotaxis

Andreas MAYER
UNIL, Lausanne, Switzerland
Organelle dynamics as determined by molecular coordination of membrane fusion and membrane fragmentation

Andrew MILLAR
University of Edinburgh, UK
Unwinding the biological clock with systems biology

Ove NILSSON
Swedish University of Agricultural Sciences, Uppsala, Sweden
The evolutionary conserved CO/FT regulon controls plant growth and development in response to seasonal variation in photoperiod

Allan PACK
University of Pennsylvania, Philadelphia, USA
Functional genomic approaches to the study of sleep

Tatiana PETROVA
CHUV/UNIL, Lausanne, Switzerland
FOXC2 and PROX1 in lymphatic vascular development and cancer

Chris PONTING
University of Oxford, UK
Travels through exotic genomes: from platypus to us?

Richard REDON
The Wellcome Trust Sanger Institute, Cambridge, UK
Copy number variation in humans and chimpanzees: new insights in evolution and disease

Ad hoc seminars

Marc ROBINSON-RECHAVI
UNIL, Lausanne, Switzerland
Constraints and opportunities after vertebrate whole genome duplication

Carmen SANDI
EPFL, Lausanne, Switzerland
Neurobiological mechanisms involved in the interactions between stress and memory formation

Dirk SCHUEBELER
Friedrich Miescher Institute (FMI), Basel, Switzerland
Epigenome reprogramming during lineage commitment and terminal differentiation of stem cells

Michele SOLIMENA
Technical University, Dresden, Germany
How do pancreatic beta cells count their secretory granules

Markus STOFFEL
ETHZ, Zurich, Switzerland
Forkhead transcription factors and the control of metabolism

Françoise STUTZ
University of Geneva, Switzerland
Anti-sense RNA stabilization and transcriptional gene silencing in yeast S. cerevisiae

Elisabetta ULLU
Yale University, New Haven, USA
RNAi machineries in trypanosomes

Bas VAN STEENSEL
Netherlands Cancer Institute Amsterdam, The Netherlands
Genome – nuclear lamina interactions

Magdalena ZERNICKA-GOETZ
University of Cambridge, UK
Pluripotency, plasticity and cell fate in the early mouse embryo

BIG SEMINARS ORGANIZED BY CIG MEMBERS

Peter FRASER
The Babraham Institute, Cambridge, UK
Transcription and nuclear organization of the genome

Susan GOTTESMANN
National Institutes of Health (NIH), Bethesda, USA
Biological circuits with Small RNA Switches

Anthony HYMAN
MPI for Molecular Cell Biology and Genetics, Dresden, Germany
Systems approaches to cell division

Thomas JENTSCH
Leibniz-Institut für Molekulare Pharmakologie, Berlin, Germany
Function and dysfunction of vesicular chloride transport: insights from mouse

"PROFESSEUR BOURSIER" CANDIDATES

Jeroen DOBBLELAERE
Wellcome Trust Sanger Institute, Cambridge, UK
Genome-wide analysis in Drosophila for genes involved in centrosome maturation

Jacques FELLAY
Duke University, Durham, USA
HIV host genomics

Thomas FLATT
Brown University Providence, USA
Endocrine regulation of aging and reproduction in Drosophila

Pierre FONTANILLAS
Harvard University Cambridge, USA
Gene expression and genome organization

David GATFIELD
University of Geneva, Switzerland
MicroRNAs as inputs and outputs of the circadian clock

Johannes JAEGER
University of Cambridge, UK
Shift happens: The developmental and evolutionary dynamics of the gap gene network

Samuel MARGUERAT
Wellcome Trust Sanger Institute, Cambridge, UK
Dynamic repertoire of the fission yeast transcriptome surveyed at single-nucleotide resolution

Andrew SHARP
University of Geneva, Switzerland
Discovery of recurrent genomic disorders from the duplication architecture of the human genome

