

# THE CENTER FOR INTEGRATIVE GENOMICS

REPORT 09-10



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

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

The CIG is currently composed of more than 200 members originating from more than 30 different countries, who together contribute to the development of its research, its core facilities and its educational activities (see chapter “people”).



## Message from the SAC

### Scientific Advisory Committee members

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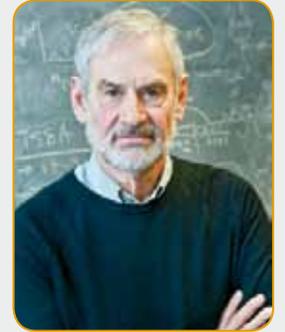
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As members of the Scientific Advisory Committee (SAC) we are in the rather unique position of being able to observe the recent development of the CIG from several distinct vantage points. We have interacted with students, postdoctoral fellows, and faculty as well as with shared resource coordinators, technical staff, and administrators at both the CIG and the University of Lausanne. At the same time we have been able to provide input regarding the hiring and promotion of faculty. Most importantly, we have watched the scientific growth of the CIG as its laboratory programs continue to develop and as the institute builds on its considerable strengths. In the view of the SAC these strengths include the diverse scientific interests of its faculty, the ready availability of cutting-edge resources in genetics and genomics, and the highly motivated and dedicated scientific, technical and administrative staffs. The scientific diversity that characterizes the CIG has led to numerous synergistic interactions among research groups within the institute as well as with the wider scientific community within Switzerland and internationally. The institute has done a remarkable job in hiring outstanding scientists from around the world, underscoring the CIG's international visibility and attractiveness. Another strength of the CIG is its culture of openness, collegiality and scientific excellence in an atmosphere where hierarchical barriers are minimized. It is likely that this culture is at least partly responsible for the genuine sense of enthusiasm evinced by students, postdoctoral fellows and other members of the staff. This is not to say that there are no problems at the CIG – what is important is that lines of communication exist such that scientists and staff have the opportunity to air and address issues as they arise.

From our perspective the success of the CIG also reflects in no small measure the efforts of the institute's director, Prof. Nouria Hernandez, and her staff. They have played a key role in not only promoting scientific excellence but in helping create a culture and work environment that will continue to attract first-rate scientists to the CIG. Strong support at many levels from the University of Lausanne has also been of paramount importance in the creation and development of the CIG.

Research institutes do not simply attain a high level and remain that way. The CIG must continue to evolve by being flexible and open to new ideas, techniques, and challenges. We believe that with its diverse staff and collegial culture the CIG is well positioned to face the future and to continue its upward trajectory.

*Robert N. Eisenman  
for the Scientific Advisory Committee*



**... we believe that with its diverse staff and collegial culture the CIG is well positioned to face the future and to continue its upward trajectory.**

*Prof. Robert Eisenman  
President of the Scientific Advisory Committee*

## Message from the Director



...we expect that graduates from the IECB program will not only be experts in experimental biology like students from more conventional programs, but will in addition be conversant in bioinformatics...

*Nouria Hernandez, CIG Director*

The 25th of October 2010, the CIG turned five, and thus became, I suppose, a “grown-up”. Thanks to the constant advice of its Scientific Advisory Committee and thanks to the efficient guidance of its chief operating officer Nicole Vouilloz, the CIG has matured into a high performing department where scientists can work and pursue their research in an exceptionally favorable environment. This does not mean, however, that the CIG will now settle into a comfortable but soporific routine. Far from it! A lot has happened since the last biannual report, and a lot will continue to happen!

One of the many exciting events of the last two years has been a gift from the Grace family from Montreux to benefit both “l’Eprouvette”, the public laboratory of the University of Lausanne, and the CIG. The Grace family has been interested for many years in helping foster public outreach as well as research in Genetics. Their gift supports the John Grace Lecture Series, the first lecture of which, hosted by Douglas Hanahan (ISREC, EPFL) and Winship Herr (CIG), was given by Nobel prize winner James D. Watson to a completely packed auditorium at the EPFL on the 11th of October 2010. We look forward to the second of these lectures, which will be given in June of 2011 in the context of the annual CIG symposium. The speaker will be Ralph Greenspan, from the University of California in San Diego, who is interested in the genes and neural networks underlying behavior. We also look forward to working with the Grace family to develop a public outreach program with the aim of creating links between CIG scientists and the local community.

Also in the general area of education, 2010 has seen, thanks to the leadership of Keith Harshman, the birth of the “Integrated Experimental and Computational Biology” thematic doctoral program, which demands from its students that they follow a core course in reasoning and logic as well as a number of courses in bioinformatics offered by the Swiss Institute for bioinformatics. We believe that this type of program addresses urgent needs in the education of future researchers in the context of a changing biology field, in which experiments that interrogate the totality of, for example, a genome or a proteome, are now common. Such experiments routinely produce millions of datapoints, which can only be processed with the help of bioinformatics. Although it is difficult and perhaps impossible to be a real expert in fields as different as experimental and computational biology, we expect that graduates from the IECB program will not only be experts in experimental biology like students from more conventional programs, but will in addition be conversant enough in bioinformatics to be able to perform some analyses of their data and communicate effectively with the bioinformatics specialists who might pursue more in-depth analyses. Reciprocally, students interested in becoming bioinformaticians will not only specialize in computational skills but will also perform some

experiments and thus get a sense of the technical limitations that must be taken into account when interpreting an experiment.

Another exciting event has been the nomination of Sophie Martin, who was supported by the Swiss National Science Foundation as a “boursier” Assistant Professor at the CIG, to the position of Associate Professor with tenure in the Department of Fundamental Microbiology. We are sorry to lose this exceptional scientist, but we are happy that she is a gain to another department of the University of Lausanne!

What about the future? The CIG still faces now a major challenge, which incidentally is faced by every academic research organization, that of maintaining a high level of scientific productivity in the long term. In some institutes, this challenge is met by the deliberate refusal to attribute tenure to its members. Just as examples, the most stable position a scientist can hope for at organizations such as Cold Spring Harbor Laboratory or the Fred Hutchinson Cancer Center is a position with a five-year contract renewed every year (“Rolling Five”) in the first instance, and a position reviewed every five years in the second. In both cases, contract renewal is subjected to evaluation of scientific production. This type of system does not exist in most if not all university environments, however. What does exist is the possibility of allocating some percentage of the resources available to a department such as the CIG according to faculty performance. Indeed, such systems already exist in some departments of the Faculty of Biology and Medicine at the University of Lausanne, such as the Department of Ecology and Evolution.

The simple and straightforward concept of allocating resources according to performance implies, however, a much more complicated aspect, that of evaluating research performance. At the University of Lausanne, this is done by a system based in large part on assigning a “bibliometry grade” based on the publication record. Each publication receives a numerical value according to the quality (as determined by the impact factor) of the journal where it was published, and then each author receives a certain percentage of this value depending on where he or she stands in the author list. The system as it is applied suffers, in my opinion, from several major problems: one of them is that at a time when political powers, major funding institutions, and indeed the Faculty of Biology and Medicine itself encourages principal investigators to collaborate and work as teams on large projects, the bibliometry grade as it is currently computed allows only proper recognition of the contribution of the group represented by the last author, and very strongly disfavors collaborators, even if they contributed close to 50% of the published work. Another problem is that many contributions to journals with very low impact factors can be equivalent to few contributions to

## Highlights of 2009-2010

high impact factor journals, even though in my mind the latter are almost always more important. Such problems could probably be easily fixed if the will to do it were there. There is, though, a more pernicious aspect to numbers; numbers give a false sense of accurate and objective evaluation, when scientific creativity as well as importance, originality, and technical difficulty of various projects cannot be accurately quantified.

What is solution, then? The Scientific Advisory Committee of the CIG evaluates CIG scientists for tenure granting and promotion decisions using the "good old method", in which the scientific output of an individual is evaluated by the work-intensive way, i.e. by reading some of the published papers, listening to a presentation of accomplishments and future plans, and reading letters provided by outside experts in the field. The Scientific Advisory Committee proposes to follow a similar procedure for the evaluation of tenured senior professors, which could then be used as a guide to reallocate internal resources, taking some away from less productive members to favor more dynamic and productive members. Would the benefits for the institution justify the weight of the procedure? Having spent most of my scientific career under conditions where 100% of my research funding depended on scientific output, I believe the answer is almost certainly yes. On the one hand, a review process, even if it leads to much less important consequences than in institutions without tenure, always puts some pressure on professors to continue to at least try to prioritize research over all other duties, in particular administrative ones, imposed upon us by the university system. In fact, a upcoming review in an excellent excuse professors can use to concentrate on research and decline other demands! On the other hand, in case somebody were to stop being a productive researcher, the review system would give a mechanism to not only allocate research resources to more productive groups but also to open a discussion as to how else the individual in question could benefit the CIG and the University. This should allow a certain dynamic in an institution that otherwise could be quite static, given the possibility for professors to spend their entire career, i.e. more than 30 years. The challenge that the CIG faces then in the next two years is to implement some review process for senior faculty, a process that will have to be voted for by the very people concerned! Given the high quality and demanding team we have at the CIG, I have no doubt that we will succeed.

Nouria Hernandez,  
CIG Director



2009		2010
	Januar	N. Hernandez is the coordinator of the new CycliX project in the SystemsX.ch program
A. Reymond is titularized Associate Professor	Februar	H. Kaessmann receives the Friedrich Miescher award
	Mars	The new artist in residence, S.Huber, arrives at the CIG L. Michalik receives the FBM "Excellence in teaching award for Biology"
W. Herr receives an honorary Doctor of Sciences from the Watson School of Biological Sciences, Cold Spring Harbor, USA	April	
Lausanne Life Science Festival, organized by CAOS Inauguration of "Light reaction - dimension of apparent invisibility", an installation by the CIG artist in residence, S.Hostettler	May	
3rd CIG Symposium "DNA repair and Human health"		4th CIG Symposium "Sensing the environment" with M.Chalfie (Nobel Prize 2008)
Inauguration of the mezzanine for "Embedded bioinformaticians" (Genopode)	Juny	2nd visit of the CIG Scientific Advisory Committee
P. Franken receives the Sleep Science Award		Launch of IMIDIA (Innovative Medicines Initiative project on Diabetes), a European project led by B. Thorens
	July	H. Kaessmann is affiliated to the SIB
CIG annual retreat		
W. Herr becomes Director of the UNIL «Ecole de Biologie» B. Desvergne becomes Vice-dean and President of the « Section des Sciences fondamentales », FBM, UNIL	August	CIG annual retreat
	September	
S. Martin becomes EMBO young investigator		S. Martin gets an ERC independent starting grant
H. Kaessmann receives an ERC independent starting grant	October	S. Martin becomes associate Professor at the Department of Fundamental Microbiology, UNIL 1st John Grace Lecture with Jim Watson
R. Benton is awarded the Eppendorf and Science Neurobiology Prize	November	D. Gatfield, a new Professeur boursier SNSF, at the CIG
B. Thorens receives the Albert Reynold Prize		B. Thorens receives an ERC advanced Investigator award
A. Reymond receives the Prix Leenaards		
Launch of the CIG blog and newsletter: <a href="http://www.genomyx.ch">www.genomyx.ch</a>	December	Launch of the IECB and the starOmics doctoral programs

RESEARCH





**Richard Benton**  
Assistant Professor



**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. He was the winner of the 2009 Eppendorf and Science Grand Prize for Neurobiology.

## Chemosensory perception in *Drosophila*: genes, circuits, behaviours and evolution

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.

Our recent work has focussed on a novel family of chemosensory receptors, the Ionotropic Receptors (IRs). IRs are structurally related to ionotropic glutamate receptors (iGluRs), a conserved class of ligand-gated ion channel present in animals, plants, and bacteria that are best characterised for their roles in synaptic communication in vertebrate nervous systems. We use the IRs as a model system to study several aspects of the function and evolution of chemosensory receptors and their circuits.

### EMERGENCE AND DIVERGENCE OF THE IRs

By comprehensive evolutionary genomics and *in situ* expression analysis we have shown that IRs are expressed in olfactory organs across Protostomia - a major branch of the animal kingdom that encompasses arthropods, nematodes, and molluscs - indicating that they represent an ancestral protostome chemosensory receptor family. We distinguished two subfamilies of IRs: conserved "antennal IRs," which are likely to define the first olfactory receptor family of insects, and species-specific "divergent IRs," which are expressed in peripheral and internal gustatory neurons, implicating this family in taste and food assessment. Comparative analysis of drosophilid IRs reveals the selective forces that have shaped the receptor repertoires in flies with distinct chemosensory preferences. These findings provide an essential foundation for our functional analysis of these receptors in both neurobiological and evolutionary studies.

### MOLECULAR ARCHITECTURE OF IRs

To elucidate how these peripheral chemosensors have evolved mechanistically from iGluRs, we have combined *in vivo* and *in vitro* physiological and cell imaging approaches. We found that IRs act in likely heterotetrameric complexes of up to three subunits, comprising individual ligand-specific receptors and one or two broadly expressed coreceptors. Heteromeric IR complex formation is necessary and sufficient for trafficking to chemosensory cilia *in vivo* and mediating ligand-evoked electrophysiological responses in heterologous cells. Structure-function analysis has begun to reveal the role of different subunits and protein domains in subcellular trafficking, chemosensory ligand recognition and ion conduction. Our findings provide insights into the conserved and distinct architecture of these chemosensory receptors and their synaptic ion channel ancestors. Moreover, they offer perspectives into the use of IRs as a novel type of custom-designed chemoreceptor. Such sensors could offer invaluable tools as genetically encoded neuronal activators or inhibitors as well as have broad practical applications, for example, in pollutant detection or clinical diagnosis.

### STRUCTURE AND FUNCTION OF IR NEURAL CIRCUITS

We have performed large-scale electrophysiological screens to identify ligands for IRs and generated genetic reagents to visualise the organisation and activity of the IR neural circuits. These efforts have allowed us to determine how chemical stimuli detected by IRs are represented in spatial and temporal patterns of neural activity in the brain. This analysis permits comparison of the properties of the IR chemosensory systems with those of sensory circuits expressing other classes of chemosensory receptors and therefore insights into the driving forces and mechanisms underlying their development and evolution. Moreover, by manipulating the function of individual IR sensory pathways, we have begun to uncover the specific innate behaviours these chemosensory circuits control.

## Group members

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## Publications

### RESEARCH ARTICLES

Benton R, Vannice KS, Gomez-Diaz C, Vosshall LB (2009) Variant ionotropic glutamate receptors as chemosensory receptors in *Drosophila*. *Cell* 136:149-62  
Ai M, Min S, Grosjean Y, Leblanc C, Bell R, Benton R, Suh GS (2010) Acid sensing by the *Drosophila* olfactory system. *Nature* 468:691-5  
Croset V, Rytz R, Cummins SF, Budd A, Brawand D, Kaessmann H, Gibson TJ, Benton R (2010) Ancient protostome origin of chemosensory ionotropic glutamate receptors and the evolution of insect taste and olfaction. *PLoS Genet* 6:e1001064

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### COMMENT

Benton R (2010) Chemosensory ecology: deceiving *Drosophila*. *Curr Biol* 20:R891-3  
Benton R (2010) Neuroscience: Sexy circuits. *Nature* 468:638-40

### BOOK CHAPTER

Benton R, Dahanukar A (2010) Chemosensory coding in single sensilla. In: *Drosophila Neurobiology: A Laboratory Manual*, Zhang B, Freeman MR, Waddell S (eds), Cold Spring Harbor Laboratory Press

## Funding

### Swiss National Science Foundation (SNSF)

Independent Basic Research Grant

### European Commission

European Research Council (ERC) Starting Independent Researcher Grant (FP7)

### Roche Research Foundation

PhD fellowship to R. Rytz

### Boehringer Ingelheim Fonds

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Postdoctoral fellowship to P. Ramdya

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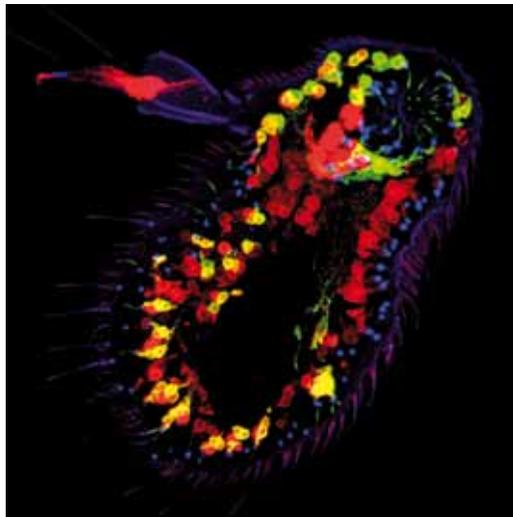
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**Béatrice Desvergne**  
Professor



**Béatrice Desvergne** was trained as a MD. In 1984, she obtained both the MD degree and the specialization in Anesthesiology and Resuscitation. After practicing medicine for a few years, she decided to devote more time to fundamental research. She thus 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 the field of Molecular Endocrinology. In 1992, she was appointed as assistant professor at the University of Lausanne. She was then recruited as associate professor at the same University, joined the Center for Integrative Genomics in 2003, and was promoted as full Professor in 2008. In addition to her teaching and research activities, she is President of the Section of Fundamental Sciences since January 2009 and Vice-Dean of the Faculty of Biology and Medicine since August 2009.

## Networking activity of PPARs during development and in adult metabolic homeostasis

As they mediate intracellular hormone action, nuclear receptors play a crucial multi-faceted role in coordinating growth during development, and homeostasis at adult stage. Among them, the peroxisome-proliferator activated receptors (PPARs) 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.

### PPARbeta IN THE CENTRAL NERVOUS SYSTEM: A REGULATORY FACTOR OF METABOLISM IN DEVELOPMENT AND ALONG TISSUE REPAIR ACTIVITY

The role of PPARbeta in tissue repair led us to test the brain response after injury. In collaboration with the CIBM and use of NMR, we demonstrated that upon transient ischemia (collaboration with the laboratory of Dr L. Hirt) PPARbeta null mice present a two fold higher levels in lactate concentration at the early time points post-injury, while other metabolites were similar to that observed in WT. Primary cultures of neural cells, particularly of astrocytes, which play a major role in neuron metabolism revealed that PPARbeta null astrocytes have a deficit in glutamate uptake, associated to an altered regulation of glycolysis. Together with more detailed mechanistic studies, our results suggest that in the brain PPARbeta activities in metabolism are integrated to those on cell survival and tissue repair.

We also pursued our exploration to understand the enlargement of lateral ventricles, which appears in a subset of PPARbeta null mice in the perinatal period and can reach major development at adult stage. The only major feature observed just at the time of appearance of the phenotype and may contribute to it is a reduced intermediate zone in the forebrain, reflecting an impairment of axon tracts development that occurred in all PPARbeta null mice. The alteration of axonal growth is accompanied by an altered expression of Ankyrin2 and L1cam, giving the first molecular clues on how PPARbeta acts as a hydrocephalus susceptibility gene.

