THE CENTER FOR INTEGRATIVE GENOMICS

REPORT 13-14

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Centre Intégratif
de Génomique

Table of Contents

THE CENTER FOR INTEGRATIVE GENOMICS (CIG) AT A GLANCE

The Center for Integrative Genomics (CIG) is a department of the Faculty of Biology and Medicine of the University of Lausanne. The institute is located in the Génopode building, situated at the Dorigny campus. The CIG has three main missions:

- The pursuit of an international competitive, first rate research program in the genomics field
- The development of core facilities, offering support through cutting-edge technologies to the Lemanic research community and beyond
- The development of an outstanding teaching program

The CIG encompasses 15 research groups, working on different aspects of genome structure, evolution and function in a wide variety of model systems and experimental settings. Research topics include the regulation of gene expression, organization of chromatin structure and mechanistic aspects of signal transduction cascades, as well as complex functions – such as embryonic development, physiological functions and behavior – from an organismal and/or genomics perspective.

Scientists at the CIG have always been and continue to be involved in numerous collaborative research projects and programs, both within Switzerland – quite often within the walls of the institute, with numerous interactions among groups, both in formal and informal settings – as well as beyond its borders, stretching out hands to the scientific community worldwide. Furthermore, research greatly benefits from technical support and theoretical advice from its core facilities, providing cutting edge knowledge and technologies in the fields of genomics and proteomics.

To train tomorrow's scientists, CIG members are involved in teaching programs of the University of Lausanne and contribute to the development of new educational programs. Moreover, the institute offers a yearly program of seminars and lectures, as well as scientific meetings where not a few scientists with a solid international reputation come to visit the Génopode building to present the latest insights within their field.

At present, the Centre for Integrative Genomics employs more than 200 people, from no less than 30 different countries, who contribute to the development of its research, technical and logistic support, its core facilities and its educational activities. They all have made the CIG to what it is: a place where excellent science is performed, by dedicated people with an open mind.

Scientific Advisory Committee members

Robert EISENMAN
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Fred Hutchinson Cancer Research Center
University of Washington School of Medicine
Seattle, USA

Steve BROWN
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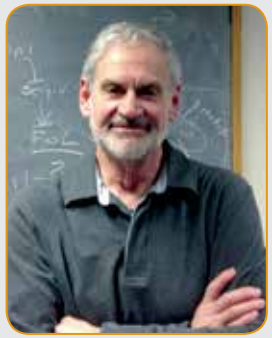
Western General Hospital
Edinburgh, UK

* member until 2013
** member since 2014

Message from the SAC

As a member of the Scientific Advisory Committee (SAC) at the CIG for the last eight years I have had a unique opportunity to observe the growth of the CIG and to gain some insight into the workings of the institute. In the view of the committee, the CIG is clearly fulfilling its promise to develop into a premier institute for biological research and training. This has been achieved through extraordinary support from, and interaction with, the UNIL, coupled with the CIG's success in recruiting and promoting a first-rate scientific faculty working at the leading edge of their fields. The faculty in turn has been able to attract an international group of motivated and talented pre-doctoral and post-doctoral trainees to their laboratories as well as an excellent technical staff. CIG faculty also play key administrative and teaching roles within the UNIL community, and the CIG continues to collaborate in numerous multi-institute initiatives. Moreover, the CIG has benefitted from its dedicated and engaged leadership with a strong commitment to scientific excellence, education, and career development of its faculty and trainees. The following pages of this Scientific Report 2013-2014 provide a snap-shot of the depth and breadth of the institute's diverse scientific agenda encompassing research on evolutionary genomics and genome organization, epigenetics and gene expression, metabolism and energy homeostasis, plant growth and development, circadian rhythm, perception, and sleep. The SAC strongly endorses this diversity of research at the CIG, noting that it reflects the multi-disciplinary nature of modern biology and fosters a unique environment for training and for synergistic interactions.

A primary goal of the June 2014 visit by the SAC was to carry out the first five-year review of the research programs of senior faculty as well as to comment on proposed faculty promotions. The proposal for formal periodic evaluations of tenured investigators was previously approved by the CIG faculty as a means of maintaining high levels of original and productive research within the institute over the long term. These evaluations entail presentations focused on current research and future directions as well as our review of confidential letters from external experts. In addition, as on other visits, the SAC met privately with other CIG faculty and leadership, the Dean of the Faculty of Biology and Medicine, groups of administrators and technical staff as well as graduate students and postdoctoral fellows (assistants). Importantly, assistants as well as administrators and technical staff indicated that they are well represented at the institute, are able to participate in decision-making and feel that in many areas their needs are being met and problems addressed. The assistants described increased interaction among CIG laboratories over the last two years as well as their plans for expanded contacts with their peers in other departments at the UNIL. From these meetings the SAC formed the impression that the CIG is moving at several levels to create an environment conducive to research and training.