Remi TERRANOVA
Friedrich Miescher Institute (FMI), Basel, Switzerland
Polycomb and nuclear organization in development and cell differentiation

OTHER "AD HOC SEMINARS"

Emilie AIT YAHYA GRAISON
Université de Paris Diderot, Paris 7, France
Classification of chromosome 21 gene expression variations in Down Syndrome

Grigoris AMOUTZIAS
UNIL, Lausanne, Switzerland
A protein interaction atlas for the nuclear receptors: properties and quality of a hub-based dimerisation network

Hubert AMREIN
Duke University, Durham, USA
Taste and pheromone perception in Drosophila

Ulrike BAUER
University of Technology, Berlin, Germany
Combinatorial biosynthesis for the generation of A47934 derivatives

Felipe BENDEZU
Case Western Reserve University, Cleveland, USA
Bacterial actin and cell shape determination in Escherichia coli

Zsigmond BENKO
University of Debrecen, Hungary
HIV and heat shock proteins: anti-vpr activities of heat shock proteins

David BENTLEY
Illumina Inc, Cambridge, UK
The Illumina Genome Analyzer: technology and applications for ultra high throughput sequencing

Roxane BLATTES
Université Paul Sabatier, Toulouse, France
Molecular basis of position effect variegation in Drosophila melanogaster

André BRAENDLI
ETHZ, Zurich, Switzerland
Molecular insights into segmentation of the vertebrate nephron

Donatella CANELLA
Michigan State University, East Lansing, USA
Characterization of the Arabidopsis CBF1 transcription factor: functional role of two evolutionarily conserved signature sequences

Carles CANTO
University Louis Pasteur, Illkirch, France
Regulation of muscle metabolism by neuregulins and AMP-activated protein kinase

Leonardo CAPPONI
University of Geneva, Switzerland
Study of microRNA 155 in a new mouse dendritic cell line

Cristina CASALS CASAS
University of Barcelona, Spain
Plasticity of AP-1 regulated genes of the immune system

Laura CATO
University of Cambridge, UK
A tale of the tail: investigating the interaction between linker histones and HMGB1

Mark CHAISSON
University of California, San Diego, USA
De novo assembly of short reads using EULER 3.0

Frédéric CHALMEL
Université de Rennes, France
The Annotation, Mapping, Expression and Network (AMEN) suite of tools and its applications to the conserved transcriptome in mammal spermatogenesis

Fred CHANG
Columbia University, New York, USA
Shaping cells with microtubules

Wah CHIU
Baylor College of Medicine, Houston, USA
Cryo-electron microscopy of viruses

Damien COLAS
Fondation Rita Levi-Montalcini, Rome, Italy
Evidence for peripheral orexin signaling in the dorsal root ganglia; implications in pain sensing

Raja DUVVURU
University of Fribourg, Switzerland
Genetic and nutritional regulation of arbuscular mycorrhizal symbiosis: lessons from Petunia

Ad hoc seminars (continued)

Vivien EXNER
ETHZ, Zurich, Switzerland
Functions of CAF-1 and its subunits in Arabidopsis

Anne FISCHER
MPI for Evolutionary Anthropology, Leipzig, Germany
Genetic variation in great apes

Johan FLYGARE
Lund University, Sweden
Towards gene therapy of Diamond-Blackfan Anemia

David FURLOW
University of California, Davis, USA
Amphibian metamorphosis: a model system for understanding nuclear receptor control of development

Peter GALLANT
University of Zurich, Switzerland
Control of size by Drosophila Myc: mechanisms o transcriptional regulation

Benjamin GANTENBEIN
AO Research Institute (ARI), Davos, Switzerland
Molecular evolutionary rates in protein-coding genes of scorpions

Robert GENTLEMAN
Fred Hutchinson Cancer Research Center, Seattle, USA
Assessing the role played by multi-protein complexes in determining phenotype

David GFELLER
University of Toronto, Canada
Specificity and cross-reaction in PDZ interaction networks