### A NEW MODEL OF PPARgamma NULL MICE

Analyses of the effects of PPARgamma deletion have been so far pre-empted by the lethality provoked by PPARgamma germ-line deletion. However, in addition to generating tissue-specific conditional null mice, we have now been able to produce fully viable mutant embryos and live pups, through an epiblastic selective PPAR deletion. This approach demonstrates that the cause of embryonic lethality as early as E10.5 in PPAR mutants is mainly due to the placental defects. Intriguingly, PPARgamma expression levels in normal placenta steadily increase along the pregnancy. By treating pregnant wild-type mice with the PPARgamma agonist rosiglitazone, we demonstrated the deleterious effects of this treatment for placental organisation and microvasculature. Further findings demonstrate that PPARgamma plays a pivotal role in controlling vascular proliferation and contributes to its quiescence in late pregnancy.

This new mouse model is now allowing us to explore the systemic role of PPARgamma. The major questions that we are presently addressing link metabolism, inflammation and tumorigenesis, three major processes altered in these mice.

### A NUCLEAR-RECEPTOR REGULATORY NETWORK IN LIVER METABOLISM

At the molecular and cellular levels, transcriptional regulation of metabolism is one key component of metabolic homeostasis. However, understanding of how the TFs involved in metabolic regulations act in connection to each other to finely tune metabolic homeostasis is still ahead of us. To explore this complexity, we have now developed a new set up with hepatocyte cells in culture that allow us to study the regulatory network formed by a subset of important metabolic transcription factors that include LXR, FXR, PPARs, HNF4, and SREBP. Analyses of the important amount of data generated by these data wet-lab experiments, as well as data mining from relevant previous reports will be performed through building up bio-informatics competences within the lab while being embedded in the strong local bioinformatic environment, and the CycliX programme. Indeed, this project synergised with our involvement in the SystemsX-funded project CycliX, which aims at identifying master transcriptional regulators that link the circadian cycle, the nutrition response cycle, and the cell division cycle, in the liver.

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## Publications

### RESEARCH ARTICLES

Ali FY, Hall MG, Desvergne B, Warner TD, Mitchell JA (2009) PPARbeta/delta agonists modulate platelet function via a mechanism involving PPAR receptors and specific association/repression of PKC alpha. **Arterioscler Thromb Vasc Biol** 29:1871-3

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### COMMENT

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## Funding and Collaborations

### FUNDING

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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. Christian Fankhauser was promoted full Professor in 2011.

## Light regulation of plant growth and development

Almost all our food, feed, fuel and fiber ultimately derive from plants. Plant growth depends on photosynthesis, the process in which light energy is harnessed for the synthesis of high energy 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. 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 allowing 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). Photon capture by these photoreceptors induces a suite of developmental responses including seed germination, seedling de-etiolation, regulation of tropic growth, shade avoidance, resetting the circadian clock and the control of flowering time.

In our lab we study 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). We concentrate our studies on the function and regulation of three members of the extended PIF family (PIF4, PIF5 and HFR1). 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. We focus our attention on phototropin-mediated growth responses (phototropism and leaf positioning) two processes requiring the PKS (Phytochrome Kinase Substrate) proteins. Finally we are studying how the phytochromes and phototropins co-

ordinately control a number of growth responses in low light environments. We combine molecular genetics, genome-wide 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. We combine molecular evolution of the phytochrome family with homology modeling to identify sites that may have led to important functional innovations in phyA.
- Determine the mechanisms by which the phytochromes control PIF-mediated growth responses. We primarily concentrate our attention on the role of HFR1, PIF4 and PIF5 during the shade avoidance syndrome. We study the transcriptional cascade initiated by these bHLH factors and how external and internal factors control their activity.
- Uncover the mode of action of PKS 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 in phytochrome and phototropin signaling 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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## Publications

### RESEARCH ARTICLES

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## Paul Franken

Maître d'Enseignement et de Recherche



**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 2009 he received the Sleep Science Award from the American Academy of Neurology.

## Genetics and energetics of sleep homeostasis and circadian rhythms

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

### GENETICS OF SLEEP

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

lines, which will be a particularly powerful community resource to map complex traits.

### CLOCK GENES & SLEEP HOMEOSTASIS

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

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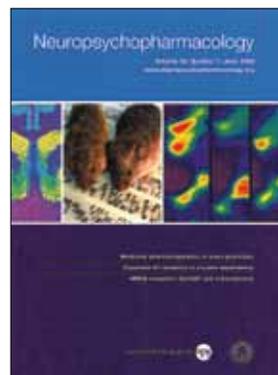
\*left the group

## Publications

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**David Gatfield**  
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A biochemist by training, **David Gatfield** performed his PhD work at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. Under the direction of Elisa Izaurralde, he studied the cellular mechanisms underlying the nuclear export and the degradation of mRNAs. He then joined the group of Ueli Schibler at the University of Geneva, Switzerland, as a postdoctoral fellow, where he developed his liking for the field of circadian rhythms. His particular interest was in the role that miRNAs play in regulating rhythmic gene expression in the liver. He joined the CIG as a Swiss National Science Foundation Professor in November 2010.

## Molecular mechanisms of circadian gene expression

Circadian clocks can anticipate daytime and orchestrate temporal gene expression and associated physiological processes in a proactive manner. Typically 2-10% of an organ's transcriptome are thus subject to circadian oscillations. According to current models, rhythmic transcription constitutes the mechanistic basis of these oscillations, both for the core clock genes and for the clock-controlled output pathways, which drive overt rhythms in physiology.

Based on the available literature, it is evident that circadian transcription, however, is not sufficient to explain many observations that have been made. The comparison of the daily changes in the mouse liver proteome and transcriptome, for example, has revealed that almost half of the cycling proteins are translated from constantly expressed mRNAs rather than from rhythmic mRNAs. This and other findings suggest that important parts of the clock circuitry still remain to be defined. In particular the role of mechanisms acting on the level of mRNA metabolism (e.g. mRNA stability and mRNA translation) has been largely ignored thus far. This includes the influence of the class of regulatory molecules known as microRNAs (miRNAs).

It should be pointed out that the circadian field does not only offer very exciting biological questions in its own right. It may also ideally serve to uncover more general principles of how gene expression is regulated in complex physiological situations. Circadian rhythms can be considered an excellent paradigm for such a complex physiological process that is amenable to studies on many levels, from biochemistry up to behavioural studies in animals. Circadian research is thus frequently multidisciplinary in itself and relevant to many fields, with numerous links to human disease. Given that circadian clocks are both cell-autonomous and under systemic control, we use both tissue culture and mouse models for our studies.

### THE OPENING MATCH: miRNAs CONTRIBUTE TO RHYTHMIC GENE EXPRESSION

Before setting up an independent research group at the CIG in November 2010, I worked as a postdoctoral fellow at the University of Geneva. The major part of my research during that time was dedicated to the analysis of miRNA functions in rhythmic gene expression. We found that the highly abundant liver miRNA, miR-122, is tightly embedded in hepatic circadian gene expression and metabolic control. The miR-122 locus is thus itself under circadian transcriptional control by the core oscillator component REV-ERB $\alpha$ . Although mature miR-122 accumulates to constant levels throughout the day due to its long half-life, we found that this miRNA regulates a disproportionately high fraction of circadian transcripts. Many of these are associated with circadian metabolic pathways, such as cholesterol and lipid metabolism. In this context, we further identified several links between miR-122 and the Peroxisome Prolifera-

tor Activated Receptor (PPAR) family of circadian metabolic regulators. The exact molecular mechanisms by which miR-122 engenders rhythmic responses of its target transcripts are still an open issue that we wish to explore over the coming years.

In an extension to this study, we contributed to identifying the circadian deadenylase Nocturnin as a direct miR-122 target. It is still unknown on which target mRNAs Nocturnin acts exactly, but it is assumed that rhythmic poly(A) tail shortening by this deadenylase leads to corresponding rhythmic changes in transcript stability and/or translatability. This example shows how rhythmic gene expression and mRNA metabolism are intricately connected – and, frankly, how poorly we still understand these connections.

### miRNAs AND RHYTHMS: TO BE CONTINUED...

As described above, we are just starting to have a glimpse at the functions miRNAs may exert within the circadian clockwork. To gain better insight, we have developed a number of tools such as loss-of-function mouse models and reporter assays to analyse the roles these molecules play in rhythmic gene expression. We shall continue these studies both in tissue culture cells and in animals.

### TIME FOR A CHANGE: RNA-BINDING PROTEINS WITH CIRCADIAN FUNCTIONS

The mammalian genome encodes several hundred predicted RNA-binding proteins (RBPs) whose functions are largely unknown. Similar to the abovementioned Nocturnin, a number of these proteins are rhythmic themselves and/or their loss-of-function has been associated with perturbed rhythms in large-scale RNAi screens. As a second focus in the lab, we would like to delve into the unknown and – starting with some exemplary candidate proteins – explore how the family of RBPs modulates functions of the core clock and clock output genes. We are on the way of developing the tools required for the analysis of circadian RBP functions, such as techniques for the purification of RBP-associated RNAs at different times of the circadian day.

### CONCLUSION

In summary, insight into circadian biology will remain limited without a thorough understanding of regulatory mechanisms operating on the level of mRNA metabolism and translational control. These have, however, so far been poorly investigated in mammals. We thus hope to make important contributions to the chronobiology field. We are optimistic that we will provide valuable food-for-thought for the RNA/miRNA fields as well.

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## Publications

### RESEARCH ARTICLES

Gatfield D, Le Martelot G, Vejnar Ce, Gerlach D, Schaad O, Fleury-Olela F, Ruskeepaa AI, Oresic M, Esau Cc, Zdobnov Em, Schibler U (2009) Integration of microRNA mir-122 in hepatic circadian gene expression. *Genes Dev* 23:1313-26

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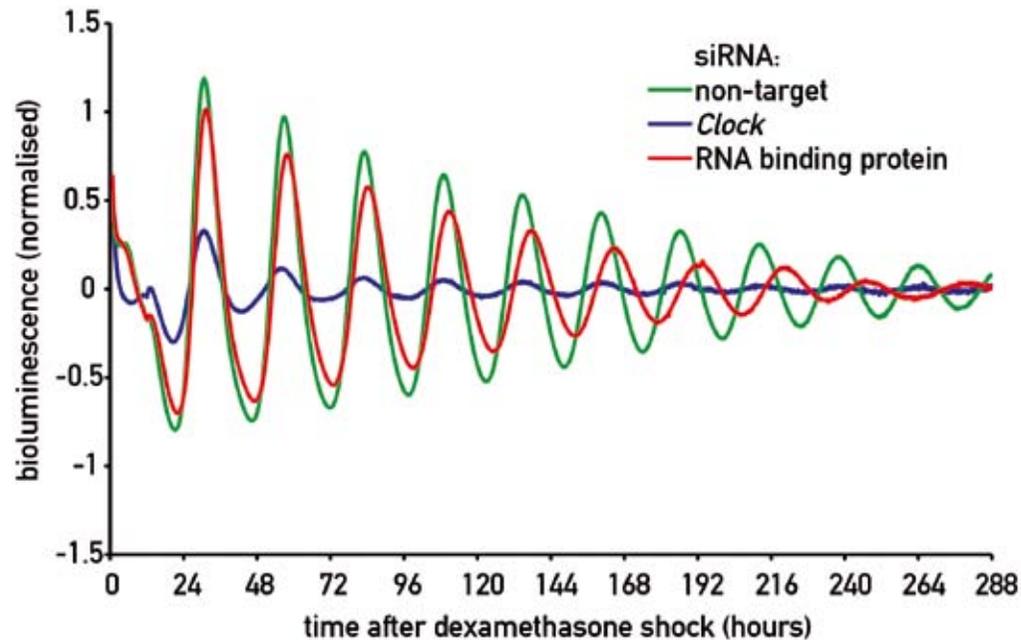
Kojima S, Gatfield D, Esau Cc, Green Cb (2010) MicroRNA-122 modulates the rhythmic expression profile of the circadian deadenylase Nocturnin in mouse liver. *PLoS One* 5:e11264

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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 the 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 first as an Associate Investigator in 1994, and as an Investigator in 1999. In 2005, she joined the faculty of the University of Lausanne as a Professor and as the Director of the Center for Integrative Genomics.

## Synthesis of non-coding RNAs by RNA polymerases II and III: mechanisms of transcription regulation

RNA polymerase III (pol III) synthesizes a collection of short RNAs that are involved in a number of essential processes including protein synthesis and transport, maturation of other RNA molecules, transcription control, etc. Pol III genes fall into three main classes characterized by different promoter structures, which recruit different transcription factors. Transcription by pol III is highly regulated with cell growth and proliferation. As pol III transcripts are generally very stable, a resting cell needs just enough pol III transcription activity to replace the low number of decaying pol III RNA products. However, a rapidly dividing cell needs high levels of pol III transcription to achieve the synthesis of an entire complement of pol III transcripts in one generation time. In fact, pol III activity seems limiting in rapidly dividing cells, as it is consistently elevated in tumor cells, and indeed elevating pol III activity is sufficient to achieve transformation in some cell types. A main regulator of pol III transcription is the repressor Maf1, which is conserved from yeast to humans. In yeast, Maf1 is essential to achieve pol III repression in response to a number of stress signals. It is inactivated by Sch9 kinase phosphorylation. Sch9 itself is controlled by TOR kinase. Thus, inhibition of TOR as a result of, for example, nutrient deprivation, results in Maf1 dephosphorylation and activation as a repressor of pol III transcription.

We have focused on two main questions: how broadly is the known pol III transcription machinery used at the genome level, and what is the function and control mechanism of human Maf1.

Gene expression arrays have long been used to characterize which genes are transcribed under any given conditions. However, this method has two serious disadvantages when it is used to estimate genomic transcriptional states: firstly, it measures RNA levels, which does not necessarily reflect transcription levels; secondly, it cannot easily be used to study pol III genes, as these genes contain a high percentage of highly repeated sequences, which are difficult to distinguish by methods based on hybridization. With the advent of methods involving chromatin immunoprecipitation followed by ultra high throughput sequencing (ChIP-Seq), we saw an opportunity to study the pol III transcriptome. As a proof of principle, we performed chromatin immunoprecipitations in actively dividing IMR90 cells with antibodies directed against pol III and several of its transcription factors. The DNA associated with the various factors was then subjected to ultra-high throughput sequencing to generate short sequence tags. We developed a bioinformatics method to analyze not only the resulting tags with unique matches in the genome but also those with many matches. This method allowed us to map

the location of pol III and its transcription factors to both unique and repeated genomic sequences. This analysis defined the pol III transcriptome in IMR90 cells. It revealed that the pol III transcription factors that have been studied by biochemical methods with only a few model genes are, in fact, broadly used by all pol III genes. It revealed new genes transcribed by pol III, whose function remains to be defined, and it showed that some microRNA genes that had been reported as being transcribed by pol III are in fact not occupied by pol III in cells. But perhaps most importantly, this study provided us with the tools to analyze, at the genome level, the pol III transcriptome under any condition we might be interested in. Indeed, this work formed a basis for a RTD grant obtained from SystemsX to perform similar studies in the mouse, and for a Sinergia grant in which we are performing systematic genome-wide analyses of the pol III transcriptome in human cells.

To characterize mammalian Maf1, we took advantage of Maf1 KO mouse embryo fibroblasts we had generated. Using such cells, we found that mammalian Maf1 is absolutely required for pol III repression in response to serum starvation or TOR inhibition by rapamycin or Torin1. We then mapped the Maf1 phosphorylation sites by purification of the protein before and after cell stress followed by mass spectrometry analysis. Further, we showed that in mammalian cells, Maf1 is not controlled by S6 kinase 1, the homologue of yeast Sch9, as might be expected, but rather by direct TOR phosphorylation. This work, performed in collaboration with Michael Hall and colleagues from the Biozentrum in Basel, describes the molecular mechanisms by which TOR controls human Maf1, and adds a new branch to the signal transduction cascade immediately downstream of TOR. The results also show that there are significant differences in how Maf1 is regulated in yeast and mammalian cells.

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## Publications

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## Funding

### Swiss National Science Foundation (SNSF)

- Independent Basic Research Grant
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- Sinergia Collaborative Project, PI: E. Dermitzakis, UNIGE
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## Winship Herr

Professor



**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.

## Molecular Epigenetics

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

### HCF-1

To investigate these processes, we study a key regulator of human-cell proliferation that is also implicated in embryonic stem cell maintenance and cancer. This protein, called HCF-1 for herpes simplex virus host-cell factor-1, binds to many promoters indirectly by recognizing a large number of site-specific DNA-binding proteins and recruits a plethora of chromatin-modifying activities - including histone acetyltransferase and deacetylase, histone methyltransferases and demethylase, phosphatase, deubiquitinase and *O*-linked beta-*N*-acetylglucosamine transferase (OGT) - resulting in both activation and repression of transcription. It also undergoes an unusual proteolytic maturation process that generates two associated HCF-1 subunits that regulate different phases of the human cell cycle: The N-terminal subunit 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.

### AN E2F CO-REGULATOR

We have previously reported 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. Our studies have previously indicated that E2F-protein association with HCF-1 plays roles in both repression and activation of transcription. During the G1-to-S phase transition, HCF-1 recruits the MLL and Set-1 H3K4 methyltransferases to E2F responsive promoters, and induces histone methylation and transcriptional activation.

Deregulation of one of the members of the E2F family, called E2F1, leads to oncogenic DNA damage and anti-oncogenic apoptosis. How E2F1 induces DNA damage and apoptosis have been poorly under-

stood. We have now shown that HCF-1 association with E2F1 stimulates both E2F1-induced DNA damage and apoptosis, and that the MLL-family of H3K4 methyltransferases plays important roles in these processes. Thus, HCF-1 plays a broader role in E2F1 function than previously appreciated. Indeed, changes in the sequence of E2F1 responsible for binding HCF-1 can modulate both up and down the ability of E2F1 to induce apoptosis indicating that HCF-1 is a limiting regulator of E2F1-induced apoptosis.

### DROSOPHILA Hcf GENETICS

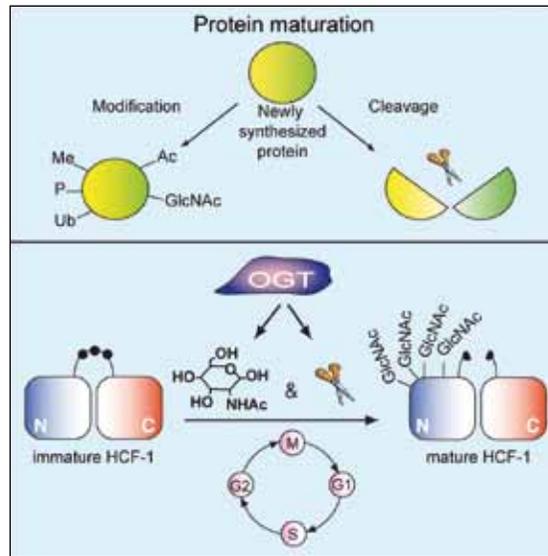
To elucidate both conserved and species-specific functions of HCF proteins, we perform genetic, genomic, biochemical, bioinformatic, and molecular studies in diverse organisms including the *C. elegans* worm and *Drosophila* fruit fly. In this vein, we have recently used reverse genetics to disrupt the gene encoding the *Drosophila* HCF-1 homolog called Hcf. Worms with a disrupted *hcf-1* gene are viable. In contrast, homozygous *Hcf*-null flies die except for during the first generation where about 50% reach adulthood owing to the presence of Hcf of maternal origin. These adults display a variety of interesting developmental phenotypes including sterility, small size, and homeotic transformations.