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

Robert N. Eisenman
President of the Scientific Advisory Committee

While the CIG continues to build on its strengths it nonetheless faces some important issues. These include securing the increased and stable funding necessary to incorporate rapidly evolving technologies, appoint and sustain scientific staff, maintain the excellent core facilities at the CIG, and launch new research initiatives. Moreover, a significant number of senior faculty members will retire over the next decade making it necessary to carefully consider future directions for the institute and to strategically fill open positions. The SAC recommends that the CIG and UNIL take steps to reduce the very lengthy period between selection of new faculty and their actual laboratory startups, as well as the time required before faculty promotions take effect.

In the beginning of 2015 Prof. Alexandre Reymond became the new director of the CIG, taking over from Prof. Nouria Hernandez who has led the institute for nearly a decade. The growth of the CIG owes a great deal to her administrative skills, vision, and energy. We have every reason to expect that under Prof. Reymond the CIG will remain a flagship research center drawing first-rate researchers and trainees to the UNIL campus and making major contributions to the national and international scientific communities.

Robert N. Eisenman
President of the Scientific Advisory Committee

Message from Nouria Hernandez, CIG Director 2005-2014

The CIG has done great, I know it will continue to do so, long live the CIG!

Nouria Hernandez,
CIG Director 2005-2014

At the end of 2014, I ended my tenure as CIG Director after nine years and 4 months. This is a good thing. After nearly 10 years, habits become engrained, comfort comes a bit too easy, in other words: it is time to change! The change was all the easier that the CIG found a great new Director, Alexandre Reymond, who just started and is already displaying the energy and enthusiasm that characterize a great Director. So, should the past Director give any advice to the new Director? Probably not, but here is some advice anyway. The CIG has great resources: they should be used to get the best possible research done. How? First, by using them to attract the best possible people – and we will have quite a few people to attract in the coming years – as CIG members are recruited to better pastures (something we should be proud of!) or reach retirement age. Second, by focusing on making it possible for each CIG group to do their research rather than on distributing core resources in a strictly egalitarian way. Egalitarian is, at any rate, very difficult to achieve: does it mean that a group working with mice should get the same support as a group with a perhaps less expensive model system, such as flies? Should groups getting very large outside grants get more or less support from their institution than groups with more limited outside funds? None of these questions have easy answers, let us just get the work done! And third, by spending some of the money to make the CIG a place of scientific exchange between different groups, in other words by spending some of the money on a CIG retreat, on apéros, and the like!

Apart from the advice the departing Director should not give to the new Director, there is something else the departing Director should do, and this is to thank people. In my case, I have many people to thank: Walter Wahli, the founding Director, who recruited me to the University of Lausanne and gave me all the support I wanted when I became Director, without ever telling me what to do. Nicole Vouilloz, who joined me as COO of the CIG about a year after I started, and made it all possible, always with a smile and good humor, even when things got difficult. The CIG faculty, who by their input during staff meetings, their passion for science, and their common desire to see the CIG succeed made it all worthwhile. The post-doctoral fellows and the students, who trusted the CIG to give them the opportunity to do great research and pursue their scientific education and who, by their comments and suggestions on the functioning of the CIG, made it a better place. The technical and administrative staff, who all care about the CIG and will do what is needed to make things work. And a very great thanks to the Scientific Advisory Committee of the CIG, who dedicated time and energy to shepherd the CIG to its current structure, a structure that will ensure that it remains a high performance research center.

The CIG has done great, I know it will continue to do so, long live the CIG!

Nouria Hernandez
CIG Director

Message from Alexandre Reymond, CIG Director

I will do all the possible to honor the responsability that you gave me.

Alexandre Reymond, CIG Director

Starting January 1st, 2015 I took over from Nouria Hernandez the Chairmanship of the Center for Integrative Genomics. While I am still getting accustomed with the nuts and bolts of this new function it is already clear that our Institute is entering an interesting period during which about 50% of its faculty members will change. Finding and attracting the best possible persons will surely be a challenge. However thanks to my CIG colleagues, and our core facilities, who created a high performance research center, I think that we have strong arguments to succeed in this endeavor. New lines of research and new ways of asking and answering questions will certainly parallel this "rejuvenation" of CIG Faculties. These will in turn benefit the CIG and the life science Lemanic community at large.

Of course none of our successes would have been possible without enthusiastic students and postdocs with the right amount of ingenuity, a dedicated technical and administrative personnel, the constructive criticisms of the Scientific Advisory Committee and the wise leadership of Walter and Nouria. Could they all be warmly thanked here?

I will finish by saying that I will do all the possible to honor the responsability that you gave me.