David GONZALEZ
Trinity College, Dublin, Ireland
Novel human genes derived from non-coding DNA

Gilbert GREUB
UNIL/CHUV Lausanne, Switzerland
Genome Sequencer 20 and Genome Sequencer FLEX for de novo genome sequencing: local experience

Yaël GROSJEAN
University of Illinois, Chicago, USA
Genderblind: a glial transporter that regulates glutamatergic synapse strength to control Drosophila mate choice

Olivier HACHET
ISREC/ EPFL, Lausanne, Switzerland
Mid1p/anillin and the Septation Initiation Network orchestrate contractile ring assembly for cytokinesis

Christoph HANDSCHIN
University of Zurich, Switzerland
Metabolic and anti-atrophic functions of PGC-1alpha

Marc HEIJDE
Ecole Normale Supérieure, Paris, France
Light responses and functional characterization of Cryptochromes in Phaeodactylum tricornutum and Ostreococcus tauri

Christophe HELIGON
ETHZ, Zurich, Switzerland
Wnt/Frizzled signaling during pronephric kidney development

David HERNANDEZ
HUG, Geneva, Switzerland
Whole bacterial genome sequencing: de novo assembly of very short reads

Wassim HODROJ
Université Claude Bernard, Lyon, France
Caractérisation fonctionnelle de l'angiotensine IV dans le développement des maladies cardiovasculaires et du diabète de type 2

James HSIEH
Washington University, St-Louis, USA
The Taspase1 proteolytic signaling pathway links MLL to cell cycle and beyond

Wolfang HUBER
EBI/EMBL, Cambridge, UK
Automated image analysis for high-throughput cell-based microscopy assays with R and bioconductor

Nahid IGLESIAS
University of Geneva, Switzerland
The ubiquitin pathway regulates multiple steps of Mex67-mediated mRNA export

David JAMES
Garvan Institute of Medical Research, Sidney, Australia
Insulin action and the path of most resistance

Nicole JAMES FARESSE
University of Geneva, Switzerland
Role of the Ccr4-Not complex in transcription initiation in the yeast Saccharomyces cerevisae

Philippe JULIEN
EMBL, Heidelberg, Germany
eggNOG: a new database to study orthologous groups

Evangelia KALLIVRETAKI
University of Bern, Switzerland
Functional significance of aromatase in zebrafish during development

Ioannis KARAKASILIOTIS
Imperial College London, UK
Interaction of Hepatitis C virus with the host hypoxia response

Jim KENT
University of California, Santa Cruz, USA
Comparative genomics – algorithms and observations

Sander KERSTEN
Wageningen University, The Netherlands
Regulation of metabolism by PPARa and angiopoietin-like protein 4

Piyush KHANDELIA
Indian Institute of Science, Bangalore, India
Diverged functions for conserved fission yeast splicing factors

Kyriakos KOKKORIS
University of Uppsala, Sweden
RNA binding properties of poly(A)-specific riibonuclease

Anders KROGH
University of Copenhagen, Denmark
Computational methods for finding transcription factor binding sites in promoter sequences

Robb KRUMLAUF
Stowers Institute for Medical Research, Kansas City, USA
Hox genes and regulation of head development

Arun KUMAR
Institute of Genomics and Integrative Biology New Dehli, India
Stress, metabolism and cell death: connecting the dots

Karine LAPOUGE
UNIL, Lausanne, Switzerland
Global regulation of biocontrol metabolites in Pseudomonas fluorescens CHA0

Frédéric LEMOINE
Université Paris Sud, France
Integration, querying and analysis of prokaryotic comparative genomics data

Manyuan LONG
University of Chicago, USA
New gene evolution in Drosophila: phenotype and mechanism

Marina LUONGO
University of Salerno, Italy
Changes in membrane physical state regulate the phosphorylation of ERK 1/2 in PC-3 cells

David MAGNANI
University of Bern, Switzerland
Novel components of copper homeostasis in bacteria