In *Drosophila*, repressed and activated transcriptional states of cell fate-determining genes are maintained throughout development by Polycomb Group (PcG) and Trithorax Group (TrxG) genes, respectively. *Hcf* mutant flies display morphological phenotypes typical of TrxG mutants and *Hcf* enhances both PcG and TrxG phenotypes, classifying *Hcf* as an Enhancer of TrxG and PcG (ETP) gene. Thus, Hcf in flies has important roles in classically defined developmental pathways.

### OGT DISPLAYS AN AMAZING ABILITY TO CLEAVE HCF-1

In closing, we have revealed an interesting role for OGT in human HCF-1 proteolytic maturation. Proteolysis occurs at six centrally located HCF-1<sub>PRO</sub>-repeat sequences and the maturation process is important for activation of HCF-1<sub>C</sub> subunit functions in M-phase progression. We have now shown that OGT binds the HCF-1<sub>PRO</sub> repeat to both *O*-GlcNAcylate the HCF-1<sub>N</sub> subunit and surprisingly directly cleave the HCF-1<sub>PRO</sub> repeat. Replacement of the HCF-1<sub>PRO</sub> repeats by a heterologous proteolytic cleavage signal promotes HCF-1 proteolysis but fails to activate HCF-1<sub>C</sub>-subunit M-phase functions. These results reveal an unforeseen nexus between OGT-directed *O*-GlcNAcylation and proteolytic maturation in HCF-1 cell-cycle regulation.

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## Publications

### RESEARCH ARTICLES

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## Funding

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### SystemX.ch

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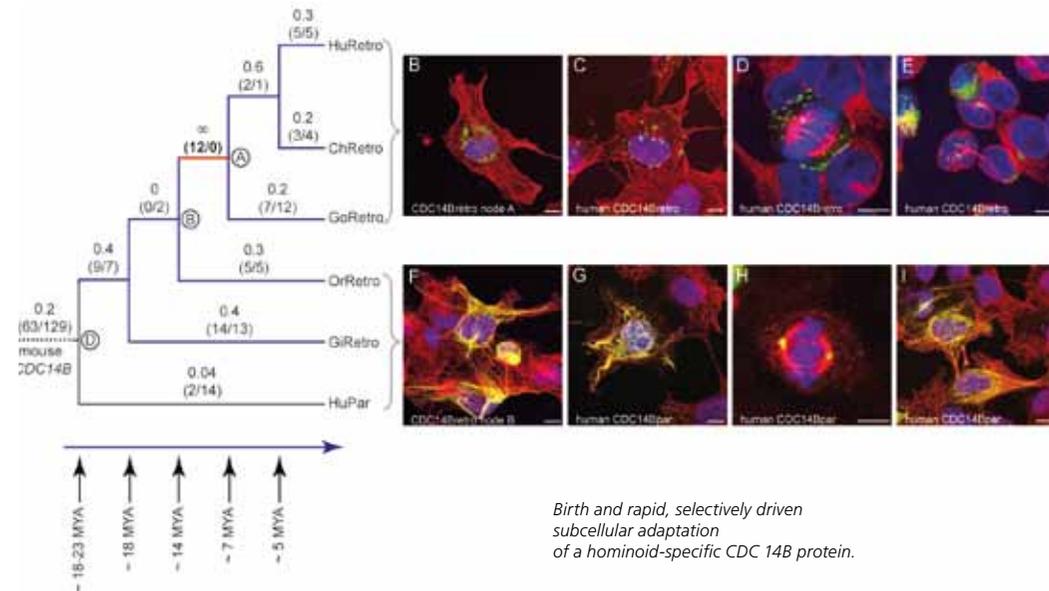
**Henrik Kaessmann** received his PhD in 2001 from the University of Leipzig after working on the genetic diversity of humans and the great apes in the laboratory of Dr. S. Pääbo at the University of Munich and subsequently at the MPI for Evolutionary Anthropology, Leipzig. He obtained his postdoctoral 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. He was awarded a European Research Council Starting Grant in 2009. In 2010, he received the Friedrich Miescher Award from the Swiss Society for Biochemistry and was elected as a group leader in the Swiss Institute of Bioinformatics.

## Functional evolutionary genomics in mammals

Our previous work on the origin and evolution of new genes led to several general findings pertaining to the functional evolution of mammalian genomes, such as a reassessment of the age of human sex chromosomes and that new gene functions often appear to arise in the testes. Partly motivated by these findings, we have in the past two years been seeking to significantly extend our work beyond new gene origination studies and explore our previous observations on a global scale using a unique combination of evolutionary analyses and experimental work.

Specifically, supported by major new grants from the European Research Council and the Swiss National Science Foundation, we have embarked on a major new series of projects pertaining to the evolution of mammalian tissue transcriptomes, which now form the core of our activities. In the framework of these projects, a large amount of qualitative and quantitative transcriptome data have been produced (by the wet lab unit of the group) for a unique collection of tissues and cell types from representative mammals using next generation sequencing technologies (RNA-Seq). Topics of major bioinformatics projects that are based on these data include the evo-

lution of gene expression levels, alternative splicing, microRNAs and their expression, X chromosome dosage compensation, and germ cell transcriptomes. We have already obtained a number of intriguing and fundamental results in the framework of these projects. For example, we have found that most transcriptome changes in mammals are effectively neutral and hence have not significantly affected the phenotype. However, our detailed analyses have nevertheless uncovered numerous concerted expression changes of groups of genes as well as of individual genes that likely underlie major phenotypic innovations in mammals (e.g., the evolution of the complex human/primate brain). Notably, many ancient transcriptome changes in mammals seem to have been associated with the emergence of mammalian sex chromosomes. Analyses performed so far have also unveiled, for example, fundamental aspects regarding the birth and functional evolution of mammalian microRNAs (e.g., the rate of miRNA gene origination) and transcriptomes of spermatogenic cells (e.g., genome-wide promiscuous transcription in meiotic and postmeiotic cells).



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

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## Funding

### Swiss National Science Foundation (SNSF)

- Independent Basic Research Grant
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Sophie Martin earned her Diploma in 1999 from the University of Lausanne 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 Trust/Cancer Research 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. In September 2007, she joined the CIG as a Swiss National Science Foundation Professor. Since November 2010, she is Associate Professor at the Department of Fundamental Microbiology of the UNIL.

## Molecular mechanisms of cell polarization

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 control. 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 provide spatial signal to polarize growth towards the extremities of the cell by transporting polarity factors to cell poles. One such factor is the microtubule-associated protein Tea4, which we had previously demonstrated binds an actin nucleator of the formin family, For3, thereby directly linking positional information provided by microtubules to actin assembly. We have now generated point mutations in Tea4 to investigate its mode of localization and regulation. Our ongoing investigations suggest that Tea4 may integrate phosphorylation and de-phosphorylation events to control cell polarization.

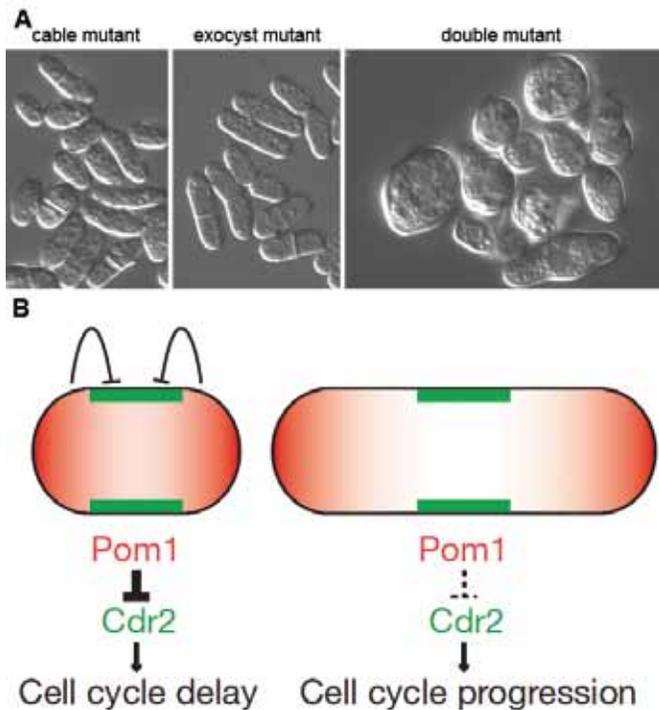
### PATHWAYS FOR CELL MORPHOGENESIS

Cell morphogenesis depends on polarized exocytosis. One widely held model suggests that long-range transport and exocyst-dependent tethering of exocytic vesicles at the plasma membrane sequentially drive this process. The actin cytoskeleton is organized at the growing cell poles. Bundles of actin filaments nucleated at cell poles by For3, also known as cables, form tracks for the movement of type

V myosin motors. Myosin-driven cargoes include membrane material and cell wall remodeling components essential for polarized cell growth. We recently discovered that this transport is surprisingly not essential for cell morphogenesis. Similarly, disruption of the exocyst complex still permits morphogenesis to proceed. However, disruption of both actin cables and exocyst led to isotropic growth. Thus, in fission yeast, long-range cytoskeletal transport and the exocyst represent parallel morphogenetic modules, raising the possibility of similar mechanisms in other cell types. We are currently pursuing two avenues of research: first, we are investigating in depth these two parallel pathways. Second, we are studying the mechanisms by which actin cables are organized inside the yeast cell.

### GEOMETRIC CONTROL OF THE CELL CYCLE

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 recently discovered a novel geometry-sensing mechanism by which fission yeast cells couple cell length with entry into mitosis. Conceptually, the system is remarkably simple: it is composed of a signal – the protein kinase Pom1 – forming concentration gradients from the ends of the cells, which inhibits a sensor – the protein kinase Cdr2, itself an activator of mitotic entry – placed at the cell equator. Since Pom1 concentration at the cell middle is higher in short cells than in long cells, this suggests a model where Pom1 inhibits Cdr2 until the cell has reached a sufficient length. Our current investigations focus on the mechanisms underlying the formation of Pom1 gradients at the cell cortex, which we found are shaped by a phosphorylation cycle.



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## Funding and Collaborations

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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 pursued 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.

## Molecular control of skin homeostasis

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

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

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

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

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

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

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

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

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## Publications

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### Faculty of Biology and Medicine (FBM), UNIL

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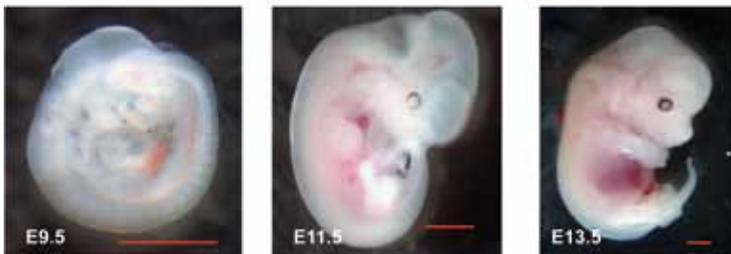
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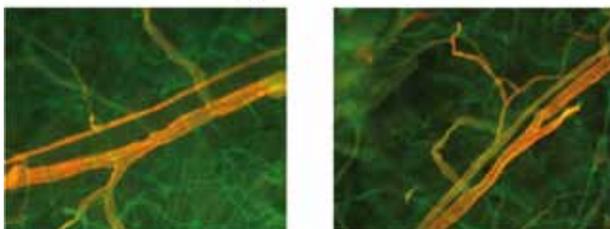
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## Skin regeneration and repair in mouse embryos



## Whole mount staining of skin microvessels

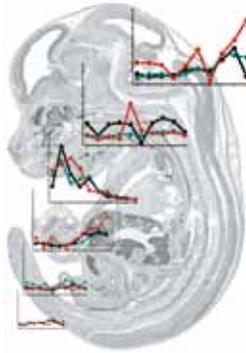


## Alexandre Reymond Genome structure and expression

Associate Professor



**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. In 2010 he was awarded the "Prix Leenaards".



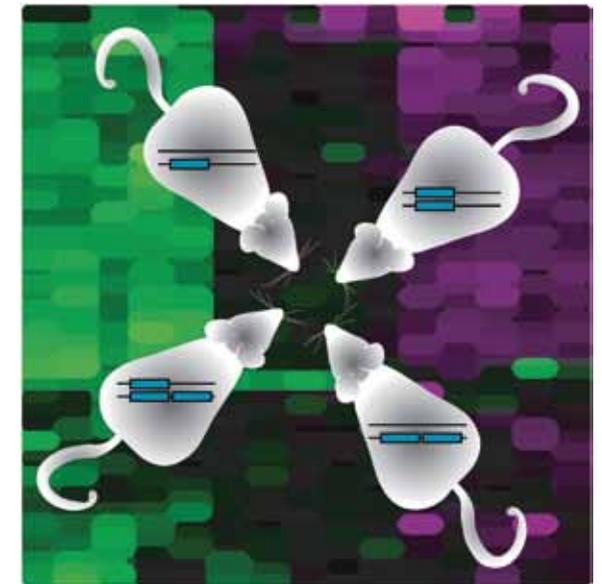
A fundamental question in current biomedical research is to establish a link between genomic variation and phenotypic differences, which encompasses both the seemingly neutral polymorphic variation, as well as the pathological variation that causes or predisposes to disease. In addition to the millions 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 its phenotypic effect is only beginning to emerge.

We have assessed the functional impact of CNVs at the genome-wide scale using the mouse as a model organism. 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 located on their flanks and sometimes those at a great distance from their boundary. 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. We demonstrate, by monitoring these effects at multiple life stages, that these controls over expression are effective throughout mouse development. Similarly, we observe that the more specific spatial expression patterns of CNV genes are maintained through life. CNV genes are significantly enriched within transcripts that show variable time-courses of expression between strains. Thus, modifying the copy number of a gene may potentially alter not only its expression level, but also the timing of its expression.

We further assessed the relative contribution of structural changes and gene dosage alterations on phenotypic outcomes with mouse models of Smith-Magenis and Potocki-Lupski syndromes. We phenotyped mice with 1n (Deletion/+), 2n (+/+), 3n (Duplication/+) and balanced 2n compound heterozygous (Deletion/Duplication) copies of the same region. Parallel to the observations made in humans, such variation in gene copy number was sufficient to generate phe-

notypic consequences: in a number of cases diametrically opposing phenotypes were associated with gain versus loss of gene content. Surprisingly, some neurobehavioral traits were not rescued by restoration of the normal gene copy number. Transcriptome profiling showed that a highly significant propensity of transcriptional changes map to the engineered interval in the five assessed tissues. A statistically significant overrepresentation of the genes mapping to the entire length of the engineered chromosome was also found in the top-ranked differentially expressed genes in the mice containing rearranged chromosomes, regardless of the nature of the rearrangement; an observation robust across different cell lineages of the central nervous system. Our data indicate that a structural change at a given position of the human genome may affect not only locus and adjacent gene expression, but also "genome regulation". Furthermore, structural change can cause the same perturbation in particular pathways regardless of gene dosage. Thus, the presence of a genomic structural change, as well as gene dosage imbalance, contributes to the ultimate phenotype.



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## Publications

### RESEARCH ARTICLES

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- Project "Comprehensive characterization and classification of the human transcriptome"

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**Andrzej Stasiak**  
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**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 Ultrastructural 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).

## Functional transitions of DNA structure

Our group is interested in the functional aspects of DNA structure and topology. More recently we become interested in the overall organization of genomes starting with arrangement of DNA in phage heads and ending with chromosome territories in higher eukaryotes. Some aspects of our interests go beyond biology, like for example statistical mechanics studies of knotted polymers. However, also these studies have biological or biophysical applications in helping to explain, for example, how DNA topoisomerases can efficiently distinguish knotted DNA molecules from unknotted ones. During recent years numerical methods used to model behavior of DNA molecules became the main method utilized by our group, although biochemistry and electron microscopy, in particular, remained essential part of our research.

### ORGANIZATION OF NUCLEAR ARCHITECTURE

We are interested in revealing the underlying physical phenomena responsible for the overall organization of chromosomal territories in interphase nuclei. Using computer simulations we addressed the following three questions:

- Why are chromosomal territories with relatively high transcriptional activity usually closer to the center of nucleus than those with lower activity?
- Why are actively transcribed genes usually located at the periphery of their chromosomal territories?
- Why are pair-wise contacts between active and inactive genes less frequent than those involving only active or only inactive genes?

Our simulation studies suggest that transcription factories-mediated interchromosomal contacts are probably the main organizers of nuclear architecture in interphase cells.

### TOPOISOMERASE PARADOX

Numerous experiments including single molecule manipulations studies revealed that type II DNA topoisomerases involved in the process of DNA replication show strong preference of action on DNA-DNA juxtapositions where the opposing duplexes wind around each other in a left-handed way. However, freshly replicated circular DNA molecules, such as bacterial chromosomes, prokaryotic and eukaryotic extrachromosomal elements and DNA viruses such as SV40, form DNA catenanes, in which the direction of winding of two sister molecules is right-handed. How then these type II DNA topoisomerases manage to be very efficient in the decatenation of freshly replicated DNA molecules? We have approached this problem using Monte Carlo and Brownian dynamics simulations. These simulations permitted us to reveal that multiply interlinked catenanes release their mechanical constraint in form of a higher order coiling with left-handed DNA-DNA juxtapositions. This observation explains why

the chirality bias of type II DNA topoisomerases that are known to be involved in DNA decatenation does not interfere with their action during initial stages of DNA decatenation.

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

Our group has a long time experience in electron microscopy imaging of functional complexes formed with DNA by various proteins participating in the process of homologous recombination. Our studies contributed in a significant way to understanding the role and the mechanism of action of such proteins as RecA, RuvAB, RAD51, RAD52, DMC1, BRCA2 or FANCM. In a collaboration project involving group of Prof. M. Takahashi, we investigated inhibitory effects of peptides derived from BRCA2 protein on the action of RAD51 protein with the aim of finding biologically active peptides that could be used as inhibitors of DNA repair processes in cancer cells. In a collaboration project with Prof. JY Masson, we recently studied interactions of PALB2 protein with DNA. This human protein plays an important control function in the process of recombinational DNA repair. This protein binds to DNA directly but also interacts with RAD51, BRCA2 and BRCA1 proteins. In vitro assays demonstrated that PALB2 protein stimulates RAD51-promoted homologous pairing. Using electron microscopy we visualized PALB2 binding to recessed ends of duplex DNA. We hope that our studies will shed additional light on the process by which mutations in PALB2 and BRCA2 lead to development of cancers in affected patients.