Alexandre Reymond,
CIG Director

Highlights of 2013-2014

2013		2014
A.Reymond and I.Xenarios join the board of SystemsX.ch	January	R. Benton and H. Kaessmann receive ERC Consolidator Grants
		L. Michalik receives an award for teaching to 1st year medical students
Launch of "Le climat entre nos mains" at the CIG, a project in the frame of "sustainability and campus"	February	W. Wahli is awarded research chair Pierre de Fermat
Lausanne Genomic Days at the Génopode		Lausanne Genomic Days at the Génopode
	March	
	April	F. Hamaratoglu becomes SNSF Professor
		L. Michalik receives funding from the fondation Pierre Mercier pour la Science
N.Hernandez gives a presentation in the "Forum des 100"	May	H. Kaessmann is elected EMBO member
CIG symposium Genome, Disease and Evolution	June	CIG symposium Rhythms in Biology
		Grace lecture by Joseph Takahashi
Grace Lecture by John Gurdon		4th visit of the CIG Scientific Advisory Committee
		H. Kaessmann receives the FBM Jürg Tschopp Life Science Award
	July	
P. Franken becomes Associate Professor	August	H. Kaessmann becomes Full Professor
H. Kaessmann appears in a David Attenborough documentary on the BBC	September	CIG annual retreat
CIG annual retreat		
V. Dion becomes SNSF Professor	October	
	November	V. Dion receives a Gebert Ruf Stiftung Grant
		H. Kaessmann receives the Cloëtta Prize
	December	

Interview with Prof. Nouria Hernandez and Prof. Walter Wahli

The CIG: its past, present & future

"We are on the map" says Prof. Nouria Hernandez, meaning that the CIG has rightfully earned its position among the international scientific community as an institute with worldwide fame. Prof. emeritus Walter Wahli agrees. Which factors contributed to that success? How can this success be consolidated and what are the challenges the CIG might possibly face? Prof. Hernandez and Prof. Wahli have both been directors of the CIG and are therefore in a unique position to comment on the past, the present and the future of the institute.

Professor Hernandez, when did you become director of the Center for Integrative Genomics?

Prof. Hernandez: in September 2005

Could you recall what happened during those days?

Prof. Hernandez: I had been in Lausanne for one year as a visiting professor, coming from the States, and September 1st was the date my official contract with the University of Lausanne would start. To be honest, I would have never imagined that I would start here as director of the CIG. But as a matter of fact things developed that way and once being director, I came to realize what unique opportunities this position had to offer. First of all, I was the head of an exceptional institute that was fully operational. Several group leaders were already hired and their research teams were up and running.

One could say that you found the CIG "in good condition"?

Prof. Hernandez: Absolutely, I inherited from Walter an internationally competitive research institute, whose star was steadily rising on the science firmament and as such one of my priorities was to consolidate what had been built up during those previous years. The second thing I tried to accomplish – given the fact that the CIG had considerable financial resources at its disposal – was to hire one more professor. This is how we recruited Richard Benton, which in retrospect turned out to be a very good decision.

So there you were, the machine was well oiled and running smoothly?

Prof. Hernandez: Yes, but it was still a brand new machine. Not all the people did know each other very well and I invested a lot in trying to bring them together and make everybody feel part of the whole group.

"I think that systems biology will become extremely important: the time is ripe to try to understand an organism as a whole."

Prof. Walter Wahli

Creating a team spirit?

Prof. Hernandez: That is correct. I felt that everybody at the CIG – and with everybody I mean not just the people involved in research and teaching, but also those involved in support of all these activities – should feel, should *know* that they had an important part to play and would therefore give their best, day after day. You know, I am utterly convinced that motivation is a very important factor – not the only one, but definitely a very important one – that contributes to the success of a research institute. So, basically that is what I tried to do, at least during those early years. And Walter was of immense help during that period. We discussed a lot and he gave me advice and suggestions, whenever I asked for. Keep in mind, I had been in the States for 20 years and I was not exactly what one would describe as an "insider", knowing the coming and going at the University of Lausanne.

Prof. Wahli: Nouria has managed her task outstandingly, and I believe to be in a position that allows me to judge. As just mentioned, the CIG was still very young: in 2002 there was nobody and by 2005 there were 150 people working in this building. The danger of getting scientists and their teams together very quickly, only to see them leave and move to another university after a couple of years, was far from imaginary. As such, the task of keeping the people together at the CIG and consolidating the whole structure and its productivity can hardly be overestimated.

Apart from attracting talented scientists, where there other decisions or events that, in retrospect, contributed to the success of the CIG?

Prof. Wahli: From the very beginning, I had been striving for setting up technical platforms for genomics, proteomics and bioinformatics, as I was convinced of their importance within the context of the research institute that was being build up. And we were lucky because at that time the Swiss Institute of Bioinformatics was starting up a novel unit and we managed to install it in this building. As a matter of fact, people from Vital-IT, as the bioinformatics unit was called, were the first ones to get settled in this building, meaning that from very early on there was access to a strong bioinformatics unit in the CIG.

Prof. Hernandez: As it turned out: a good move, which has really paid off.

Prof. Wahli: I agree.