Nicole MALGRAS
ETHZ, Zurich, Switzerland
Functional characterization of the Killer Protein 6 produced by the basidiomycete Ustilago maydis

Ernest MARTINEZ
University of California, Riverside, USA
Multiprotein complexes in regulation of chromatin, transcription & MYC oncoprotein functions

Cristian MICHELETTI
International School for Advanced Studies (SISSA), Trieste, Italy
Dynamics-based alignment: a novel tool for comparing large-scale movements in proteins with the same or different folds

Sohan MODAK
Institute of Genomics and Integrative Biology, Delhi, India
Darwins dream: construction of multiparametric phylogenetic tree in 3D space

Gaëlle MONGELARD
University of Bern, Switzerland
Zinc transport in plants: characterization of new Zn transporters in Solanum lycopersicum and Arabidopsis thaliana

Mauro MONTANARO
Universidad Nacional de La Plata, Buenos Aires, Argentina
Regulation of fatty acid desaturases in diabetes mellitus rat models

Anamaria NECSULEA
Université de Lyon, France
The relationship between DNA replication and human genome organization

Edward OAKELEY
Friedrich Miescher Institute (FMI), Basel, Switzerland
Gene expression on Affymetrix tiling and exon arrays

Teresa ODORISIO
Istituto Dermopatico dell'Immacolata IRCCS, Rome, Italy
Placenta Growth Factor in skin angiogenesis and repair

François PARCY
CNRS/INRA/CEA/ Grenoble University, France
Structure and evolution of the LEAFY floral regulator

Heidi PETERSON
Estonian Biocenter, Tartu, Estonia
Using gene expression for pathway (re)construction

Sergio POLAKOF
University of Vigo, Spain
Glucose intolerance in fish: from glucose sensing to nutrient interaction

Peter QUAIL
University of California, Berkeley, and Plant Gene Expression Center, Albany, USA
Phytochrome photosensory signaling networks

Laure QUIGNODON
Ecole Normale Supérieure, Lyon, France
Mouse genetic to understand how Thyroid Hormone Receptor alpha 1 controls neurodevelopment

Oliver RAU
Johann Wolfgang Goethe University, Frankfurt am Main, Germany
Orphan receptors adopting phytochemicals – PPAR a case study

David RECTOR
Washington State University, Pullman, USA
High speed optical imaging of the brain

Florent REVEL
Université Louis Pasteur, Illkirch, France
Neuroendocrine Orchestration of Seasonal Physiology – Focus on Reproduction

Michael RHODES
Applied Biosystems, Foster City, USA
SOLiDTM System A revolution in next generation sequencing technology

Guénola RICARD
Radboud University Nijmegen Medical Centre, The Netherlands
Evolution and genome structure of anaerobic Ciliates

Pierre-Yves RISOLD
Université de Besançon, France
Anatomie des systèmes producteurs de l'hormone de mélano-concentration (MCH) et hypocrétines/oréxines (Hcrt) dans l'hypothalamus du rat

Ida RUBERTI
CNR Institute of Molecular Biology and Pathology Rome, Italy
Regulatory networks for the shade avoidance response

Hitomi SANNO
University of Heidelberg, Germany
Rho GTPases play a role in proper formation of layer IV and V in sometosensory cortex

Alexandra SAPETSCHNIG
Philipps-University Marburg, Germany
Mechanisms of SUMO-mediated transcriptional repression

Christoph SCHMID
Swiss Institute of Bioinformatics (SIB) and ISREC/EPFL, Lausanne, Switzerland
ChIP-seq – new prospects for transcriptional regulation

Kristina SCHOONJANS
University Louis Pasteur, Illkirch, France
Role of LRH-1 in health and disease

Koichiro SHIOKAWA
Teikyo University, Tokyo, Japan
Cloning of Xenopus S-adenosylmethionine decarboxylase (SAMDC) and discovery of maternal program of apoptosis executed at midblastula transition (MBT), with a few slides about our new Department of Judo Therapy