### CHROMATIN AS Topo II INHIBITOR?

Theoretical predictions and our own computer simulations revealed that formation of chromosomal territories can proceed spontaneously when modeled chromatin fibers are not permitted to pass through each other. This has led us to propose that type II DNA topoisomerases are unable to perform passages between unperturbed chromatin fibers. Of course, type II DNA topoisomerases are essential for decatenation of freshly replicated DNA and for the elimination of positive DNA supercoiling arising due to progressing strand separation. However this action may happen when the regular chromatin structure is not yet reestablished after DNA replication or when the chromatin is distorted by positive supercoiling that is known to induce dissociation of histones. Such distorted chromatin fibers with protein-free DNA regions could of course serve for Topo II-mediated passages just like it is the case in standard in vitro reactions involving protein-free DNA. Our proposal that regular chromatin structure prevents topo II-mediated passages between chromatin fibers is mainly relevant during decondensation of chromosomes after mitosis and during establishing chromosome territories in interphase nucleus.

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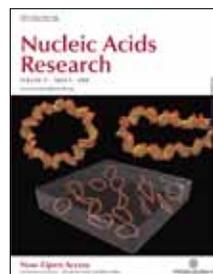
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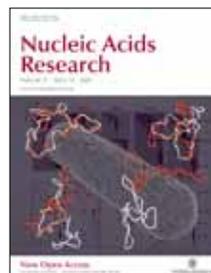
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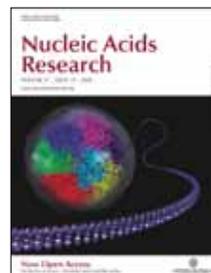
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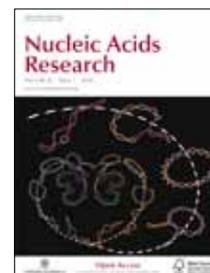


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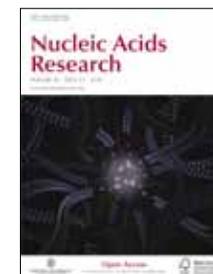


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**Mehdi Tafti** received his PhD from the University of Montpellier (France) in 1991 after completing his doctoral thesis on sleep regulation in human narcolepsy. He performed a postdoctoral fellowship with Dr. Mignot and Dr. Dement and was a Research 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. Since November 2006, he is co-directing the Center for Investigation and Research in Sleep (CIG-CHUV). He was promoted full Professor in 2011.

## Genetics of sleep and sleep disorders

Two major projects are underway in my laboratory:

### GENETICS AND CELLULAR BASIS OF SLEEP

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

### GENETICS OF NORMAL SLEEP AND SLEEP DISORDERS

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

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

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## Publications

### RESEARCH ARTICLES

Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M (2009) Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. **Neurology** 73:1333-4

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### REVIEW

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## Funding

### Swiss National Science Foundation (SNSF)

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**Bernard Thorens** received his PhD from the University of Geneva for studies on the biosynthesis of immunoglobulins in pre-B lymphocytes. He then did a first postdoctoral fellowship in Geneva working on hematopoietic growth factors with Pierre Vassalli. In 1986 he moved to the Whitehead Institute for Biomedical Research in Cambridge (USA) for a postdoctoral fellowship in Harvey Lodish laboratory. In 1991 he came back to Switzerland to take a Career Development award from the SNSF and to establish his laboratory at the Department of Pharmacology and Toxicology. Since 2002 he is Professor and joined the Center for Integrative Genomics in 2005.

## Physiological genomics of energy homeostasis

### PANCREATIC BETA-CELLS IN HEALTH AND TYPE 2 DIABETES

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

We are identifying novel mechanisms that regulate beta-cell number and secretion capacity. To this end we are evaluating how the glucorecretin hormones GLP-1 and GIP stimulate mature beta-cell proliferation, how they protect these cells against apoptosis, and how they regulate their secretion capacity. We have demonstrated the role of an autocrine loop that depends on IGF-2 secretion and activation of the IGF-1R. This autocrine mechanism is activated by GLP-1, which induces expression of the IGF-1R; on the other hand, nutrients increase IGF-2 biosynthesis and secretion. Activation of this autocrine loop is the mechanism by which GLP-1 stimulates proliferation, increases glucose competence and protects beta-cells against apoptosis. These studies are continued by evaluating *in vivo* the role of IGF-2, as well as of IGF2BP2, a protein regulating IGF-2 biosynthesis identified as a diabetes susceptibility gene, using mice with beta-cell selective inactivation of these genes. Based on yeast two hybrid screens, we are characterizing novel proteins interacting with the GLP-1R and involved in novel intracellular signalling processes.

### BRAIN GLUCOSE SENSING AND CONTROL OF GLUCOSE HOMEOSTASIS

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

We are identifying glucose sensitive neurons that express the glucose transporter isoform Glut2, which is also required for glucose sensing by pancreatic beta-cells. Using mice that express a highly fluorescent protein in Glut2 neurons (Figure) we have demonstrated that Glut2 neurons of the basolateral medulla are activated by glucose whereas those from the nucleus of the tractus solitarius (NTS) are activated by hypoglycemia. Initial studies based on *c-Fos* immunodetection studies are now being completed by electrophysiological (patch clamp) analysis of Glut2 neurons in the NTS. These are activated by hypoglycemia and are GABAergic interneurons.

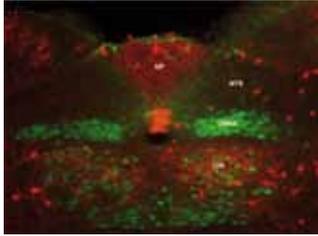
In parallel, we are investigating the physiology of mice with brain-specific Glut2 inactivation. A major defect is the progressive appearance of glucose intolerance, with impaired insulin secretion and a reduction in beta-cell number. Direct electrophysiological recordings have shown that this was secondary to a defect in autonomic nervous activity, in particular as controlled by glucose. Thus, these data indicate that central Glut2 expressing cells are indeed important sensors of glycemia that control autonomic nervous activity and endocrine pancreas function. We are pursuing these studies to better characterize the Glut2 expressing cells in the brain and their anatomical relationship with autonomic nerves.

### LIVER METABOLIC PATHWAYS CONTROLLING HEPATIC STEATOSIS

Hepatic steatosis is associated with obesity, insulin resistance and the metabolic syndrome; it can also lead to development of inflammation, fibrosis, and cirrhosis. The metabolic pathways that underlie steatosis development are not fully elucidated and may differ between individuals of diverse genetic backgrounds.

We identified liver metabolic pathways associated with resistance to diet-induced steatosis using comparative transcriptomic and lipidomic analysis of the livers from different strains of mice, which are susceptible or resistant to diet-induced obesity. We identified three lipid metabolic pathways that may participate in resistance to steatosis. First, we found a coordinated up-regulation of 10 peroxisomal genes, in particular of the L-PBE bifunctional enzyme that catalyzes the second and third steps of beta-oxidation. Second, an increase in microsomal elongase 5 and desaturases 1 and 2, which detoxify saturated fatty acids but also convert n-6 unsaturated fatty acids into arachidonic acid. Lipidomic analysis confirmed increased levels of 2-arachidonylglycerol (2-AG), a cannabinoid receptor agonist. This activates the Kupffer cell CB2 receptors to inhibit IL-1beta and G-CSF production explaining part of the reduced pro-inflammatory state of the steatosis resistant mice. Third, early after initiating high fat diet feeding, we found a transient up-regulation of OxPhos genes with increased mitochondrial oxygen consumption and increased uncoupling, thereby providing a means to dissipate energy in response to fat intake. More detailed analysis of these pathways is underway. In particular, we are studying L-PBE knockout mice. These develop massive and rapid liver inflammation and fibrosis when fed a high fat diet indicating major role of this gene in the adaptive response to high fat diet. The mechanisms leading to this response are now being investigated.

## Group members



Coronal section of the brainstem of a mouse showing glucose sensitive *Glut2* neurons expressing the red fluorescent protein *TdTomato* and cholinergic parasympathetic motor neurons (*DMNX*) and hypoglossal neurons (*12N*) (choline acetyltransferase labelling, green). AP: area postrema; NTS: nucleus of the solitary tract (Hitomi Sanno, David Tarussio)

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### RESEARCH ARTICLES

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## Funding and Collaborations

### FUNDING

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• Independent Basic Research Grant  
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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 also 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 multifaceted roles of PPARs

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

In the past two years, we have analyzed diverse functions of PPARs using different experimental models.

Although gender differences in fat metabolism are known, most metabolic studies are conducted in male animals. Therefore, our understanding of the molecular mechanisms underlying sex specificity in metabolism remains incomplete, which prompted us to explore if PPARalpha, a master regulator of hepatic lipid metabolism is involved in this sexual dimorphism. First, we observed that PPARalpha sumoylation is dimorphic, being more pronounced in females compared to males. By analyzing hepatic PPARalpha protein complexes we found three proteins that interact preferentially with PPARalpha in female liver. We identified the interaction motif of one of them and explored its coregulator abilities. To better understand the physiological significance of this sexual dimorphism, we concentrated on gene expression. Expression profiling using microarrays revealed that in female mice, PPARalpha has repressive actions on hepatic genes involved in steroid metabolism. Using the steroid oxysterol 7alpha-hydroxylase cytochrome P4507b1 (Cyp7b1) gene as a model, we elucidated the molecular mechanism of this sex-specific PPARalpha-dependent repression. Initial sumoylation of the ligand-binding domain of PPARalpha triggered the interaction of PPARalpha with GA-binding protein alpha (GABPalph) bound to the target Cyp7b1 promoter. DNA and histone methyltransferases were recruited, and the Sp1-binding site, which is adjacent to the GABP binding sites, and histones were methylated. These events resulted in the loss of Sp1-stimulated expression and thus downregulation of Cyp7b1. Physiologically, this repression confers protection against estrogen-induced intrahepat-

ic cholestasis, suggesting a novel therapy against the most common hepatic disease during pregnancy. Collectively, these data identify PPARalpha as a key actor of hepatic sexual dimorphism. The ongoing characterization of this function aims to unveil why the female liver is more resilient to inflammation and cancer.

PPARs exert their anti-inflammatory effects by inhibiting the induction of pro-inflammatory cytokines, adhesion molecules and extracellular matrix proteins or by stimulating the production of anti-inflammatory molecules. To investigate the role of PPARs in inflammatory responses, we are using mouse skin as a model. We have studied the role of PPARbeta/delta in the healing of wounds, which proceeds via a well-tuned pattern of events that include inflammation, re-epithelialization, and tissue remodeling. These events are regulated spatiotemporally by a variety of growth factors and cytokines. Activation of PPARbeta/delta triggers keratinocyte survival and amplifies a cellular internal signal required for keratinocyte directional sensing and migration. In addition, IL-1 produced by the keratinocytes activates PPARbeta/delta expression in the underlying fibroblasts, which in turn inhibits the mitotic activity of keratinocytes via inhibition of the IL-1 signaling pathway.

In numerous cancer types, PPARs regulate autonomous processes in tumor cells, such as apoptosis, proliferation, and differentiation, by interacting with major pathways promoting tumor development. We found that PPARbeta/delta is involved in skin tumor development after UV irradiation through the control of c-Src expression and downstream signaling pathways, eventually leading to the stimulation of epithelial-mesenchymal transition (EMT) markers.

Gastrulation is a key process in early development involving formation and placement of the embryonic germ layers to shape the body plan of the mature organism. We found that PPARbeta/delta is essential for normal gastrulation. It regulates a mid-gastrula switch from late germ layer specification to early lineage differentiation of mesodermal and neuroectodermal cells, allowing the anterior-posterior axis to differentiate and elongate. At the molecular level, PPARbeta/delta orchestrates the termination of Nodal signaling by several mechanisms, including direct repression of Nodal-related gene promoters. PPARbeta/delta directly interferes with the T-cell factor 3 (Tcf3) and represses its association with beta-catenin, an activator of Nodal-related gene expression. Our work documents how the balance between multipotency and differentiation is regulated in the developing embryo by the interplay among PPARbeta/delta, Nodal, and Tcf3/beta-catenin, which is also likely to be of importance in cancer development.

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Artist's view of female-specific PPARalpha sumoylation. (see Leuenberger et al., *J Clin Invest* 2009) by Muriel Matolo Wahli.

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## Publications (continued on next page)

### RESEARCH ARTICLES

Chong HC, Tan MJ, Philippe V, Tan SH, Tan CK, Ku CW, Goh YY, Wahli W, Michalik L, Tan NS (2009) Regulation of epithelial-mesenchymal IL-1 signaling by PPARbeta/delta is essential for skin homeostasis and wound healing. *J Cell Biol* 184:817-31

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Vegiopoulos A, Muller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, Ostertag A, Berriel Diaz M, Rozman J, Hrabe de Angelis M, Nusing RM, Meyer CW, Wahli W, Klingenspor M, Herzig S (2010) Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 328:1158-61

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\* W.Wahli is a member of the Eumodic Consortium

## Publications (continued)

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### BOOK CHAPTER

Leuenberger N, Wahli W (2010)  
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## 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@UNIL) 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.

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## Understanding signalling pathways controlling inflammatory cell functions

Understanding the molecular mechanisms controlling memory T cell functions is a pre-requisite to their targeting in anti-tumor therapy. Inappropriate assembly of signalling complexes has been shown to profoundly impact signalling and to be associated with cancer. We report T cell receptor signalling complex assembly in minute amounts of ex-vivo isolated human memory CD4 T cells using reverse phase protein arrays. Second- to fourth-order T cell receptor interacting proteins were accurately quantified, making this strategy well-suited to the analysis of membrane-associated signalling complex in clinical specimen.

Infiltration of monocytes or macrophages is a common feature of inflammation and tumor angiogenesis, which is receiving increasing attention in an attempt to develop novel therapeutic strategies. The ability of tumoricidal macrophages to recognize and selectively destroy neoplastic cells has been demonstrated in a wide range of experimental systems while tumor-associated macrophages were also reported to promote tumor development, progression and metastasis. The functional heterogeneity of macrophages is likely to reflect their plasticity and adaptation to suit the microenvironment in which they reside made of a complex network of pro-angiogenic and pro-inflammatory mediators. In 2005, a unique population of highly pro-angiogenic monocytes expressing Tie-2 receptor tyrosine kinase has been identified in human and mice and designated TEM for Tie-2-expressing monocytes. In mouse model, TEM recruited to tumors accounted for all angiogenic activity of bone marrow-derived cells, and their ablation fully suppressed angiogenesis. However, the molecular basis of their proangiogenic and protumoral activities is largely unknown.

We report that in breast cancer, TEM exposure to tumor microenvironment is required for the acquisition of their proangiogenic activity and we identified critical tumor-derived factors synergistically promoting TEM proangiogenic and protumoral activities in patient. Furthermore, we identified in TEM derived from breast tumor signalling axes as new candidate therapeutic intervention points for anti-angiogenic therapies (in collaboration with Pr Ioannis Xenarios, Vital-IT and Pr Jean-François Delaloye, CHUV). Our data show that the tumor microenvironment plays a key role by shaping the phenotype and the function of inflammatory cells. However, to date, the available technical approaches to profile inflammatory and angiogenic proteins in specific tumor zones are extremely limited.

In order to address this issue, we produced in collaboration with Dr. Sandro Carra (EPFL), a biosensor based on the memristive effect in Schottky-barrier silicon nanowires functionalized with specific antibodies. This completely novel memristive detection principle senses low concentrations of bio-molecules due to interactions occurring at the nanoscale between the molecular charges trapped by the bio-layer at the surface of the wire and the ambipolar carriers supporting the memristive conductivity into the wire.

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## Publications

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

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The main focus of the group is to contribute to the understanding of the effects of somatic and germline genome variation to the aetiology of cancer, with an emphasis on melanoma. Melanoma is a cancer of the pigment-producing cells in the skin. High rates of metastasis and limited treatment options translate into very poor disease prognosis, with a five year survival rate of only 16%. We have undertaken a comprehensive molecular characterisation of seven low passage cell lines derived from metastatic melanomas with the goal of improving our understanding of the oncogenic processes underlying the development of this disease. Karyotype analysis of the tumour cell lines revealed extensive heterogeneity in chromosome copy number, ranging from 40 to 70 chromosomes per cell. CGH and SNP array results confirmed the widespread amplifications and deletions seen in chromosome spreads, and provided a high resolution picture of the copy number status of every gene in each of the cancer genomes. The effect of somatic copy number alteration (SCNA) on gene expression in each cell line was assessed by RNA-seq using human melanocytes as a reference. Altogether, we identified over 1700 genes affected by amplification or deletion and with altered expression relative to melanocytes. Using a protein network-guided approach we identified ten pathways significantly enriched in SCNA-genes in five or six of the cell lines. These pathways included G protein, WNT and cadherin signalling, angiogenesis and melanogenesis. Our data indicate that network-guided approaches are useful to identify recurrent events in cancer, even in small sample sizes.

In a parallel study to identify somatic mutations in these cell lines that may contribute to the oncogenic phenotype, we determined the exome sequence of each sample, and that of donor matched controls, using Illumina next generation sequencing technology. Differences between the exome sequence of each cell line and its matched control defined somatic mutations. In agreement with other recent studies, we found an altered mutation spectrum with an excess of single and dinucleotide C>T/G>A transitions indicative of exposure to UV light. We also found mutations in components of the RAS/MAPK pathways. Additionally, comparison of each control sequence with the reference human sequence plus information from the database of human single nucleotide polymorphisms (dbSNP) revealed patient-specific variations that may favour the development of melanoma (predisposition alleles). Validation of these results in a larger collection of melanomas and their matched controls is underway. This is a collaboration between the universities of Lausanne and Geneva, their teaching hospitals, Vital-IT/SIB and the Ludwig Institute for Cancer Research.

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

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

The group has developed SwissDock ([www.swissdock.ch](http://www.swissdock.ch)), a free docking web service to predict the molecular interactions that may occur between a target protein and a small molecule. The web interface of SwissDock aims at lowering the technical barrier of docking software, and generalizing the use of docking tools beyond the traditional molecular modeling community. The group is currently developing other web services for computer-aided rational drug design and molecular modeling, like SwissParam (<http://www.swissparam.ch>) which provides topology and parameters for the molecular modeling of small organic molecules, and SwissADME (<http://www.swissadme.ch>) which estimates physico-chemical properties of small molecules in relation with their pharmacokinetic, pharmacodynamic and druglikeness characteristics. We have employed these tools to design new inhibitors of IDO, an enzyme involved in the immune escape mechanisms used by cancer cells, and obtained compounds with affinities in the nanomolar range. We have also started a drug design project targeting EGFR, whose mutations have been associated with several cancers.