Prof. Hernandez: Another important decision was made in the field of high throughput sequencing. We should praise ourselves lucky to have hired Keith Harshmann, who joined the CIG as early as 2002 as coordinator of the Genomics Technologies Facility. I remember vividly one day, during a seminar, how the speaker pointed out that high throughput sequencing machines should not only be looked upon as DNA sequencers, but also as "molecule counters". These instruments can actually *count* molecules – having a working range, in those days, of 25 million molecules; now their range is five times higher – and this made me appreciate the enormous power of this technology. So, Keith and myself agreed that we had to get this technology in the house and Keith started exploring and comparing the sequencing machines that were available at that time. Finally, following Keith's advice, it was decided to purchase an Illumina instrument. The CIG was the first academic institution in Switzerland to perform high throughput sequencing.

What are your dreams for the future of the CIG? Please, feel free to speculate.

Prof. Hernandez: I can tell you what my dreams for the future of the CIG are, but I am afraid that reality will not permit them to be finalized, at least not in the near future. I strongly believe that too large or too small research structures are not very efficient. The CIG is considered a medium to large department by Swiss standards, but actually it is minuscule when put in comparison with other research institutions worldwide. I think that the CIG, in order to reach maximum efficiency, should be at least twice as big as it is now. So, I would like to see the CIG grow bigger and reach a critical mass for maximal scientific output and efficiency. I believe however that it will be politically very difficult to realize. One way of bypassing this obstacle is to make alliances and synergies with other departments.

Prof. Wahli: I agree with your point of view. The CIG has become part of the University of Lausanne, which turned out to be a good decision. On the other hand, I could imagine that an expansion of the institute, as envisioned by Nouria, would be more accomplishable if the CIG would have been part of both the Universities of Geneva and Lausanne and the EPFL.

What do you consider to be the main challenges for the future?

Prof. Wahli: I think that systems biology will become extremely important: the time is ripe to try to understand an organism as a whole. At the moment, a lot of scientists are doing some sort of phenotyping, at a large scale. However much necessary and important this may be in the process of understanding biological mechanisms, it remains an initial step. The true challenge lies in capturing a living organism as a complex entity, without neglecting the molecular details.

Combining the so-called reductionist approach with the holistic approach?

Prof. Wahli: You can name it like that, if you like. Somehow both ways of studying life have to come together if we want to understand biological phenomena at an organismal level. This is another argument why you need a critical mass for an institute: you need enough scientists of several disciplines working together.

Prof. Hernandez: At the moment, rumours are circulating that a new department for computational biology will be started up at the Dorigny campus. That would certainly be something to welcome, given the recent development of trying to understand biological mechanisms from a strong quantitative and mathematical angle, where computational modeling has become prominent. This might offer opportunities: synergies with such a department and the CIG would certainly be very productive for both.

Do you have some advice for Alexandre Reymond, the new CIG director?

Prof. Wahli: You don't give advice to the new director. You wish him all the best. (general laughter)

Prof. Hernandez: The CIG covers a lot of research topics. On the one hand, scientists are discovering that an enzyme glycosylating another protein can likewise cleave that protein – research in the near crystallographic range – or are trying to understand how light captured by plants is translated into growth, whereas some of their colleagues are studying entire genomes, try to answer developmental questions or are in the process of elucidating how flies communicate with each other. This diversity is one of the great strengths of the CIG and something we should cherish because it allows us – provided of course that we work together and never cease to communicate with one another – to look at scientific questions within our own field from different angles. Actually my advice for the next director would be that he remains attentive that the centrifugal forces in the institute are compensated and that people never cease to talk to one another – meaning, among other things, that they attend all seminars to stay in touch – and seek each other´s opinion about experiments. But I am convinced that Alexandre will be a great director, who will learn whatever he needs to know – some things the easy way, some other things maybe the not so easy way – like I had to learn. Another advice I would give him is that he should think really hard about the CIG during the day, but then put everything on hold till the next morning – how difficult that may be sometimes – when he goes home in the evening.

"I am utterly convinced that motivation is a very important factor – not the only one, but definitely a very important one – that contributes to the success of a research institute." *Prof. Nouria Hernandez*

Interview with Prof. Walter Wahli

How did it start? Interview with the founding director of the CIG

On the 28th of October 2005, the Center for Integrative Genomics was officially inaugurated. A month earlier, the first director of the institute, Prof. emeritus Walter Wahli had given the CIG in the hands of his successor. And although he keeps on repeating that the "he did not do it alone" and that "many others made important contributions", nobody will question the essential role of Prof. Wahli in the ontogenesis of the CIG. Time to look back, together with the founding director, on how it all began.

Professor Wahli, you are the founding director of the Center for Integrative Genomics. Could you bring back into memory the facts that ultimately led to the birth of this institute? What happened during those early days?