Mehmet SOMEL
MPI for Evolutionary Anthropology, Leipzig, Germany
Our juvenile brains: brain maturation at the gene expression level in humans and chimpanzees

Li-Ping (Bolin) SONG
Institute of Health Sciences, Shanghai, Rep. of China
Differentiation-inducing therapy: hypoxia and leukemic cell differentiation

Caroline TAUXE
UNIL/CHUV, Lausanne, Switzerland
Regulation of P-selectin glycoprotein ligand 1 (PSGL-1) interactions with selectins: role of the decamers and of the cytoplasmic domain

Juilee THAKAR
University of Maryland, University Park, USA
Modeling systems-level regulation of host immune responses

Juliane TROEGER
University of Zurich, Switzerland
Phospholipid stimulation and downstream target identification of the PAS domain kinase PASKIN

David VALLOIS
INSERM, Paris, France
Genetics factors and type 1 diabetes development in the NOD mouse

Laurie VUILLET
Université de Montpellier, France
Bacteriophytochromes and control of Light Harvesting Complexes synthesis in Rhodopseudomonas palustris

Zhenghui WANG
University of Québec, Canada
The role of oxidative stress in heat shock-induced apoptosis in Chinese hamster ovary cells

Martin WELLS
Nonlinear Dynamics / Geneva Bioinformatics (Genebio) SA, Geneva, Switzerland
Seminar and workshop in quantitative proteomics

Jonathan WIDOM
Northwestern University, Evanston, USA
The genomic code for nucleosome positioning

Yanfang YE
Osaka City University, Japan
Molecular functions of geranylgeranyl diphosphate synthase in fission yeast

Akadiri YESSOUFOU
Université d'Abomey-Calavi, Cotonou, Bénin
Rôle de PPARalpha et des acides gras oméga-3 dans la modulation du diabète gestationnel et de la macrosomie

Keji ZHAO
National Institutes of Health (NIH), Bethesda, USA
Characterization of human epigenomes

Philip ZIMMERMANN
ETHZ, Zurich, Switzerland
Meta-profiling microarray data provides another perspective on gene expression

CIG SYMPOSIUM

Encouraged by the success of its inaugural symposium in 2005, the CIG decided to establish a yearly symposium on a few broad topics that would rotate every year. Accordingly, the CIG symposium is now organized every year by the CIG director and CIG faculty members whose research is connected to the topic explored that year.

The CIG symposium encourages interactions between junior and senior scientists. Thus, junior scientists can submit abstracts and present their work during a poster session or through oral presentations selected from the abstracts.

see also: www.unil.ch/cigsymposium

CIG Symposium 2008: Metabolism and Cancer

ORGANIZERS
N. Hernandez, B. Thorens, W. Wahli

Johan AUWERX
University Louis Pasteur, Illkirch, France
Transcriptional cofactors as master regulators of metabolism

Sadaf FAROOQI
University of Cambridge, UK
Regulation of human appetite and body weight: insights from genetics

Philippe FROGUEL
Institut Pasteur de Lille, France
Genome wide associations studies bring breakthrough in obesity, diabetes and associated metabolic disorders

Grahame HARDIE
University of Dundee, UK
AMP-activated protein kinase: a drug target in metabolic disorders and in cancer?

Rudolf KAAKS
German Cancer Research Center, Heidelberg, Germany
Nutritional energy balance and cancer; epidemiological evidence for the implication of metabolic and hormonal risk factors

Daniel P. KELLY
Washington University School of Medicine, St. Louis, USA
Cardiac nuclear receptor signaling in health and disease

Matej ORESIC
VTT Technical Research Centre of Finland, Espoo, Finland
Metabolomics in diabetes research

Philipp SCHERER
UT Southwestern Medical Center at Dallas, USA
The role of the adipocyte in metabolism and cancer

Bruce SPIEGELMAN
Dana-Farber Cancer Institute Harvard Medical School, Boston, USA
Transcriptional control of energy homeostasis in health and disease