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

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

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### Publications

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# CORE FACILITIES





MASTERMIXES

TEMPLATES

FOR PCR  
MP 2Pos Flow

DAFL

MASTERPLATE 3 P...

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## 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 Genomic Technologies Facility since November of 2002.

## Genomic Technologies Facility (GTF)

## DESCRIPTION OF SERVICES

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

- Illumina HiSeq 2000 ultra high throughput DNA sequencing instruments
- Affymetrix GeneChip oligonucleotide arrays for the analysis of mRNA and DNA
- Agilent oligonucleotide arrays for the analysis of small non-coding RNA
- The Applied Biosystems 7900HT Sequence Detection Systems for as quantitative real-time PCR analyses
- Sample handling robots for the production of custom spotted DNA and protein arrays

The GTF provides users with training and supervision in all aspects of the molecular biology and instrument manipulations associated its technology platforms. In many cases, the GTF will perform all of the steps of the experiment, beginning with nucleic acids provided by the user. A key aspect of the GTF service platform is the bioinformatics support and consultation service it provides at the stages of experimental design, data collection and storage, image analysis and, when appropriate, higher level data analysis. The facility allows users to carry out their experiments in its laboratories by providing equipment and bench space. Furthermore, the GTF maintains computer workstations and software with which users can analyze their data.

## EXPANDING THE GTF SERVICE BASE

The period 2009-2010 saw a continued expansion of the GTF's service base. A second ultra high throughput DNA sequencing instrument was installed at the end of 2009 which, along with an associated expansion of the data management system, has allowed the GTF to increase the resources available to sequencing projects. This was facilitated by a close collaboration with Vital-IT Project of the SIB/Swiss Institute of Bioinformatics in the area of data management and storage. The facility also saw increased use of its array-based mRNA expression profiling, quantitative real-time PCR and miRNA analysis platforms.

## EDUCATIONAL ACTIVITIES

The GTF is also lively as an educational resource. Its principal activities have been in organizing a annual week-long microarray use and application course under the auspices of the *Schweizerische Kommission fuer Molekularbiologie* (SKMB) and the *III<sup>ème</sup> Cycle Romand en Sciences Biologiques*. Additionally, the GTF 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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**Manfredo Quadroni**  
Maître d'Enseignement et de Recherche



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

## Protein Analysis Facility (PAF)

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

### IMPROVED OFFER OF SERVICES

The SILAC (Stable Isotope Labeling with Amino Acids in Culture) workflow introduced in 2008 gained some popularity and was applied to several project in 2009-2010. The platform was able to offer to users a complete solution including the necessary isotope labeled cell culture media as well as comprehensive data analysis.

Due to the increased demand for high-throughput work, an expansion of the capacity of the platform became necessary. With funding from the Swiss National Foundation and UNIL we purchased in 2010 a second high resolution LC-MS system (LTQ-Orbitrap Velos). Also thanks to this acquisition the PAF was able to introduce a new service, a so-called iTRAQ workflow, which allows multiplex quantitative profiling of proteins in complex mixtures. Based on chemical labeling, this technology enables the analysis of samples that cannot be metabolically labeled and as such is a perfect complement to the SILAC approach.

### INDEPENDENT R&D PROJECTS

A first research project ongoing at the PAF was aimed at correcting the bias that the sole use of trypsin as the proteolytic enzyme introduces in large-scale proteome analysis. We first showed that large peptides obtained after trypsin digestion are poor subjects for MS-based protein identification. However, enrichment of a fraction of such large tryptic peptides by size exclusion chromatography and secondary digestion with orthogonal proteases lead to recovery of many sequences not mapped after trypsin-only digestion. This approach was especially interesting for the analysis of the phosphoproteome in conjunction with phosphopeptide enrichment. This project was carried out by B.Tran, a Post-Doc, with funding from SystemsX.ch. In a second grant-funded project we continued our investigations on the use of SILAC-style metabolic labeling of proteins for various pur-

poses. The next aim is to develop tools to measure not only total protein amounts, but also rates of protein synthesis and degradation on a proteome scale. Such a technique has the potential to shed some light on the basic mechanisms used by cells to modulate protein concentrations, more precisely to dissect the contribution of changes in protein synthesis or degradation to net changes in protein concentration. The project started in 2010 and is ongoing.

### COLLABORATIVE PROTEOMICS STUDIES

We have continued our fruitful collaboration with the group of Prof. M.Monod at the dermatology department of the CHUV, focused on the characterization of sets of proteases secreted by pathogenic and non pathogenic fungi. A new research direction aiming at determining immunogenic fungal and bacterial antigens was developed in 2009-2010 in the context of these collaborative studies. In another collaboration with the group of Prof. P. Moreillon (UNIL, Dept. of Fundamental Microbiology DMF) we are mapping and quantifying pathogenesis-related surface proteins of *Staphylococcus aureus* (adhesins). Preliminary results indicate that the expression of several of these adhesins varies as a function of growth conditions and correlates with pathogenicity of the bacteria. Further on we initiated a collaboration with Dr. M.Molinari at the Institute for Research in Biomedicine in Bellinzona, centered on the study of ER-resident components of the protein folding quality control machinery. This will be achieved by studying the interactome of folding-competent vs that of folding-defective polypeptides. The largest SILAC study performed so far at the PAF was a collaboration with Christian Iseli at the Lausanne branch of the Ludwig Institute for Cancer research for the proteome comparison of 6 melanoma cell lines among themselves and with melanocytes. This study is part of a larger effort by the Ludwig to characterize melanoma samples at multiple levels (genome sequencing, mRNA expression, copy number analysis, karyotype and more).

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## Publications

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## Funding and Collaborations

### FUNDING

**Swiss National Science Foundation (SNSF)**  
Basic Research Grant

### COLLABORATIONS

**W. Herr**  
UNIL, Lausanne, Switzerland

**C. Iseli**  
Ludwig Institute for Cancer Research and SIB, Lausanne, Switzerland

**M. Molinari**  
Institute for Research in Biomedicine, Bellinzona, Switzerland

**M. Monod**  
Centre Hospitalier Universitaire (CHUV) and UNIL, Lausanne, Switzerland

**P. Moreillon**  
UNIL, Lausanne, Switzerland

## CORE FACILITIES ASSOCIATED WITH THE CIG

In addition to the Genomics Technologies Facility (GTF) and to the Protein Analysis Facility (PAF), a number of core facilities are associated with the CIG, either because they are directed by CIG members and/or because they are located within the Génopode. 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 supports the Lausanne and Swiss research community in the statistical data analysis and data mining.

The BCF, associated to the Swiss Institute of Bioinformatics, periodically organizes workshops, courses and tutorials on statistical principles and methods and on practical data analysis tools and procedures. It also offers hands-on data analysis services, consulting and the development of software solutions.

The BCF is actively running scientific collaborations with academic and industry researchers in which it provides advanced bioinformatics know-how for biomedical projects that use high throughput arrays or sequencing based technologies, with a specialty in the development and validation of diagnostic, prognostic and treatment-personalization biomarkers.

#### DIRECTOR

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#### BIOSTATISTICS CONSULTING

**Frédéric Schütz**

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*<http://bcf.isb-sib.ch/>*

### The Cellular Imaging Facility (CIF)

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

The CIF is organized around three complementary activities:

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

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

On the Bugnon campus, the facility occupies five rooms of the Medical School building (Bugnon 9). On the Dorigny campus, the CIF is using one room of the Biophore building and eight rooms in the Génopode building. In Epalinges, the CIF is located in Building F.

#### DIRECTOR

**Jean-Yves Chatton**

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#### TECHNICAL MANAGER AT THE CIG

**Yannick Kemp** (Bugnon)

**Arnaud Paradis** (Dorigny)

**Florence Morgenthaler** (Epalinges)

#### WEBSITE

*<http://cifweb.unil.ch>*

## 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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**Raphael Heinzer** (CHUV)  
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### WEBSITE

[www.unil.ch/cig/page42710\\_fr.html](http://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.

### DIRECTOR

**Bernard Thorens**  
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### COORDINATOR

**Frédéric Preitner**  
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### WEBSITE

[http://www.unil.ch/cig/page41381\\_fr.html](http://www.unil.ch/cig/page41381_fr.html)

## 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-performance 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.

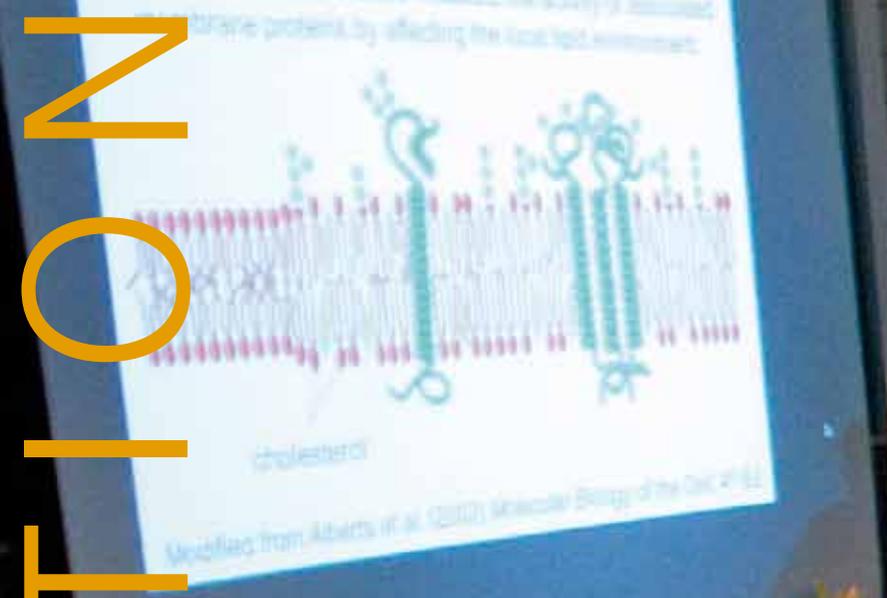
### DIRECTOR

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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 or members of core facilities, give courses at the Bachelor, Master and PhD levels at the UNIL and other organizations. We are proud that in 2010, the FBM award for excellence in teaching went to CIG member Liliane Michalik! Doctoral students and postdoctoral fellows actively participate in teaching activities, in particular for what concerns laboratory courses. The CIG is further heavily involved in the organization of teaching; Winship Herr is the Director of the UNIL School of Biology, Christian Fankhauser heads the master "Molecular Life Sciences" (MLS), Keith Harshman the new doctoral program "Integrated Experimental and Computational Biology" (IECB), and Nouria Hernandez the new CUSO (Academic Conference of Western Switzerland) doctoral program StarOmic.

The CIG hosts a large number of PhD students and post-doctoral fellows pursuing research projects in individual laboratories. CIG PhD students have, in addition to their PhD advisor, and "academic mentor", who can offer a complementary support in areas such as the development of career plans. However, another important role of the academic mentor is to give advice in case of any conflicts that may arise with the PhD advisor. In 2010, the CIG SAC recommended that the CIG organize a system to allow post-doctoral fellows to get help and advice in case of conflict with their advisors. We are very pleased that Prof. Jacques Dubochet accepted to become ombudsman for CIG postdoctoral fellows.

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

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

## Courses and lectures given by CIG members

### Biology curriculum, UNIL

#### BACHELOR LEVEL

**Richard BENTON**  
**Béatrice DESVERGNE**  
**Christian FANKHAUSER**  
**Sophie MARTIN**  
 Génétique des modèles eucaryotes

**Richard BENTON**  
**Liliane MICHALIK**  
 Body patterning  
**Béatrice DESVERGNE**  
 Biologie animale et génétique

**Christian FANKHAUSER**  
 Circadian clocks  
 Perception et réponses à la lumière chez les plantes

**Christian FANKHAUSER**  
**Henrik KAESSMANN**  
**Alexandre REYMOND**  
 Structural genomics and mutation

**Paul FRANKEN**  
 Sleep and circadian rhythms: from molecules to performance  
 Neurobiology

**Nouria HERNANDEZ**  
**Walter WAHLI**  
 Régulation génétique des eucaryotes

**Winship HERR**  
 Génétique moléculaire et générale  
 Epigenetics  
 Viruses-hosts

**Henrik KAESSMANN**  
 Molecular evolution

**Liliane MICHALIK**  
 Introduction à l'embryologie animale  
 Biologie cellulaire et moléculaire

**Alexandre REYMOND**  
 Du Génome au Phénome

**Andrzej STASIAK**  
 DNA repair and its defects  
 Cell cycle DNA replication and recombination

**Mehdi TAFTI**  
 Du Phénome au Génome  
 Quantitative genetics

**Erwann VIEU**  
**Johann WEBER**  
 Practicals in molecular biology

**Walter WAHLI**  
 Chapitres choisis de Développement

#### MASTER LEVEL

**Richard BENTON**  
 Evolution and development of insects and plants

**Béatrice DESVERGNE**  
 Médiation et communication scientifiques  
 Régulation transcriptionnelle du métabolisme

**Christian FANKHAUSER**  
 Effets de l'environnement sur le développement  
 Cartographie, séquençage et structure des génomes

**Paul FRANKEN**  
 Problem-based learning in methodology

**Paul FRANKEN**  
**Keith HARSHMAN**  
**Manfredo QUADRONI**  
**Mehdi TAFTI**

**Johann WEBER**  
 Génomique, Protéomique et Génétique quantitative

**Keith HARSHMAN**  
 Design experimental

**Winship HERR**  
 Gene expression and Cell Cycle

**Henrik KAESSMANN**  
**Alexandre REYMOND**  
 Comparative genomics

**Sophie MARTIN**  
 Le cytosquelette: molécules de la morphogénèse

**Liliane MICHALIK**  
**Nicolas ROTMAN**  
 Développement précoce et voies de signalisation

**Manfredo QUADRONI**  
 Protein analysis  
 Proteomics

**Walter WAHLI**  
 Récepteurs nucléaires et régulation génétique  
 Development of skeletal muscle and adipose tissue

#### PhD LEVEL

**Christian FANKHAUSER**  
**Paul FRANKEN**  
 Horloges circadiennes

**Winship HERR**  
 Raisonnement et logique en génétique et en biologie moléculaire et cellulaire

## Courses at other organizations

### Richard BENTON

Olfactory physiology  
Cold Spring Harbor Laboratory,  
New York, USA

### Richard BENTON

Invertebrate olfaction  
University of Geneva, Switzerland

### Christian FANKHAUSER

Perception de la lumière  
et signalisation  
University of Geneva, Switzerland

### Paul FRANKEN

Genetics of sleep  
ESRS meeting training course  
University of Lisbon, Portugal

### Paul FRANKEN

Training in Sleep Research  
and Sleep Medicine  
Bertinoro, Italy

### Paul FRANKEN

Year in Review  
San Antonio, USA

### Otto HAGENBÜCHLE

### Nouria HERNANDEZ

Exercice de biologie  
Biologie moléculaire II  
EPFL, Lausanne, Switzerland

### Nouria HERNANDEZ

Transcription regulation  
by RNA molecules  
NCCR Frontiers in genetics

### Winship HERR

Proteolytic maturation of a  
human epigenetic cell-cycle  
regulator  
NCCR Frontiers in Genetics

### Liliane MICHALIK

PPARs: skin repair and cancer  
NCCR Frontiers in Genetics

### Liliane MICHALIK

Des gènes à l'être humain  
Collège des Sciences, Switzerland

### Alexandre REYMOND

Formation pratique à la biologie  
moléculaire  
Centre Suisse de Formation  
Continue et UNIL-Eprouvette,  
Lausanne, Switzerland

### Alexandre REYMOND

Functional genomics  
EPFL, Lausanne, Switzerland

### Nicolas ROTMAN

Nuclear Receptor, in particular  
PPARs, as controllers of  
embryonic development  
NCCR Frontiers in Genetics

### Mehdi TAFTI

Neurobiologie des états  
de vigilance  
University of Geneva, Switzerland

### Bernard THORENS

Integration by the brain of  
peripheral signals to control  
energy homeostasis  
NCCR Frontiers in Genetics

### Nicolas ROTMAN

### Walter WAHLI

Introduction to Nuclear Recep-  
tors and Functions of PPARs in  
energy homeostasis  
NCCR Frontiers in Genetics

## Undergraduate students

## Master students

### Laetitia BASTERRA

Group Martin

### Thierry BOUDUBAN

Group Thorens

### David BOVARD

Group Thorens

### Cynthia DAYER

Group Herr

### José Manuel DELLEPIANE

Group Tafti

### Marianna DI CHIARA

Group Desvergne

### Jean-Gaël DISERENS

Group Desvergne

### Céline FAVROD

Group Tafti

### Joëlle GERVAIX

Group Kaessmann

### Diego GONZALEZ

Group Herr

### Gael GROSSENBACHER

Group Fankhauser

### Olivier HILFIKER

Group Fankhauser

### Nourhene KHALED

Group Wahli

### Nicolas LAPIQUE

Group Herr

### Cristina LEONI

Group Michalik

Group Benton

### Andrea MARAN

Group Fankhauser

### Marco MEHR

Group Hernandez

### Cyril MIKHAIL

Group Tafti

### Josselin MOOSBRUGGER

Group Herr

### Sophie NICOD

Group Kaessmann

### Damien NICOLAS

Group Herr

### Emilie PERSON

Group Wahli

### Aurélie RIGHETTI

Group Michalik

### Clémence ROGGO

Group Fankhauser

### Samuel ROPPO

Group Tafti

### Nadège ROSSIER

Group Thorens

### Lauren SHIELDS

Group Thorens

### Zaira SNOZZI

Group Michalik

### Pich MOLY SUN

Group Tafti

### Faïda WALHA

Group Reymond

## 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 belong to the doctoral school of the UNIL Faculty of Biology and Medicine (FBM), which determines the program and sets the rules of PhD studies.

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

Graduate students at the CIG benefit from a mentoring program. Through this program, each student is coupled to a mentor, in general a faculty member working in a different field than the one pursued by the graduate student. This mentor is available for scientific or non-scientific discussions and advice.

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

see also [www.unil.ch/cig/page62067.html](http://www.unil.ch/cig/page62067.html)

## The doctoral programs

### THE DOCTORAL PROGRAM IN INTEGRATED EXPERIMENTAL AND COMPUTATIONAL BIOLOGY (IECB)

The program is coordinated by Keith Harshman. It is founded on the principle that the biologists of the future will benefit from being competent in both experimental lab bench and computational bioinformatic approaches. It involves several departments of the UNIL FBM and offers PhD topics spanning the study of molecules, cells, organisms and their environment, and covering developmental biology, physiology, cancer biology, neuroscience, behaviour and evolutionary biology. This program, which is part of the Doctoral School of the University of Lausanne's Faculty of Biology and Medicine, harbours an international group of students working in a multidisciplinary, English-speaking research environment.