Prof. Wahli: First of all, it is important to point out that the founding of the CIG was not only about scientific issues, there was also a great deal of politics involved. Some decisions that were made have to be seen in that context. The story goes back as far as 1995. During that year discussions were going on between the rectors of the Universities of Lausanne and Geneva and the president of the EPFL (École Polytechnique Fédérale de Lausanne). The general feeling persisted that some of the scientific tasks between the three schools should be redistributed – for example in the fields of mathematics, physics and chemistry, there was considerable complementarity and sometimes overlap – as to make a more efficient structure. Such efficiency could for instance be achieved if the EPFL on the one hand would incorporate physics, mathematics and chemistry, whilst the University of Lausanne would concentrate on the biological sciences and medicine…

…the Life Sciences, one could say?

Prof. Wahli: Exactly. So, this became the general plan around 1996 -1997. I also felt that this restructuring could somehow offer new opportunities and I started to discuss this idea with colleagues, and gradually the picture of a new institute emerged. Allow me to point out the scientific constellation – we are talking about the biological sciences of course – at the end of the previous century. During that period, we were all aware how important the genetics approach to understand biological phenomena was going to become in the near future. And indeed, a couple of years later, in February 2001, the human genome and shortly thereafter the mouse genome – December 2002, if I recall correctly – were sequenced and set a new type of biological research into motion. Likewise, we were convinced that this new type of approach – let's call it the genomics approach – would go hand in hand with the development of new, possibly far reaching technologies. At that time, there was no institute in Switzerland that was devoted to genomics research and we all felt that there was an urge and that now would be the time to call such an institute into being, supported by the three universities. The first ideas for the founding of the CIG were conceptualized around 1999 by Denis Duboule and myself and – following many discussions – were crystallized into a document "Institut Suisse de Génétique biomédicale: Concept et Esquisse d'un Avant-Project Intégrant les Hautes Ecoles de l'Arc Lémanique", which was the vision of what would eventually become the CIG. I presented this document on the 9th of March 1999. In retrospect, one could say that this is the beginning of the Center for Integrative Genomics.

" It is important to point out that the founding of the CIG was not only about scientific issues, there was also a great deal of politics involved." *Prof. Walter Wahli*

Could you briefly summarize the content of this document?

Prof. Wahli: The document is a blueprint for how we planned the structural organization of this new institute. It was agreed upon that it should encompass 4 divisions. One division would have a strong emphasis on basic genetics, including ageing, cancer, metabolism and population genetics. We also envisioned to incorporate a division of human medical genetics, but that idea could not be finalized as we thought. The third division would be devoted to the analysis of genomes in its broadest sense: genomic and proteomic analysis, genomic engineering, bioinformatics and database management. And finally, there would be a division for the modeling of genomic and genetic activities. This unit would focus on the understanding of gene interplay and gene networks, mainly from a theoretical perspective and would as such have close links with bioinformatics…

… Systems Biology, "avant la lettre"?

Prof. Wahli: Yes, I suppose you could put it like that. The document further describes where the institute was going to be located – we had reached a consensus that it would be at the Dorigny campus – how big the (estimated) running costs would be, and so on. This report, a feasibility study, was then put into the arena for general discussions and was finally presented to the rectors of the University of Lausanne and Geneva and the president of the EPFL, in early Fall of the year 1999.

Did they like it?

Prof. Wahli: Yes, one could say that, in general, the project was well received by the community. Fortunately, Denis Duboule and myself had started to think about this project far in advance, not only about the scientific aspects but also, as I just came to mention, about the practicalities and logistics. We had done already more than just circulating ideas.

It was a solid report?

Prof. Wahli: Definitely. So, when the project was put into competition with others, we had an advantage that we managed to materialize: the CIG project was accepted. Although this turned out to be not the end of the discussions. The decision to host the CIG at the Dorigny campus got intertwined with a debate about the restructuring of the *École Romande de Pharmacie*, with its two locations: Lausanne and Geneva. At the end it was decided that there would only be one site for the *École Romande de Pharmacie*, which would become located at the University of Geneva. This meant that the Lausanne branch of the school would be transferred to Geneva. As such, the emptied building thus became available for the new Center for Integrative Genomics.

And everybody was happy?

Prof. Wahli (laughs): Not exactly. There were strong disagreements and endless disputes. Keep in mind, after all we were discussing the removal of Pharmacy from Lausanne, although it remained part of both Universities. People did not want to leave, quite understandable I would say. On the other hand, given the low numbers of pharmacy students, this rotation to Geneva made perfect sense.

Were you involved in those discussions?

Prof. Wahli: Oh yes, especially in the context of the start of the CIG. It got very complicated. Nevertheless, I want to emphasize that the discussions with the director of the Pharmacy School at that time, a young and very talented professor, Jean-Luc Wolfender, were always in an atmosphere of mutual respect and aimed towards finding a solution to a rather tricky problem. One must stress that the move to Geneva also offered opportunities, which in retrospect were more than realized.

So, eventually this building became available.

Prof. Wahli: Correct. So, the time came to implement what we had been striving for and start up the CIG. One day, during this early phase, the rector from the University of Lausanne came to me and told me that I should become Director of the institute. His argument was that I had been involved in both the science and the politics of the CIG project and that nobody else understood the situation and the context better than I did. I must admit that I was not happy about this.