Antonio VIDAL-PUIG
University of Cambridge, UK
Adipose tissue expandability, lipotoxicity and the metabolic syndrome

Eileen WHITE
Rutgers University, Piscataway, USA
Tumor suppression by autophagy through management of metabolic stress

SELECTED TALKS

Michelangelo FOTI
University of Geneva, Switzerland
Unsaturated fatty acids promotes hepatocytes proliferation and carcinogenesis through downregulation of the tumor supressor PTEN

Barbara HAENZI
FMI, Basel, Switzerland
Role of Memo in premature aging and breast cancer

Sander KERSTEN
Wageningen University, The Netherlands
Exploring the role and regulation of Angptl4 in mouse and human

Stéphanie MARET
GUENIN PRIZE 2008
UNIL, Lausanne, Switzerland
Homer1a is a core brain molecular correlate of sleep loss

SYMPOSIA CO-ORGANIZED BY THE CIG

Symposia were co-organized with the following partners:

- Department of Ecology and Evolution (DEE), UNIL
- Department of Medical Genetics (DGM), UNIL
- Department of Plant Molecular Biology (DBMV), UNIL
- EPFL, Lausanne, Switzerland
- University of Geneva, Switzerland
- Swiss Institute for Bioinformatics (SIB)
- USGEB (Union of the Swiss Societies for Experimental Biology)

USGEB 2008

Biology Meets Engineering

ORGANIZERS
W. Herr, H. Kaessmann, A. Reymond, B. Thorens, C. Brisken, H. Lashuel, T. Lasser, S. Sidjanski, O. Staub, M. Swartz, D. Trono, G. van der Goot

Naama BARKAI
Weizmann Institute of Science, Rehovot, Israel

Mitra HARTMANN
Northwestern University, Evanston, USA

Laurent KELLER
UNIL, Lausanne, Switzerland

Stanislas LEIBLER
The Rockefeller University, New York, USA

Uwe SAUER
ETHZ, Zurich, Switzerland

Pamela SILVER
Harvard University Boston, USA

Melody A. SWARTZ
EPFL, Lausanne, Switzerland

Lausanne Genomics Days

MONITORING GLOBAL CHANGES IN GENE EXPRESSION (2007)

ORGANIZERS
K. Harshman, S. Pradervand, O. Hagenbüchle, V. Jongeneel, M. Delorenzi, J. Beckmann

Rudolf AEBERSOLD
ETHZ, Zurich, Switzerland

Uri ALON
Weizmann Institute, Rehovot, Israel

Jean-Laurent CASANOVA
Université de Paris, France

Philippe FROGUEL
Institut Pasteur de Lille, France,

Robert KINGSTON
Massachusett General Hospital, Boston, USA

Inder VERMA
Salk Institute, San Diego, USA

ECOLOGICAL AND EVOLUTIONARY GENOMICS (2007)

ORGANIZERS
C. Fankhauser, L. Keller, P. Reymond

Andrew CLARK
Cornell University, Ithaca, USA

Charalambos KYRIACOU
Leicester University, UK

Sarah MATTHEWS
Harvard University, Cambridge, USA

Magnus NORDBORG
University of Southern California, Los Angeles, USA

Edward RUBIN
DOE Joint Genome Institute, Walnut Creek, USA

Gregory VELICER
Indiana University, Bloomington, USA

BIOLOGICAL NETWORKS AND COMPLEX TRAITS (2008)

ORGANIZERS
K. Harshman, O. Hagenbüchle, J. Beckmann, F. Naef, M. Robinson-Rechavi

Marc BIGGIN
Lawrence Berkeley Laboratory, Berkeley, USA

Edwin CUPPEN
Hubrecht Institute, Utrecht, The Netherlands

Jonathan FLINT
Wellcome Trust Sanger Institute, Cambridge, UK

Andrew C. OATES
MPI Dresden, Germany

Richard REDON
Wellcome Trust Sanger Institute, Cambridge, UK

Jussi TAIPALE
University of Helsinki, Finland

ECOLOGICAL AND EVOLUTIONARY GENOMICS (2008)