The IECB program, working in close association with the Swiss Institute of Bioinformatics-SIB, provides training and experience in the reasoning, logic and abilities inherent to both experimental and computational approaches and educates students in quantitative analysis of biological questions. Students are offered instruction in genome-wide and proteome-wide data analysis, biological modelling, quantitative image analysis, programming and statistics, in addition to a thorough education in experimental biology, through a didactic program that complements both their individual research topic and background. Thus, PhD students become conversant in both experimental and computational approaches and acquire the ability to integrate quantitative and experimental methods in their own research. Graduates from this program will have unprecedented scientific competence to permit them to become future leaders in biological research and beyond.

More information : <http://www.unil.ch/iecb>

### THE DOCTORAL PROGRAM STAROMICS

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

More information : <http://www.unil.ch/iecb>

## 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 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](http://www.unil.ch/cig/page62072.html)

## PhD students

**Monica ALBARCA**  
Group Herr

**Ali ALFAIZ**  
Group Reymond

**Rati BELL**  
Group Benton

**Tanja BHUIYAN**  
Group Herr

**Naomi BOREL**  
Group Gatfield

**Nicolas BONHOURE**  
Group Hernandez

**David BRAWAND**  
Group Kaessmann

**Jean-Marc BRUNNER**  
Group Desvergne

**Francesca CAPOTOSTI**  
Group Herr

**Leonardo CAPPONI**  
Group Herr

**Evelyne CHAIGNAT**  
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**Vincent CROSET**  
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**Dimitry DEBRIEUX**  
Group Fankhauser

**Gwendoline DEGUEURCE**  
Group Michalik

**Davide DEMURTAS**  
Group Stasiak

**Antonia DI MICCO**  
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**Julien DORIER**  
Group Stasiak

**Stéphane DORSAZ**  
Group Tafti

**Ilhem ELKOCRAIRI**  
Group Wahli

**He FU**  
Group Desvergne

**Sophie GUERNIER**  
Group Herr

**Matthew HALL**  
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**Patricia HORNITSCHEK THIELAN**  
Group Fankhauser

**Cédric HOWALD**  
Group Reymond

**José IGLESIAS**  
Group Wahli

**Philippe JULIEN**  
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**Manasi KELKAR**  
Group Martin

**Markus KOHNEN**  
Group Fankhauser

**Kyriakos KOKKORIS**  
Group Martin

**Francesco LA SPADA**  
Group Franken

**Alexandra LAVERRIÈRE**  
Group Thorens

**Nicolas LEUENBERGER**  
Group Wahli

**Sha LI**  
Group Tafti

**Libera LO PRESTI**  
Group Martin

**Gianina LUCA**  
Group Tafti

**Géraldine MANG**  
Group Franken

**Patrick MEYLAN**  
Group Michalik

**Honey MODI**  
Group Thorens

**Dhaval PATEL**  
Group Thorens

**Virginie PHILIPPE**  
Group Wahli

**Lukasz POTRZEBOWSKI**  
Group Kaessmann

**Jaime REINA**  
Group Hernandez

**Marianne RENAUD**  
Group Hernandez

**Gianina RUSU LUCA**  
Group Tafti

**Raphaël RYTZ**  
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**Audrey SAMBEAT**  
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**Chiara SARDELLA**  
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**Anantha Krishna SIVASUBRAMANIAM**  
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**Magali SOUMILLON**  
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**Raphaël TERRIER**  
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**Sajit THOTTATHIL OOMMEN**  
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**Julie VIENNE**  
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**Marta WAWRZYNIAK**  
Group Michalik

**Ralf WIMMER**  
Group Franken

**Robert WITWICKI**  
Group Reymond

## PhD theses obtained at the CIG

**Monica ALBARCA**  
Group Herr  
Etude des rôles génomiques du régulateur de la transcription HCF chez la drosophile (2010)

**Jean-Marc BRUNNER**  
Group Desvergne  
Canine Distemper Virus: Persistence and pathology in the central nervous system (2009)

**Francesca CAPOTOSTI**  
Group Herr  
Mechanisms of HCF protein proteolytic maturation (2010)

**Evelyne CHAIGNAT**  
Group Reymond  
Influence des CNVs (Copy number variants) au cours du temps (2010)

**Mara COLZANI**  
PAF  
Development of metabolic labelling strategies to study changes in protein expression (2010)

**Marion CORNU**  
Group Thorens  
Control of pancreatic beta-cell mass and function by glucagon-like peptide hormones: Identification of novel regulatory mechanisms for the treatment of diabetes (2009)

**Dimitry DEBRIEUX**  
Group Fankhauser  
Looking for factors involved in the light-dependent degradation of phytochrome A (2009)

**Matthieu DE CARBONNEL**  
Group Fankhauser  
PKS2: A link between phototropin signalling and auxin transport – a study on how plants sense and respond to light (2009)

**Davide DEMURTAS**  
Group Stasiak  
Optimisation de la cryo-microscopie électronique pour les études des minicercles d'ADN (2009)

**Ilhem EL KOCHAIRI**  
Group Wahli  
Hypolipidemic therapeutics and muscle metabolism (2009)

**Sophie GUERNIER**  
Group Herr  
Régulation de la fonction d'HCF-1 via sa maturation protéolytique et l'interaction de ses deux sous-unités (2010)

**Hyun HOR**  
Group Tafti  
Molecular genetics of narcolepsy (2010)

**José Alfredo IGLESIAS**  
Group Wahli  
Modulation of pancreatic beta cell growth and insulin secretion by PPARbeta/delta (2009)

**Nicolas LEUENBERGER**  
Group Wahli  
Sex and clock to discover new PPARalpha functions (2009)

**Virginie PHILIPPE**  
Group Wahli  
Involvement of PPARbeta/delta in mesenchymal-epidermal interactions during skin wound healing (2009)

**Lukasz POTRZEBOWSKI**  
Group Kaessmann  
RNA-based gene duplication sheds new light on mammalian sex chromosome evolution (2009)

**Jaime REINA**  
Group Hernandez  
The role of human Maf1 in RNA polymerase III transcription (2009)

**Julie VIENNE**  
Group Tafti  
Les effets du gamma-hydroxybutyrate, du baclofène et des récepteurs GABA (B) sur l'activité du cerveau et le sommeil chez la souris et l'homme (2010)

## DOING A POSTDOC AT THE CIG

The number of postdoctoral fellows at the CIG has considerably increased with the development of the Center over the past few years. Various initiatives have been implemented to offer them support and provide them with surroundings favoring their career development.

Postdocs can join CAOS (the CIG Association Of Scientists), which has been organizing the seminar series "Careers for Biologists" in 2009 and 2010. Further, following advice from the CIG Scientific Advisory Committee, the CIG established a new function to support postdocs, that of ombudsman. The CIG is particularly happy that an emeritus UNIL professor with a broad background in the life sciences (and life itself!), Prof. Jacques Dubochet, accepted to play this role, and is confident that this collaboration will be an enrichment for the CIG postdocs.

## The CIG Association of Scientists (CAOS)

CAOS, or CIG Association of Scientists, is an association founded by the PhD students and postdoctoral 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 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 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 throughout 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

**Denis BARRON**  
Nestlé Research Center  
Lausanne, Switzerland

**Diego BRAGUGLIA**  
VI Partners AG  
Zug, Switzerland

**Olivier DESSIBOURG**  
Le Temps  
Geneva, Switzerland

**Jean FLACH**  
Covance Central Laboratory  
Services SA  
Meyrin, Switzerland

**Maude GREUTERT**  
Alcimed Sàrl  
Lausanne, Switzerland

**Tomas GRUEBL**  
Roche Diagnostics Ltd.  
Rotkreuz, Switzerland

**Christophe GRUNDSCHÖBER**  
F. Hoffmann-La Roche Ltd  
Basel, Switzerland

**Nicole RENGGLI-ZULLIGER**  
European Patent Office  
Munich, Germany

**Chikako SHINDO**  
Bayer BioScience N.V.  
Gent, Belgium

**Ioannis XENARIOS**  
Vital-IT  
Lausanne, Switzerland



## Prizes awarded to CIG students and postdoctoral fellows

### Marion CORNU

Group Thorens  
Prix de la Recherche de la  
Fondation Suisse du Diabète  
2009

### Vincent CROSET

Group Benton  
Prize of the Faculty of Biology and  
Medicine (FBM), UNIL, for his  
Master's thesis (2009)

### Matthieu DE CARBONNEL

Group Fankhauser  
Best Poster Prize, CIG annual  
retreat 2009

### Charlotte HENRICHSEN & Nicolas VINCKENBOSCH

Group Reymond & group  
Kaessmann  
Prix d'Excellence du jeune  
chercheur of the Faculty of  
Biology and Medicine (FBM),  
UNIL 2009

### Nicolas LEUENBERGER

Group Wahli  
Prix Guenin 2010

### Anamaria NECSULEA

Group Kaessmann  
Postdoctoral researcher travel  
award of the Society for  
molecular biology and evolution  
2010

### Lia ROSSO

Group Kaessmann  
Investigator in Training award  
of the Faculty of Biology and  
Medicine (FBM), UNIL, 2009

### Magalie SOUMILLON

Group Kaessmann  
Best Poster Prize, CIG annual  
retreat 2010

### Julie VIENNE & Stéphane DORSAZ

Group Tafti  
Travel grant from the European  
Sleep Research Society to attend  
the 20th Congress in Lisbon

### Ralf WIMMER

Group Franken (co-PI)  
Asher-Hess young investigator  
prize 2010

## Academic courses for non biologists

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

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

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



**«Le Deuxième Sexe»**  
Le Deuxième Sexe de Beauvoir affirme que la condition féminine n'est définie que par la société et la culture. Pour l'auteur, la femme est de toutes les femmes mammifères celle qui est le plus profondément aliénée à l'espace et qui refuse le plus violemment cette aliénation.

**(Sciences)<sup>2</sup> – la parenthèse qui changera votre façon de voir le monde.**  
Donnez du relief à votre cursus grâce aux nouveaux cours optionnels de sciences naturelles pour les étudiantes et étudiants en sciences humaines !  
Le programme d'enseignement (Sciences)<sup>2</sup>, c'est des crédits, mais aussi bien plus que cela : une nouvelle manière de comprendre l'homme et le monde dans lequel il vit.  
Présentation vidéo des cours et toutes les informations utiles sur :  
[www.unil.ch/sciencesauccarre](http://www.unil.ch/sciencesauccarre)

**Chromosome X**  
Le rôle des chromosomes dans la détermination génétique du sexe est variable selon les espèces. Chez l'homme, le sexe mâle dépend de la présence du chromosome Y, alors que chez la drosophile c'est le rapport entre le nombre des X et celui des autosomes qui est décisif.

Unil  
UNIL | Université de Lausanne  
(Sciences)<sup>2</sup>

## The CIG and the public

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

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

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

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

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

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

see also: [www.unil.ch/cig/page16994.html](http://www.unil.ch/cig/page16994.html)

## Activities proposed (non-exhaustive)

### «L'ADN fait son cinema»

L. Michalik

A conference on the realities of genetics and modern biology based on extracts from movies such as «Jurassic Park», «Spiderman» etc.

### «L'horloge interne»

F. LaSpada, et al., lab. P. Franken

An activity explaining the study of the influence of the circadian rhythms on the life of human beings and vertebrates in general

### «Analyses d'ADN»

GTF

A visit of the Genomic Technology Facility and an explanation on genomics

### «Les yeux des plantes»

L. Vuillet, S. Lorrain, et al.

lab. C. Fankhauser

A visit of the Fankhauser lab and explanation on the perception of light by plants

### «La perception des odeurs par les mouches»

lab R. Benton

A visit of the Benton lab and an explanation on how odors are perceived

### «L'enquête du Professeur Erudix»

L. Michalik, et al.

An enquiry on a « laugh epidemic » introducing children to basic analysis in the laboratory

### «La vie du chercheur»

N. Hernandez, L. Michalik

A visit of the CIG and a discussion aimed at prospective biology students

### «La vache sans taches»

lab A.Reymond

See p.59

## The CIG in the media (non-exhaustive)

### Discover what a good night's sleep is

WRS (World Swiss Radio),  
13.08.2010

M. Tafti

### Die «Sprache Gottes» nicht verstanden

Sonntag, 6.06.2010

A. Reymond

### The faces of Swiss excellence

Reflex, 11.05.2010

H. Kaessmann

### Maladies auto-immunes: la solution est-elle dans l'assiette ?

36,9, TSR (Swiss French TV),

04.05.2010

W. Wahli

### Stammzellen – alte und neue Hoffnungsträger

DRS 2 (Swiss German Radio),

12.04.2010

B. Thorens

### Les Prix Leenaards visent les maladies rares

Le Temps, 26.03.2010

A. Reymond

### Warum manche Menschen plötzlich einschlafen

Basler Zeitung, 16.02.2010

M. Tafti

### L'odorat des insectes révolutionne l'évolution

24H, 16.10.2009

R. Benton

### Le patrimoine génétique de la vache percé à jour

TSR (Swiss French TV, news),

23.04.2009

A. Reymond

### La cellule sait quand elle doit se diviser

Agence Télégraphique Suisse SA, 27.03.2009

S. Martin

### Faut-il avoir peur du plastique ?

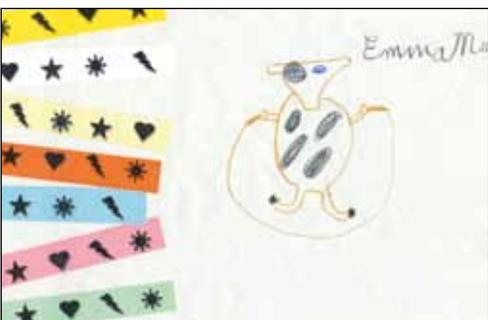
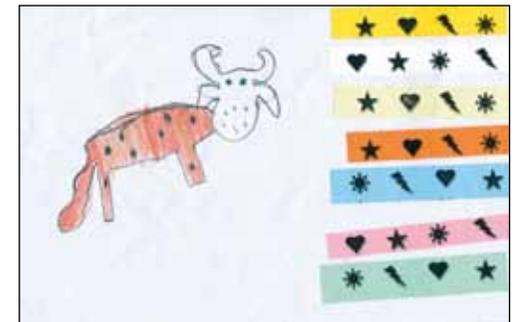
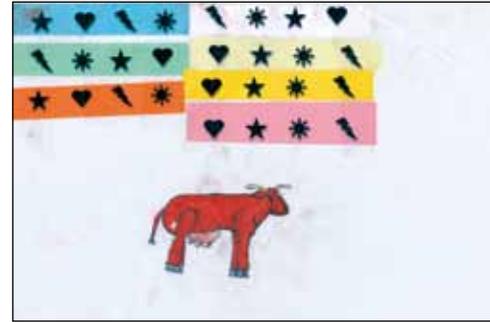
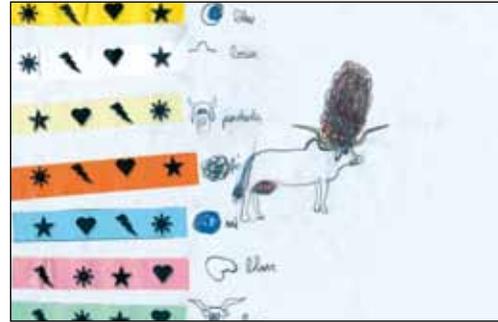
Femina, 01.02.2009

W. Wahli

## LA VACHE SANS TACHE

«La vache sans tache» is an activity which was proposed by the Raymond laboratory during the Mysteres de l'UNIL (UNIL open doors). Following the sequencing of the cow genome, children and adults were explained the bases of genetics through an activity which led them to draw cows with specific phenotypes based on an imaginary DNA molecule.

«La vache sans tache» was adapted from the activity «a recipe for traits» from <http://learn-genetics.utah.edu>



## CIG SYMPOSIA

Encouraged by the success of its inaugural symposium in 2005, the CIG established a yearly symposium whose topic varies from year to year but is always related to research done at the Center. The aims of the CIG symposia are:

- to bring together the best European and non-European scientists working in a particular field
- to foster interactions between junior and senior scientists
- to promote a dialogue between scientists using different approaches to study a similar topic

A highlight in the series was the presentation given in 2010 by Prof. Martin Chalfie, 2008 Nobel Prize laureate.

See also: [www.unil.ch/cigsymposium](http://www.unil.ch/cigsymposium)

The CIG thanks the following organizations, who made these events possible :

Merck Serono, Novartis, Roche, Nestlé, Fondation Herbette, Fondation du 450<sup>ème</sup> anniversaire de l'UNIL, Fonds du Docteur E. Rub, Fonds National Suisse de la Recherche Scientifique.