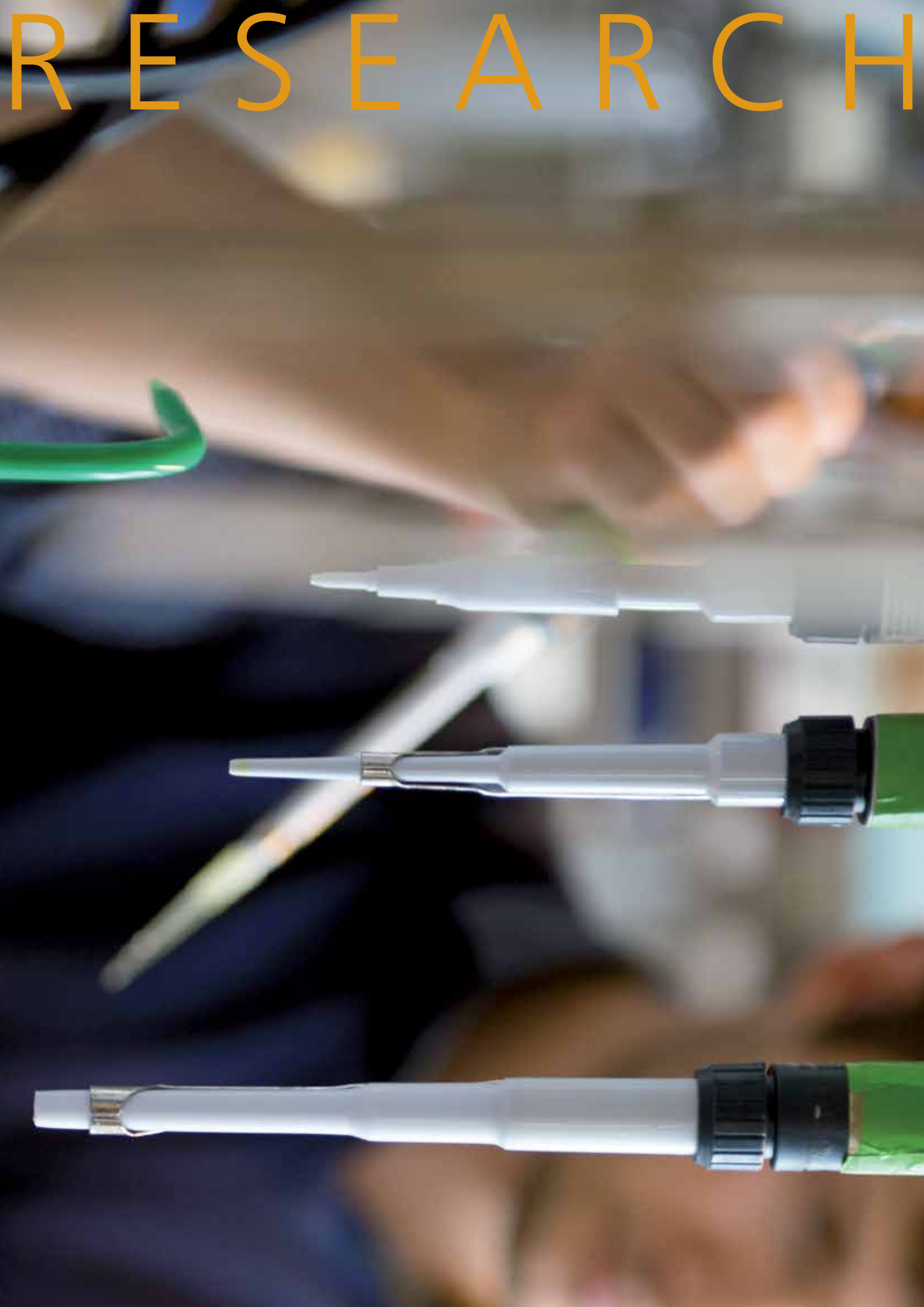
You had "mixed feelings" as it often becomes formulated afterwards.

Prof. Wahli: To say the least. Anyway, I thought it over and accepted the position for a period of about four years, the time I estimated to get the CIG on track. This is how, in January 2002, I became the first Director of the Center for Integrative Genomics. One of my priorities during that early period was to create favourable conditions (building infrastructure, start up grants, research versus teaching duties) enabling us to recruit scientists that would give the institute an international reputation, within the following years.

You had to convince them to come over.

Prof. Wahli: Precisely. We had to create opportunities and show interested group leaders what the CIG was supposed to become – mind you, we were starting from scratch – and that we had the financial means to realize our objectives. I was convinced that the quality of the scientists we would attract during those early days would set the path of the CIG for years to come. They could, and most probably would, make the difference between success or failure. Luckily we got very talented people from the very beginning. I remember that the first scientist we hired was Henrik Kaessmann. Shortly thereafter came several others, like Nouria Hernandez, Winship Herr, Alexandre Reymond, Mehdi Tafti and Christian Fankhauser, to name a few: all gifted scientists with a vision, who made the CIG to what it is today.