ORGANIZERS
C. Fankhauser, P. Reymond, M. Robinson-Rechavi, F. Naef, L. Keller

Douglas L. CRAWFORD
University of Miami, USA

Michael HERMAN
Kansas State University, Manhattan, USA

Molly PRZEWORSKI
University of Chicago, USA

David QUELLER
Rice University, Houston, USA

Amira SEHGAL
University of Pennsylvania, Philadelphia, USA

Dani ZAMIR
Hebrew University, Tel Aviv, Israel

SKMB Gene Regulation Workshop

ORGANIZERS
N. Hernandez, F. Karch,
W. Reith, M. Strubin

2007

Bruno AMATI
University of Milan, Italy

Anne EPHRUSSI
EMBL, Heidelberg, Germany

Witold FILIPOWICZ
FMI, Basel, Switzerland

Shiv GREWAL
National Cancer Institute,
Bethesda, USA

Steven HAHN
Hutchinson Cancer Research
Center, Seattle, USA

James MANLEY
Columbia University,
New York, USA

Tim RICHMOND
ETHZ, Zurich, Switzerland

2008

Denise BARLOW
University of Vienna, Austria

Claude DESPLAN
New York University, USA

Mitzi KURODA
Harvard University, Boston, USA

Carol PRIVES
Columbia University,
New York, USA

Mark PTASHNE
Sloan-Kettering Institute,
New York, USA

Wolf REIK
The Babraham Institute,
Cambridge, UK

Rick YOUNG
Whitehead Institute,
Cambridge, USA

Implementing the "Collaborative Cross" in Lausanne

ORGANIZERS
P. Franken, W. Herr, D. Trono

Gary CHURCHILL
The Jackson Laboratory,
Bar Harbor, USA

Richard MOTT
Oxford University, UK

David THREADGILL
University of North Carolina,
Chapel Hill, USA

Rob WILLIAMS
University of Tennessee,
Memphis, USA

1st Aneuploidy Workshop

ORGANIZERS
A. Reymond, J. Wuarin,
S. E. Antonarakis

Emmanouil T. DERMITZAKIS
Wellcome Trust Sanger Institute,
Cambridge, UK

Evan EICHLER
University of Washington,
Seattle, USA

Uta FRANCKE
Stanford University,
Palo Alto, USA

Katheleen GARDINER
University of Denver, USA

Craig GARNER
Stanford University,
Palo Alto, USA

Matt HURLES
Wellcome Trust Sanger
Institute, Cambridge, UK

James R. LUPSKI
Baylor College of Medicine,
Houston, USA

Chengbiao WU
Stanford University,
Palo Alto, USA

Roger H. REEVES
Johns Hopkins University,
Baltimore, USA

Steve W. SCHERER
The Hospital for Sick Children,
Toronto, Canada

Orsetta ZUFFARDI
Università degli Studi di Pavia,
Italy

Eugene YU
Roswell Park Cancer Institute,
Buffalo, USA

FENS 2008 Satellite Symposium: Sleep Function: Approaches towards the Roles of Sleep in Neuronal Functions

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Ultra High Throughput Sequencing

1ST MEETING: COMPUTATIONAL ANALYSIS OF UHT SEQUENCING DATA

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2ND MEETING: UHT APPLICATIONS AND CHALLENGES

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Swiss Academy of Sciences

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Applied Biosystems

Axon Lab

Biolabo Scientific Instruments

Bio-Rad Laboratories

Bucher Biotec

Illumina

Life Systems Design

NuGEN Technologies

Operon Biotechnologies

Quiagen

Roche Diagnostics

Starlab

Syngenta

Tecan

UCB Pharma

Umetrics

Witec AG

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Novartis

Hoffmann-La Roche

Merck Serono

THE CIG ANNUAL RETREAT

The CIG organizes a yearly annual retreat where all CIG members, whether students, postdoctoral fellows, professors and group leaders, or technicical and administrative staff, are invited.