## CIG Symposium 2009: DNA Repair and Human Health

### ORGANIZERS

**N. Hernandez**  
**W. Herr**  
**L. Michalik**  
**A. Stasiak**

**Maria A. BLASCO**  
Spanish National Cancer  
Research Centre,  
Madrid, Spain  
*Role of telomeres in cancer  
and aging*

**Angelos CONSTANTINOU**  
UNIL, Lausanne, Switzerland  
*FANCM ensures the progression  
of replication forks*

**Peter DROGE**  
Nanyang Technological  
University, Singapore  
*HMG2A exhibits dRP/AP site  
cleavage activity and protects  
cancer cells from DNA-damage-  
induced cytotoxicity during  
chemotherapy*

**Edward EGELMAN**  
University of Virginia,  
Charlottesville, USA  
*Nucleoprotein complexes:  
from DNA segregation to  
recombination*

**Marco FOIANI**  
Istituto FIRC di Oncologia  
Molecolare, Milano, Italy  
*Mechanisms protecting  
the integrity of replicating  
chromosomes*

**Errol C. FRIEDBERG**  
UT Southwestern Medical  
Center at Dallas, USA  
*Tolerance of DNA damage by  
translesion DNA synthesis*

**Thanos HALAZONETIS**  
University of Geneva,  
Switzerland  
*Mechanisms of recruitment of  
DNA damage response proteins  
to sites of DNA breaks*

**Philip C. HANAWALT**  
Stanford University, USA  
*Multiple mechanisms for  
genomic maintenance*

**Jan H. HOEIJMAKERS**  
Center for Biomedical Genetics,  
Erasmus University  
Rotterdam, The Netherlands  
*DNA damage problem in the  
context of cancer, aging and  
longevity*

**Maria JASIN**  
Memorial Sloan-Kettering  
Cancer Center, New York, USA  
*Repair of chromosome breaks  
and human disease*

**Josef JIRICNY**  
Institute of Molecular Cancer  
Research, University of Zurich,  
Switzerland  
*Interference of base- and  
mismatch repair in somatic  
hypermutation*

**Joachim LINGNER**  
EPFL, Lausanne, Switzerland  
*Telomeres and telomerase:  
RNA-dependent machines at  
chromosome ends*

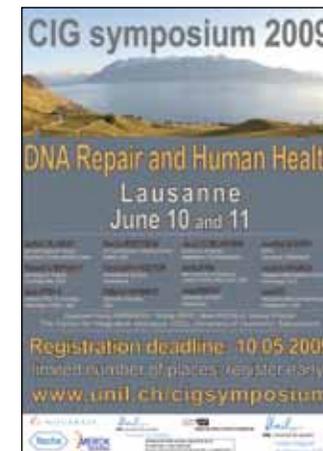
**Lee ZOU**  
Massachusetts General Hospital,  
Charlestown, USA  
*Sensing and signaling of DNA  
damage by the checkpoint  
kinases ATR and ATM*

### SELECTED TALKS

**Vincent DION**  
Friedrich Miescher Institute,  
Basel, Switzerland  
*The mobility of spontaneous  
and DNA damage induced  
Rad52 foci*

**Hélène GAILLARD**  
University of Seville, Spain  
*Genome-wide analysis of  
factors affecting transcription  
elongation and DNA repair: a  
new role for PAF and Ccr4-not in  
transcription-coupled repair*

**Barbara VAN LOON**  
University of Zurich, Switzerland  
*A novel DNA repair pathway  
to prevent C : G to A : T  
transversion mutations after  
oxidative damage*



## CIG Symposium 2010: Sensing the environment



Martin Chalfie,  
2008 Nobel Prize laureate

**ORGANIZERS**  
R. Benton  
C. Frankhauser  
N. Hernandez

**Detlev ARENDT**  
EMBL Heidelberg, Germany  
*Sun, moon and larval settlement:  
sensory systems controlling the  
marine life cycle*

**Marie-Christine BROILLET**  
UNIL, Lausanne, Switzerland  
*Danger detection in mice*

**Martin CHALFIE**  
Columbia University, New York,  
USA  
*Mechanosensory transduction  
in *C. elegans**

**George COUPLAND**  
Max Planck Institute for Plant  
Breeding Research, Cologne,  
Germany  
*Flowering of *Arabidopsis* in  
response to seasonal changes  
in day length*

**Caroline DEAN**  
John Innes Centre, Norwich, UK  
*Sensing the prolonged  
cold of winter*

**Consuelo DE MORAES**  
Penn State University, USA  
*Chemical ecology of host-  
parasite interactions*

**Claude DESPLAN**  
New York University, USA  
*Color vision in *Drosophila**

**Russell FOSTER**  
University of Oxford, UK  
*The light regulation of rhythmic  
biology*

**PRESENTATION OF THE 2010  
GUÉNIN PRIZE:**

**Christine PETIT**  
Collège de France, Institut  
Pasteur, Paris, France  
*From deafness genes to sound  
processing by the hair bundle*

**Steven REPERT**  
University of Massachusetts,  
Worcester, USA  
*Navigational mechanisms of  
migrating Monarch butterflies*

**Ivan RODRIGUEZ**  
University of Geneva,  
Switzerland  
*Mammalian olfactory  
chemosensors:  
from genes to behavior*

**Leslie VOSSHALL**  
Rockefeller University  
New York, USA  
*Blood lust: the control of  
mosquito host-seeking behavior*

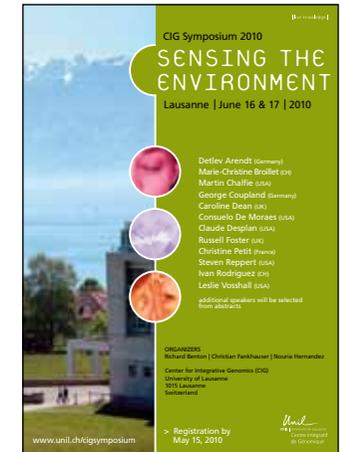
**SELECTED TALKS**

**Friederike BRÜSSOW**  
UNIL, Lausanne, Switzerland  
*Insect eggs suppress plant  
defense against chewing  
herbivores*

**Vincent CROSET**  
UNIL, Lausanne, Switzerland  
*Chemosensory *iGluRs*: an  
ancient protostome-specific  
mechanism for tasting and  
smelling*

**Matthias HEINEMANN**  
ETH, Zurich, Switzerland  
*Bacterial adaptation through  
distributed sensing of metabolic  
fluxes*

**Nicolas LEUENBERGER**  
UNIL, Lausanne, Switzerland  
*Sex and clock to discover new  
PPARalpha functions*



## 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, makes it an ideal place to hear and learn about different fields of research.

Interactions with external scientists are 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.

## THE GRACE LECTURE

On October 11, the CIG, in partnership with the EPFL, organized a lecture presented by Nobel prize winner James D. Watson: "Why Francis Crick and I found the Double Helix". This event was the first of a public lecture series, the John Grace Lecture series, given by world leading scientists thanks to the support of the UNIL Grace fund.

The UNIL Grace Fund was established in July 2010 following a donation from the Grace family. It is dedicated to supporting, educating, and inspiring current and future genetic researchers and to making science more accessible and relevant to the community. It achieves this mission by supporting activities at the Center for Integrative Genomics (CIG) and at L'Éprouvette, the public laboratory of the University of Lausanne (UNIL).

## CIG seminars

### Asifa AKHTAR

EMBL Heidelberg, Germany  
*Dosage compensation in Drosophila: A paradigm to study chromatin and epigenetic regulation*

### Enrique AMAYA

University of Manchester, UK  
*The inflammatory response during embryonic wound healing*

### Stylianos ANTONARAKIS

University of Geneva, Switzerland  
*Functional analysis of the genome*

### Johan AUWERX

EPFL, Lausanne, Switzerland  
*Integrating metabolism through NAD sensors*

### Yves BARRAL

ETH, Zurich, Switzerland  
*About cellular aging and rejuvenation, and their links to asymmetric cell division*

### Doris BACHTROG

University of California, Berkeley, USA  
*Evolutionary genomics of sex chromosomes in Drosophila*

### Richard BENTON

UNIL, Lausanne, Switzerland  
*Olfactory genes, circuits and behaviours*

### Ewan BIRNEY

European Bioinformatics Institute, Hinxton, UK  
*Individual-specific and allele-specific chromatin signatures in diverse human populations*

### Job DEKKER

University of Massachusetts, Worcester, USA  
*Long range gene regulatory architecture of the human genome*

### Reinhard FAESSLER

Max-Planck Institute of Biochemistry, Martinsried, Germany  
*Genetic analysis of integrin signalling in mice*

### Andrew G. FRASER

Donnelly CCB, Toronto, Canada  
*Natural variation in loss-of-function phenotypes in C. elegans*

### Eileen FURLONG

EMBL Heidelberg, Germany  
*A global view of cis regulatory networks during development*

### Anne-Claude GAVIN

EMBL Heidelberg, Germany  
*The social network of a cell: dynamic protein interactions*

### Walter GEHRING

University of Basel, Switzerland  
*New perspectives in eye evolution*

### James GOODRICH

University of Colorado, Boulder, USA  
*Activation and repression of mammalian mRNA transcription*

### Anne GRAPIN-BOTTON

EPFL, Lausanne, Switzerland  
*From pancreas development to regenerative therapies*

### Ralph GREENSPAN

The Neuroscience Institute, San Diego, USA  
*Functional strategies shared by invertebrate and vertebrate nervous systems*

### Doug HANAHAN

EPFL, Lausanne, Switzerland  
*Mechanisms of multi-step tumor development and progression*

### Steven KLIEWER

University of Texas Southwestern Medical Center, Dallas, USA  
*Nuclear receptor-FGF-pathways: from feast to famine*

### Pierre LÉOPOLD

Université de Nice, France  
*An interplay between TOR and Insulin/IGF signaling controls growth in Drosophila*

### Joachim LINGER

EPFL, Lausanne, Switzerland  
*Telomerase and telomeric repeat containing RNA at chromosome ends*

### Mark MCCARTHY

Oxford Centre for Diabetes, Endocrinology and Metabolism, UK  
*Thinking big: lessons from large scale genetic studies in diabetes and obesity*

### Steve MCKNIGHT

UT Southwestern Medical Center, Dallas, USA  
*Discovery of a pro-neurogenic, neuroprotective chemical*

### Jean-Claude MARTINO

University of Geneva, Switzerland  
*Mechanisms of mitochondrial membrane permeabilization during apoptosis*

### Liliane MICHALIK

UNIL, Lausanne, Switzerland  
*The nuclear hormone receptor PPARbeta as a regulator of skin healing and carcinogenesis*

### Tarjei MIKKELSEN

Broad Institute, MIT and Harvard University, Cambridge, USA  
*Sequencing mammalian epigenomes*

### Joachim LINGER

EPFL, Lausanne, Switzerland  
*Telomerase and telomeric repeat containing RNA at chromosome ends*

### Paul MARTIN

University Walk, Bristol, UK  
*Studies of repair and inflammation in flies and fish and mice*

### Janet PARTRIDGE

St. Jude Children's Research Hospital, Memphis, USA  
*Mechanism of assembly of heterochromatin at fission yeast centromeres*

### Ivan RODRIGUEZ

University of Geneva, Switzerland  
*Chemoreceptors: from genes to behavior*

**Michael ROSBASH**

Brandeis University, Howard Hughes Medical Institute, Waltham, USA  
*Circadian regulatory mechanisms in flies and mice*

**Géraldine SEYDOUX**

Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, USA  
*Cell cycle regulation of a DYRK kinase during the oocyte-to-embryo transition*

**Frank SLACK**

Yale University, New Haven, USA  
*MicroRNAs and Cancer*

**Joseph S. TAKAHASHI**

UT Southwestern Medical Center, Dallas, USA  
*Genetic analysis of circadian clocks in mammals*

**Iva TOLIC-NORRELYKKE**

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany  
*Microtubules and motors : Creating order in a living cell*

**Toshio TSUKIYAMA**

Fred Hutchinson Cancer Research Center, Washington, USA  
*In vivo functions of chromatin regulation revealed by new approaches*

**Isabelle VERNOS**

Centre de Regulació Genòmica, Barcelona, Spain  
*Mechanism of mitotic spindle assembly and dynamics*

**Mark A. WAINBERG**

McGill Faculty of Medicine, Montreal, Canada  
*Molecular basis and clinical significance of HIV subtype differences in the selection of drug resistance*

**Ian WILLIS**

Yeshiva University, Einstein Medical School, New York, USA  
*Synthetic genetic interactions in lipid droplet biogenesis*

**BIG SEMINARS ORGANIZED BY CIG MEMBERS****Leif ANDERSSON**

University of Uppsala, Sweden  
*Domestic animals – a treasure trove for studies of genotype-phenotype relationships*

**Andrew FIRE**

Stanford University School of Medicine, USA  
*Contributions of small RNAs and other flexible effectors to regulatory simplicity and complexity*

**Martin HEISENBERG**

Würzburg University, Germany  
*A fly brain full of memories*

**Svante PÄÄBO**

Max-Planck Institute for Evolutionary Anthropology, Leipzig, Germany  
*A neanderthal perspective on human origins*

**Ad hoc seminars****Daniel ABERDAM**

INSERM U898, Nice, France and INSERTCH, Haifa, Israel  
*Pluripotent stem cells as cellular models for skin and cardiac physiopathologies*

**Pappas APOSTOLOS**

The Johnson & Johnson Skin Research Center, Skillman, USA  
*The essential role of lipid metabolism in skin*

**Nils ARRIGO**

University of Neuchâtel Switzerland  
*Hybridization in the Triticum-Aegilops complex*

**Anne-Sophie AY-BERTHOMIEU**

Genoway, Lyon, France  
*Role of TIF1gamma in TGFbeta signaling*

**Vera BELYAEVA**

Lomonosov Moscow State University, Russia  
*Influence of structural features of RNA-polymerases on transcription through the nucleosome*

**Sylvain BLACHON**

IRISA, INRIA, Rennes, France  
*Exploiting qualitative properties for knowledge discovery in cancer post-genomic data*

**Nicolas BONHOURE**

University of Glasgow, UK  
*RNA polymerase II movement and splicing*

**Amélie BONNEFOND**

CNRS UMR8199, Lille, France  
*Enrichment of rare loss-of-function mutations in exons of the type 2 diabetes associated /MTNR1B/ gene in diabetic individuals*

**John BOWMAN**

Monash University, Melbourne, Australia and College of Biological Sciences, Davis, USA,  
*Patterning genes in land plants*

**Etienne BUCHER**

University of Geneva, Switzerland  
*Epigenetic control of transcription in plants*

**Massimo CAINE**

University of Padua, Italy  
*An assessment of the cytotoxicity of human protein tau in a yeast model for Alzheimer's Disease*

**Julie CARRIER**

University of Montreal, Canada  
*N-REM sleep oscillations in aging*

**Jorge J. CASAL**

University of Buenos Aires, Argentina  
*Light signalling in a fluctuating environment*

**John CHRISTIE**

University of Glasgow, Scotland  
*Structure, function and application of phototropin receptor kinases*

**François-Xavier CLARET**

University of Texas, Houston, USA  
*JAB1: a new player in cell cycle control and therapeutic target for HER2 + breast cancer*

**Diego CORTEZ**

Institut Pasteur, Paris, France  
*Viral genes in prokaryotic genomes and the Xer/dif system in Archaea*

**Meike DAHLHAUS**

University of Rostock, Germany  
*The role of miRNAs in acute leukemias*

**Ilenia D'ERRICO**

Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy,  
*PGC1alpha suppresses intestinal tumorigenesis via mitochondrial ROS-mediated apoptosis*

**Valeria DI GIACOMO**

University of Bologna, Italy  
*MST4 and YSK1: new mediators of LKB1 - mediated polarization in intestinal epithelial cells*

**Nicolas DI-POI**

University of Geneva, Switzerland  
*Atypical relaxation of structural and functional constraints in squamata hox genes*

**David DOMBROWICZ**

Institut Pasteur, Lille, France  
*Regulation of atopic dermatitis by PPAR and Fc receptors*

**Kalina DUSZKA**

University of Technology, Graz, Austria  
*Nur77-dependent deregulation of PPARgamma in fasted white adipose tissue*

**Gregory EMERY**

University of Montreal, Canada  
*An endocytic cycle spatially restricts seceptor tyrosine kinase activity to control border cell migration*

## Ad hoc seminars (continued)

### Dave FEATHERSTONE

University of Illinois,  
Chicago, USA  
*The role of glial glutamate  
in regulation of synaptic  
transmission: From flies to mice*

### Ivo FIERRO-MONT

University of Dublin, Ireland  
*Understanding protein  
function: a combined cell and  
molecular biology, biochemical,  
and quantitative proteomics  
approach*

### Yann FILAUDEAU

Agilent Technologies Europe,  
Nice, France  
*The agilent sureSelect DNA  
target enrichment system: target  
enrichment technology for next-  
generation sequencing*

### Ana Victoria GARCIA

INRA/CNRS - URGV, Evry, France  
*Intracellular dynamics during  
Arabidopsis immune responses*

### Kevin GARDNER

UT Southwestern Medical  
Center, Dallas, USA  
*Environmentally-regulated  
protein/protein interactions:  
A versatile way to build a  
biological switch*

### Federica GILARDI

University of Milano, Italy  
*From 3D-structure to biological  
activity: design of a new dual  
PPARalpha/gamma ligand with  
antidiabetic properties and  
reducing fat deposition*

### Carolina GOMEZ DIAZ

University of Oviedo, Spain  
*Are cAMP and IP3 cascades  
involved in olfactory  
transduction in Drosophila  
melanogaster?*

### Erwan GOURANTON

University of Aix-Marseille I & II,  
Marseille, France  
*Lycopene, a bioactive molecule  
on the adipose tissue biology*

### Marina GRANOVSKAYA

EMBL, Heidelberg, Germany  
*Genome-wide characterization  
of the complex transcriptome  
architecture of S. cerevisiae with  
tiling arrays*

### Andreas GSCHWIND

University of Bern, Switzerland  
*Mating of common voles versus  
the monogamy gene avpr1a*

### Katerina GUSCHANSKI

Imperial College London,  
Ascot, UK  
*Molecular ecology, population  
history and phylogenetics of  
African primates*

### Christoph HANDSCHIN

Biozentrum, University of Basel,  
Switzerland  
*Coordination of metabolic  
flexibility in skeletal muscle  
through PGC-1alpha*

### Eija HEIKKILÄ

University of Helsinki, Finland  
*Molecular basis of the kidney  
filtration barrier: role of the  
nephrin protein complex*

### Uniza W. KHAN

HA/Norwegian University of Life  
Sciences, Aas, Norway  
*Melanocortin Receptors:  
Polymorphisms, Phenotypic  
Variations and Physiological  
Implications*

### Vicky KATSANOU

GSK, Medical Department –  
Clinical operations, Greece  
*The RNA binding protein HuR in  
immune physiology & disease*

### Dominika KAUSS

ETH, Zurich, Switzerland  
*FLU, a regulator of chlorophyll  
biosynthesis, is physically linked  
to the site of protochlorophyllide  
production and consumption*

### Shigeaki KATO

The University of Tokyo, Japan  
*Epigenetic regulators supporting  
nuclear receptor function*

### Norliana KHAIRUDDIN

The University of Queensland,  
Woolloongabba, Australia  
*Bifunctional siRNAs versus  
monofunctional siRNAs for the  
treatment of cancer*

### Arnaud KREBS

IGBMC, Strasbourg, France  
*Specific roles of Gcn5 containing  
complexes in mES cells*

### Gerrit KUHN

Field Application Specialist  
Applied Biosystems  
*miRNA profiling using advanced  
qRT-PCR based methods*

### Gerrit KUHN

Senior Specialist Support SOLiD,  
Europe, Life Technologies  
Corporation &  
**Richard DIXON**  
Senior Specialist Support  
Bioinformatics – Europe, Life  
Technologies Corporation  
*A Practical Look at the SOLiD  
UHT sequencing workflow: from  
benchwork to bioinformatics*

### Erika M. KVIKSTAD

The Pennsylvania State  
University, USA  
*Mechanisms of indel  
mutagenesis: what's in a name?*

### Hans-Peter LANDOLT

University of Zurich, Switzerland  
*Sleep, genes, and performance*

### Thorsten LEMKER

Applied Biosystems, Darmstadt,  
Germany  
*Taqman OpenArray Genotyping  
System: robust and convenient  
nanoliter genotyping using  
Taqman SNP Assays*

### Fransiska MALFAIT

Hôpital universitaire  
de Gand, Belgique  
*Le syndrome d'Ehlers-Danlos:  
aspects cliniques*

### Orlando MANI

University of Bern, Switzerland  
*The role of ATP-binding cassette  
(ABC) lipid transporters in  
mammary gland physiology -  
findings and perspectives*

### Mario MARDIROSIAN

University of Trieste, Italy  
*Identification of E. coli  
genes involved in decreased  
susceptibility to the antimicrobial  
peptide LL-37*

### Aoife MCLYSAGHT

University of Dublin, Ireland  
*Interacting gene clusters  
in the human genome*

### Julien MEUNIER & Claude BERNARD

University of Lyon, France  
*Primate genome evolution  
and genomic mechanisms:  
recombination, methylation and  
substitution rates*