RESEARCH



Richard Benton
Associate Professor

Richard Benton received his PhD in 2003 from the University of Cambridge, and was an EMBO/Heley Hay Whitney postdoctoral fellow at The Rockefeller University, New York. He joined the Center for Integrative Genomics in September 2007 as Assistant Professor and promoted to Associate Professor in August 2012. His group's research has been recognised by award of several prizes, including the Eppendorf & Science Prize for Neurobiology (2009), the Friedrich Miescher Award (2012) and the AChemS Young Investigator Award for Research in Olfaction (2012), as well as financial support from an ERC Starting Grant (2008-2013) and ERC Consolidator Grant (2013-2018), the EMBO Young Investigator Programme (2011-2014) and an HFSP Young Investigator Award (2011-2014).

Chemosensory perception and evolution in insects

We have a longstanding interest in the molecular basis of odour detection by the Ionotropic Receptor (IR) family of chemosensory receptors, which have derived from the ancestral ionotropic glutamate receptor family of ligand-gated ion channels. Through comprehensive comparative bioinformatic analyses of IR repertoires in animal genomes, we have studied the evolutionary origin, expansion and diversification of this family of chemosensory receptors, and how these properties relate to individual species' chemosensory ecology. Using electrophysiological and cell biological approaches *in vivo* and heterologous cells, we have studied IR complex formation and stoichiometry, and their trafficking, ion conduction and ligand-recognition properties. Our results provide insights into the conserved and distinct architecture of these chemosensory receptors and their synaptic ancestors. In current work, we collaborate with structural biologists to visualise the three-dimensional organisation and dynamics of the *apo* and odour-bound IR ligand-binding domain by X-ray crystallography and Nuclear Magnetic Resonance to understand the molecular basis and evolution of their odour recognition properties.

PHEROMONE SIGNAL TRANSDUCTION

Pheromones form one of the major sensory mechanisms by which animals communicate with members of their own species. These signals are often chemically distinct from other environmental chemical cues, because they derive from internal metabolic pathways, such as those for lipids or peptides. Consistently, the molecular machinery that detects pheromones also appears to be highly specialised. In previous work, we and others have characterised a set of proteins, including the olfactory receptor OR67d, the CD36-related transmembrane protein SNMP1, and the extracellular Odorant Binding Protein, LUSH, which are each required for detection of the fatty acid-derived *Drosophila* sex pheromone *cis*-vaccenyl acetate. We are investigating the role of these proteins in mediating the sensitive and specific neuronal responses to *cis*-vaccenyl acetate through *in vivo* structure-function and biochemical analysis.

CHEMICAL BIOSENSOR DEVELOPMENT

Harnessing our knowledge of chemosensory receptors, we are involved in developing novel types of chemical biosensors as part of the Nano-Tera Envirobot project. Our aim is to integrate known chemosensory receptors or custom-designed receptors of desired specificity into a chemosensing robot to enable remote and real time tracking of environmental pollutants.

NEUROANATOMY AND PHYSIOLOGICAL FUNCTIONS OF CHEMOSENSORY CIRCUITS

We have completed a comprehensive neuroanatomical and physiological analysis of the IR olfactory circuits, in which we have identified odour ligands and central circuit organization for the vast majority of IR olfactory pathways. By comparing our findings with the properties of the circuits expressing Odorant Receptors (ORs), we can begin to explain how and why two complementary olfactory subsystems have evolved in insects. Recently, we have found that a large number of IRs are selectively expressed in small subpopulations of neurons in peripheral and internal gustatory neurons, suggesting roles for these receptors in taste detection and internal food assessment. We are currently defining the ligands detected by these sensory pathways, identifying their higher order circuit elements and exploring the taste-evoked behaviours they underlie.

OLFACTORY CIRCUIT EVOLUTION

Much of our current work focuses on obtaining mechanistic explanations for how novel olfactory pathways evolve, through three main approaches. First, we are investigating the evolutionary forces affecting patterns of genetic variation within chemosensory gene repertoires between geographically-distinct populations of *D. melanogaster*, and elucidating phenotypically important changes within these loci. Second, we are performing comparative transcriptomics analyses of olfactory subsystems, as well as of individual olfactory pathways within these subsystems, to identify and characterise loci that have driven the developmental and functional diversification of these sensory circuits. Third, we are expanding our efforts to genetic, physiological and behavioural analysis of drosophilid species that have distinct chemosensory preferences to *D. melanogaster*, to identify the genetic basis of their ecologically-important olfactory adaptations. We believe these studies will provide general insights into the mechanisms of, and constraints on, nervous system evolution.