The retreat provides an opportunity for researchers to exchange on their work progress and future plans, as each group presents an update of its research to the full Génopode scientific community in talks and poster sessions. In addition, faculty members prepare presentations to introduce their work to non-scientific staff, and these efforts are greatly appreciated as they allow all CIG personnel to take part in the excitement of scientific discovery.

The CIG annual retreat is also an unmatched opportunity for informal discussions between CIG members, and an opportunity for all to interact in a relaxed atmosphere.

The retreat was organized in 2007 and 2008 in Saas Fee, a beautiful location in the Swiss mountains.

PRIZES AWARDED AT THE CIG ANNUAL RETREAT

Marie FABLET
Group Kaessmann
Best poster 2007

Christina HERTEL
Groupe Herr
Best poster 2008

Gilles BOSS
Stéphane PORCHET
CIG central services
UNIBAT
Special poster prize

THE CIG AND THE PUBLIC

The CIG being a university department, its first teaching duties are of course to students and other members of the academic staff. However, in a world where the development of knowledge and technology in 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 citizen and maybe tomorrow's researchers. The Center organizes every year visits within the framework of the "Passeports Vacances", which organizes activities for children, during their holidays. It also welcomes children visiting with their schoolteachers.

Anyone can come to the Center, visit the laboratories and discuss with the scientists during the UNIL open doors (les Mystères de l'UNIL) and on other occasions such as the "Jours du Gène".

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 the communication of science to non-scientists, whether it be children, teenagers or adults.

Overall, about a thousand members of the public at large visit the CIG each year on these different occasions.

see also: www.unil.ch/cig/page63732_en.html
Communication to the public can take the form of press releases. The CIG issued 10 press releases on its research results, which were then featured by the local, national, and international media.

see also: www.unil.ch/cig/page16994.html

PARTNERS

For its activites 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).

ARTIST IN RESIDENCE AT THE CIG

As part of its activities with the public at large, the CIG collaborated in 2008 with the program "Artist-in-Labs" (AIL), a collaboration between the Zurich University of the Arts, Institute for Cultural Studies in the Arts ICS and the Bundesamt für Kultur BAK. AIL finances a nine month residency for an artist in a swiss research laboratory.

Sylvia Hostettler, an artist from Bern with a background in sculpture, installation, and photography was thus integrated in the CIG laboratory of Prof. C.Fankhauser, a new experience for both the scientists and the artist. The result of this interaction is an installation visible in the Génopode in 2009: "Dimensions of Apparent Invisibility".

see also: www.artistsinlabs.ch/english/index.htm
www.unil.ch/cig/page63732.html
www.sylviahostettler.ch/

PEOPLE

The CIG activities and dynamism result not only from the work of the group leaders and faculty members, but in a large part from the contributions of people in training: master- and graduate students, and postdoctoral fellows. Laboratory technicians are key to research, as is the other technical and administrative staff as well as all the people from the CIG and the UNIL who make it possible for the researchers to do research and for the people in training to learn. The CIG is currently composed of about 190 members originating from 26 different countries on 5 continents. There are 16 group leaders and faculty members, about 45 PhD students, 50 postdoctoral fellows, 50[1] specialists and laboratory technicians (including trainees), and 25[1] persons employed in the administrative and the logistic services (including trainees).

[1]many members of the support staff work part-time.

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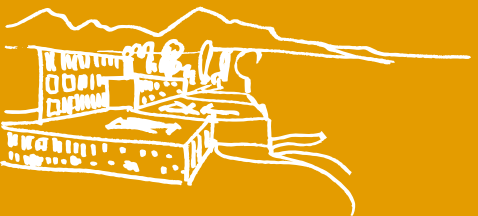

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