### Edit MIKO

University of Debrecen, Hungary  
*Differentially expressed  
microRNAs and the role of miR-  
126 in small cell lung cancer*

### Stavros MILATOS

Biomedical Sciences Research  
Center "Alexander Fleming",  
Athens, Greece  
*The RNA binding protein HuR at  
the crossroads of development  
and cancer*

### Akira NAGATANI

Kyoto University, Japan  
*Structural basis of phytochrome  
A-specific properties*

### Laszlo NAGY

University of Debrecen, Hungary  
*Nuclear receptors linking lipid  
metabolism and inflammation*

**Aurélien NALDI**

INSERM U928, Marseille, France  
*Logical modelling of helper T cell differentiation*

**Sylvie NESSLER**

University of Paris XI, France  
*Structural analysis of a new family of bacterial tyrosine kinases involved in capsule formation*

**Julia NEUWIRT-ALEGUE**

Applied Biosystems, Switzerland  
*Ambion technical seminar: From sample to Chip: sample preparation and amplification for various array platforms*

**Dipak PANIGRAPHY**

Children's Hospital, Boston, USA  
*Epoxyeicosatrienoic acids control angiogenesis-dependent regeneration, cancer and metastasis*

**William PEARSON**

University of Virginia, Charlottesville, USA  
*Sequence similarity searching – What we do well, what to do better*

**Bozena POLOK**

Institut de Recherche en Ophthalmologie, Sion, Switzerland  
*Human hereditary ophthalmic diseases – Fish swim into view*

**Marc PRENTKI**

University of Montreal, Canada  
*Pancreatic Beta-cell metabolic signaling in health and diabetes*

**Danilo PRESOTTO**

UNIL, Lausanne, Switzerland  
*Study of the interaction between the HOXC10 homeobox protein and the CAK sub-complex of the transcription factor II H*

**Tobias PREUTEN**

Humbolt University, Berlin, Germany  
*Good things come in small packages – The Arabidopsis mitochondrial genome: Few copies and high variability*

**Gianpaolo RANDO**

University of Milano, Italy  
*Taxonomy of SERM activity in vivo*

**Yann RAVUSSIN**

Columbia University, New York, USA  
*Effects of chronic weight perturbation on energy homeostasis, brain structure, and microbial gut composition in mice*

**Paolo RIBECA**

Center for Genomic Regulation, Barcelona, Spain  
*My all-time favourite scientific algorithms (with particular emphasis on short-read mapping)*

**Janet RICHMOND**

University of Illinois, Chicago, USA  
*The role of tomosyn in regulation of synaptic transmission: From worms to flies*

**Jonathan ROY**

NanoString Technologies, Seattle, USA  
*NanoString nCounter Technology: a simple solution for enzyme free*

**Klaus SCHUGHART**

Helmholz Center for Infectious Disease, Braunschweig, Germany  
*Host genetic susceptibility to influenza A infections*

**Flavie SICARD**

University of Rouen, Mont-Saint-Aignan, France  
*Multifactorial control of adrenal gland activity: Regulation of steroidogenesis, tumorigenesis and tissue formation*

**E-ri Maria SOL**

Uppsala University, Sweden  
*Mechanisms of impaired glucose-stimulated insulin secretion induced by levated levels of palmitate and/or glucose in INS-1E*

**Zhixi SU**

Fudan University, Shanghai, China  
*The functional divergence and compensation of duplicated genes*

**Lakxmi SUBRMANIAN**

University of Edinburgh, UK  
*Maintenance of telomeres and centromeres in fission yeast*

**Daphne SUNG**

Baylor College of Medicine, Houston, USA  
*Regulation of Cyclin T1 expression by microRNAs in HIV-1 target cells*

**Ajam TAHEREH**

Shahid Chamran University, Ahvaz, Iran  
*Association between P1635 polymorphism in the intron 4 of DTNBP1 gene and Schizophrenia in Iranian population*

**Nicola VANNINI**

EPFL, Lausanne, Switzerland  
*Molecular mechanism of novel anti angiogenic compounds*

**Liviu VANOAIKA**

EPFL, Lausanne, Switzerland,  
*Analysis of mice with rerritin H deletion*

**Guy VERGERES**

Agroscope Liebefeld-Posieux, Bern, Switzerland  
*Functional nutritional biology of dairy products – from classical nutrition research to nutrigenomics*

**Antoine VIOLA**

University of Basel, Switzerland  
*Contribution of PER3 polymorphism to sleep EEG, endocrine and molecular circadian rhythms, autonomic control and cognitive performance*

**Masamitsu WADA**

Kyushu University, Fukuoka, Japan  
*How to solve the mechanisms of chloroplast movement?*

**Lirong YANG**

EPFL, Lausanne, Switzerland  
*Rat bladder muscle regeneration induced by local delivery of an engineered insulin-like growth factor 1 in fibrin gels*

**Damien YTHIER & Joseph FOURIER**

University, Grenoble, France  
*La protéine ING2: nouvelles tumeurs et régulation par sumoylation*

**Giovanna ZACCHETTI**

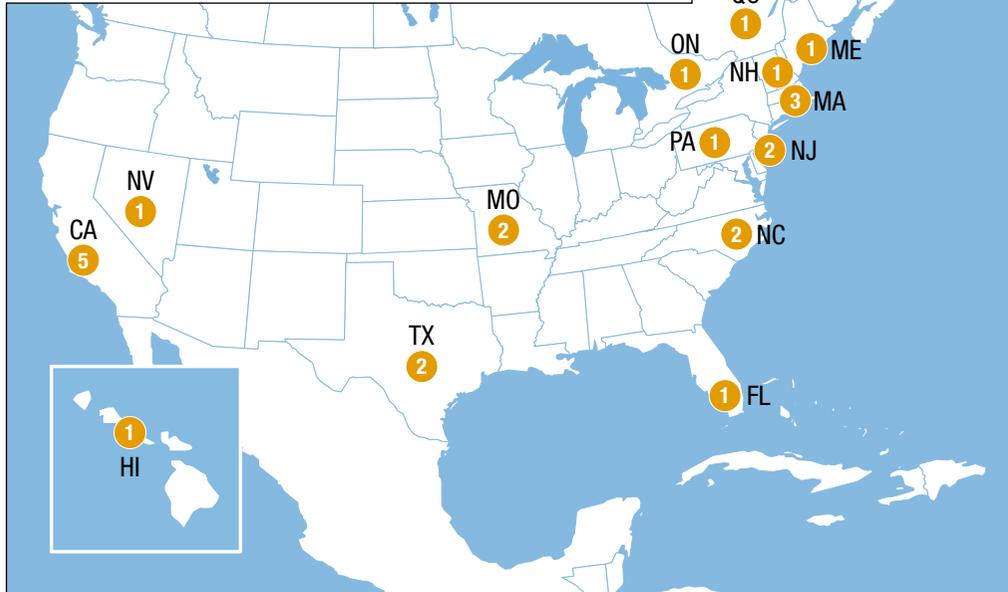
HUG, Geneva, Switzerland  
*Related genetic mechanisms of hox function in mammalian limb and gut development*

**Thomas ZWAKA**

Center for Cell and Gene Therapy, Houston, USA  
*Ronin and caspases in embryonic stem cells: a new perspective on regulation of the pluripotent state*

### SEMINARS GIVEN BY CIG MEMBERS

CIG members are often invited to give talks at research institutions around the world or to present their work at international conferences. Within the years 2009 and 2010, there have been more than 130 such presentations, in 27 different countries. The locations where CIG members presented their work are shown on the map.



## CONFERENCES CO-ORGANIZED BY CIG MEMBERS

Besides the CIG symposia, CIG members also organize or co-organize conferences and symposia with colleagues from other research institutions, in Lausanne or at other locations around the planet.

## Conferences at the Génopode

### Lausanne Life Sciences festival 2009

#### GENETICS, EPIGENETICS AND DEVELOPMENT

##### ORGANIZERS

CAOS, the association  
of the CIG assistants

##### Bart DEPLANCKE

EPFL, Lausanne, Switzerland

##### Denis DUBOULE

UNIGE/EPFL, Geneva/Lausanne,  
Switzerland

##### Denis DUPUY

Institut Européen de Chimie et  
Biologie, Bordeaux, France

##### Patrick LEMAIRE

IBDML, Marseille, France

##### Colin LOGIE

Radboud University, Nijmegen,  
The Netherlands

##### Lazlo TORA

IGBMC, Strasbourg, France

### Lausanne Genomics Days

#### GENOMICS IN BIOLOGY AND MEDICINE (2009)

##### ORGANIZERS

J. Beckmann, O.Hagenbüchle,  
K. Harshman, F. Naef

##### Patrick CRAMER

University of Munich, Germany

##### Wouter DE LAAT

Erasmus Medical Center,  
Rotterdam, The Netherlands

##### Tom HUDSON

Ontario Institute for Cancer  
Research, Toronto, Canada

##### Andreas LADURNER

EMBL, Heidelberg, Germany

##### Sarah TEICHMANN

MRC, Cambridge, UK

##### Herman WIJNEN

University of Virginia, Charlot-  
tesville, USA

#### GENOMICS IN ECOLOGY AND EVOLUTION (2010)

##### ORGANIZERS

C. Fankhauser, L. Keller,  
P. Reymond

##### Laurence HURST

University of Bath, UK

##### Steve KAY

University of California, San  
Diego, USA

##### Joel LEVINE

University of Toronto,  
Mississauga, Canada

##### John PARSCH

University of Munich, Germany

##### Johanna SCHMITT

Brown University,  
Providence, USA

##### David STERN

Princeton University, USA

### SKMB Gene Regulation Workshop

#### 2009

##### ORGANIZERS

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

##### Bruno AMATI

University of Milano, Italy

##### Henry KRAUSE

University of Toronto, Canada

##### Jane MELLOR

Oxford University, UK

##### B. Franklin PUGH

Pennsylvania State University,  
University Park, USA

##### Oliver RANDO

University of Massachusetts  
Medical School, Worcester, USA

##### Robert TJIAN

University of California,  
Berkeley, USA

##### Bas VAN STEENSEL

Netherlands Cancer Institute,  
Amsterdam, The Netherlands

#### 2010

##### ORGANIZERS

N. Hernandez, F. Karch,  
F. Stutz

##### Wendy BICKMORE

MRC, Edinburgh, UK

##### James GOODRICH

University of Colorado,  
Boulder, USA

##### Edith HEARD

Institut Curie, Paris, France

##### Tom MANIATIS

Columbia University Medical  
Center, New York, USA

##### Danesh MOAZED

Harvard Medical School,  
Boston, USA

##### Steve SMALE

University of California,  
Los Angeles, USA

##### Didier TRONO

EPFL, Lausanne, Switzerland

## Minisymposium Ultra High Throughput Sequencing

2009

**ORGANIZERS**  
P. Bucher, L. Falquet,  
K. Harshman, C. Iseli

**Loïc BAERLOCHER**  
FASTERIS SA, Geneva,  
Switzerland

**Laurent FARINELLI**  
FASTERIS SA, Geneva,  
Switzerland

**David HERNANDEZ**  
HUG, Geneva, Switzerland

**Claudio LOTTAZ**  
Max Planck Institute,  
Berlin, Germany

**Milos PJANIC**  
EPFL-UNIL, Lausanne,  
Switzerland

**Michael STADLER**  
FMI, Basel, Switzerland

**Werner VAN BELLE**  
ETH, Zurich, BSSE, Basel,  
Switzerland

**Daniel ZERBINO**  
EMBL-EBI, Hinxton, UK

2010

**ORGANIZERS**  
P. Bucher, L. Falquet,  
K. Harshman, V. Ioannidis,  
C. Iseli, J. Rougemont

**Henrik KAESSMANN**  
UNIL/SIB, Lausanne, Switzerland

**Daan NOORDERMEER**  
EPFL, Lausanne, Switzerland

**Edward J. OAKELEY**  
Novartis Institutes for  
BioMedical Research (NIBR),  
Basel, Switzerland

**Guillaume REY**  
EPFL, Lausanne, Switzerland

**Luca SANTUARI**  
UNIL, Lausanne, Switzerland

**Mihaela ZAVOLAN**  
University of Basel/SIB,  
Basel, Switzerland

## Swiss Drosophila Meeting 2009

**ORGANIZERS**  
R. Benton, W. Herr,  
T. Kawecki, B. LeMaitre

Invited speakers

**Bambos KYRIACOU**  
University of Leicester, UK

**Michael LEVINE**  
University of California,  
Berkeley, USA

## HEPADIP - Final Meeting (2010)

**ORGANIZERS**  
D. Langin, Y. Le Marchand-  
Brustel, B. Thorens

**Peter ARNER**  
Karolinska University Hospital  
Huddinge, Stockholm, Sweden

**Karine CLÉMENT**  
Institut National de la Santé  
et de la Recherche Médicale,  
Paris, France

**Keith N. FRAYN**  
Oxford Centre for Diabetes,  
Endocrinology  
and Metabolism, UK

**Hans J. HAUNER**  
Technische Universität  
München, Germany

**Folker KUIPERS**  
Groningen University,  
Netherlands

**Dominique LANGIN**  
Institut National de la Santé  
et de la Recherche Médicale,  
Toulouse, France

**Yannick  
LE MARCHAND-BRUSTEL**  
Institut National de la Santé  
et de la Recherche Médicale,  
Nice, France

**José Maria MATO**  
Centro de Investigacion  
Cooperativa en Biociencias,  
Derio, Spain

**Pirjo NUUTILA**  
University of Turku, Finland

**Mateij ORESIC**  
Technical Research Centre of  
Finland, Helsinki/Espoo, Finland

**Kim OVERVAD**  
Aalborg Hospital,  
Copenhagen, Denmark

**Oluf PEDERSEN**  
Hagedorn Research Institute,  
Copenhagen, Denmark

**Ulf SMITH**  
Göteborgs Universitet, Sweden

**Thorkild SORENSEN**  
Institute of Preventive Medicine,  
Copenhagen, Denmark

**Bart STAELS**  
Institut Pasteur de Lille, France

**Vladimir STICH**  
Charles University, Prague,  
Czech Republic

**Marja-Riitta TASKINEN**  
Helsinki University Central  
Hospital, Helsinki, Finland

**Bernard THORENS**  
UNIL, Lausanne, Switzerland

**Luc VAN GAAL**  
Universiteit Antwerpen, Belgium

**Nathalie VERCRUYSE**  
Communauté Européenne,  
Brussels, Europe

**Antonio VIDAL-PUIG**  
University of Cambridge, UK

**Hannele YKI-JÄRVINEN**  
Helsinki University Central  
Hospital, Finland

## Other conferences

**The Central Dogma  
and Beyond (2009)**  
Villars, Switzerland

**ORGANIZERS**  
O. Hagenbüchle,  
N. Hernandez, W. Herr,  
J. Paszkowski

**FASEB Summer Research  
Conference: Glucose  
Transporter Biology and  
Diabetes (2009)**  
Lucca, Italy

**ORGANIZERS**  
D.E. James, B. Thorens

**2nd AnEuploidy Workshop  
(2010)** Split, Croatia

**ORGANIZERS**  
D. Nizetic, A. Reymond

**Aging and Longevity (2010)**  
Changins, Switzerland

**ORGANIZERS**  
I. Decosterd, O. Gaide,  
J. McKinney, S. Martin,  
P. Tozzi, C. Widmann

**EMBO conference, Nuclears  
Receptors: from Molecular  
Mechanisms to Molecular  
Médecine (2010)** Cavtat/  
Dubrovnik, Croatia

**ORGANIZERS**  
B. Desvergne, L. Nagy

**Statistical Physics and  
Topology of Polymers with  
Ramifications to Structure and  
Function of DNA and Proteins  
(2010)** Kyoto, Japan

**ORGANIZERS**  
T. Deguchi, A. Stasiak,  
H. Hayakawa, K. Shimokawa

**Gordon Research Conference:  
Photosensory Receptors and  
Signal Transduction (2010)**  
Lucca, Italy

**CHAIR:** K.Gardner  
**CO-CHAIR:** C.Fankhauser

**ESF-EMBO Conference,  
Functional Neurobiology  
In Minibrains: From Flies To  
Robots, And Back Again  
(2010)** Sant Feliu, Spain

**ORGANIZERS**  
R. Benton, B. Gerber, M. Louis

## ARTIST IN RESIDENCE AT THE CIG

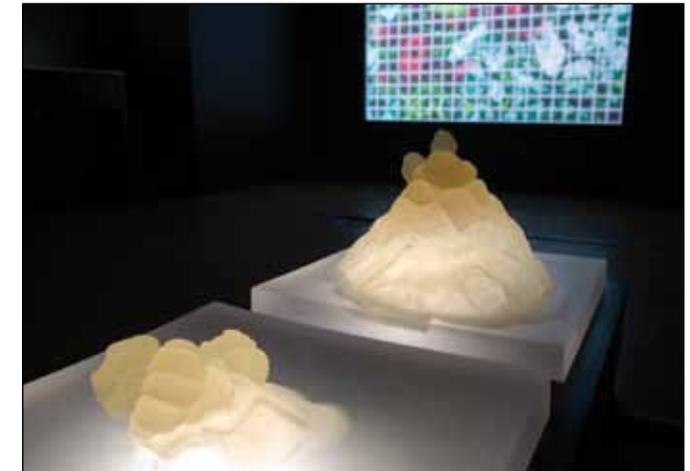
As part of its activities with the public at large, the CIG participated in the program "Artists-in-Labs" (AIL), a collaboration between the Zurich University of the Arts, Institute for Cultural Studies in the Arts ICS and the Federal Office for Culture (Bundesamt für Kultur, BAK). AIL finances a nine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

In 2008, 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 scientist and the artist. The result of this interaction was an installation visible in the Génopode in 2009: "Light reaction – Dimensions of apparent Invisibility".

*For more information: [www.sylviahostettler.ch/](http://www.sylviahostettler.ch/)*

In 2010, Sandra Huber, a Swiss-Canadian writer, joined the laboratory of Dr. Paul Franken to become more familiar with sleep research, a topic she had already worked on previously. Sandra was also welcome in the "Centre d'Investigation et de Recherche sur le Sommeil" at the CHUV, co-directed by Mehdi Tafti. She elaborated a project for an installation "sleep/writing/rooms", that the CIG hopes to present at the Génopode in 2011.

*For more information: <http://verysmallkitchen.com/2011/02/21/vsk-project-sandra-huber-sleep-writing-rooms-1/>*



*"Light reaction – Dimensions of apparent Invisibility",  
an installation at the Génopode by Sylvia Hostettler*

## 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 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 200 members originating from 34 different countries. There are 17 group leaders and faculty members, about 40 PhD students, 45 postdoctoral fellows, 65\* specialists and laboratory technicians (including trainees), and 30\* persons employed in the administrative and the logistic services (including trainees).

\*many members of the support staff work part-time

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