CHEMOSENSORY AND SOCIAL BEHAVIORS IN FLIES AND ANTS

We have used simple chemosensory preference assays to define the innate behaviours mediated by a number of olfactory and gustatory pathways and also examined the role of chemosensory signals in controlling sexual behaviours. Current efforts are directed towards development of novel behavioural assays in which we can precisely control the temporal patterns of odour stimuli, and video-track single or groups of flies in a high-throughput manner. These technical advances are allowing us to describe previously unobservable individual and group-level behaviours in *Drosophila*. Finally, in a new research direction, we are studying how chemical communication can control colony organisation in a eusocial insect, the carpenter ant *Camponotus floridanus*.

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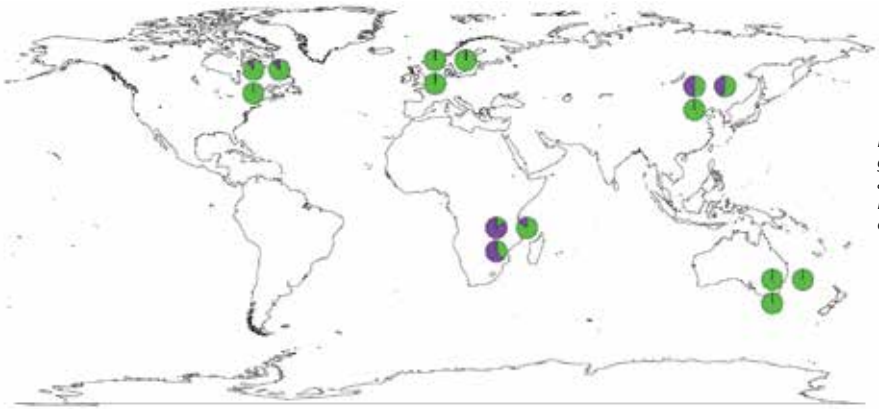

Patterns of genetic variation in a D. melanogaster chemosensory gene: the pie charts indicate the relative frequencies of three amino acid-changing single nucleotide polymorphisms in D. melanogaster population samples in five different regions of the world.

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 for fundamental research. She thus carried out a postdoctoral 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 full professor in 2008. In addition to her teaching and research activities, she was elected President of the Section of Fundamental Sciences from January 2009 to July 2012 and was appointed vice dean of the faculty of Biology and Medicine from August 2009 to July 2012. In August 2012, she has been elected Dean of the Faculty of Biology and Medicine.

Networking activity of nuclear receptors during development and in adult metabolic homeostasis

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

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

A NEW MODEL OF PPARgamma NULL MICE

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

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

PPARγ null mice allowed us to demonstrate the crucial role of paracrine activities of the adipose tissue. First in the skin, where we show that the lack of sub-cutaneous adipose tissue provokes a delay in hair morphogenesis and we are now searching the adipocyte-generated paracrine signal that acts onto hair follicle initial development. Later in age, a phenotype of cicatricial alopecia develops, but this is likely due to the lack of PPARγ in the hair follicle cells, and more particularly in sebocytes. Second, in the bone marrow niche, where we show that the absence of bone marrow adipocytes itself promotes myelopoiesis and de-represses osteoclastogenesis. The subsequent higher activity of osteoclasts alters the stem cell niche and causes a severe cortical porosity in midshaft of long bones. Deletion of PPARγ also activates LT-HSC differentiated into multi-potential progenitors and mobilizes progenitors into circulation.

NUCLEAR RECEPTOR REGULATORY NETWORK IN LIVER AND WHITE ADIPOSE TISSUE METABOLISM

The study of the metabolic regulations has long been focused on mechanisms affecting the rate-limiting steps along a given pathway. However, metabolic homeostasis relies on the cross talk between various regulatory pathways. We thus now shifted our exploration towards understanding the role of the nuclear receptors within regulatory networks, focusing on the liver and white adipose tissue (WAT), which are important metabolic organs with respect to energy homeostasis.

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

A second project along this axis is linked to the SystemsX.ch project CycliX, where we explore how the interplay between transcription factors coordinate cell, nutrition, and circadian cycles. Our group focused on exploring the sterol regulatory element binding protein 1 (SREBP1) activity, which is both nutrient-responsive and influenced by the circadian clock. Hepatic binding of SREBP1 to its targets was evaluated around the clock in wild type mice and showed an oscillatory profile, with a maximum around ZT18, which is consistent with the RNA expression and nuclear localization of the protein. Importantly, the expression profile of SREBP1 targets is not strictly following SREBP1 binding in wild type mice, whereas in Bmal1KO mice all SREBP1 target genes are synchronized with SREBP1 binding. This observation suggests that transcription factors linked to circadian expression participate in assuring the correct temporal expression profile of SREBP1 target genes. Our results give the first tools to comprehensively explore how SREBP1 activity is connected to circadian-driven regulatory events and are being extended now with the study of RXR binding pattern in the physiological context of both rhythmic food absorption and circadian rhythm.

We are now exploring the WAT, a very dynamic tissue whose distribution and function change dramatically throughout life. After developing a new method allowing making ChIP in WAT, we are investigating, at genome-wide levels, the chromatin remodelling process taking place in this tissue upon aging and in diet-induced obesity.

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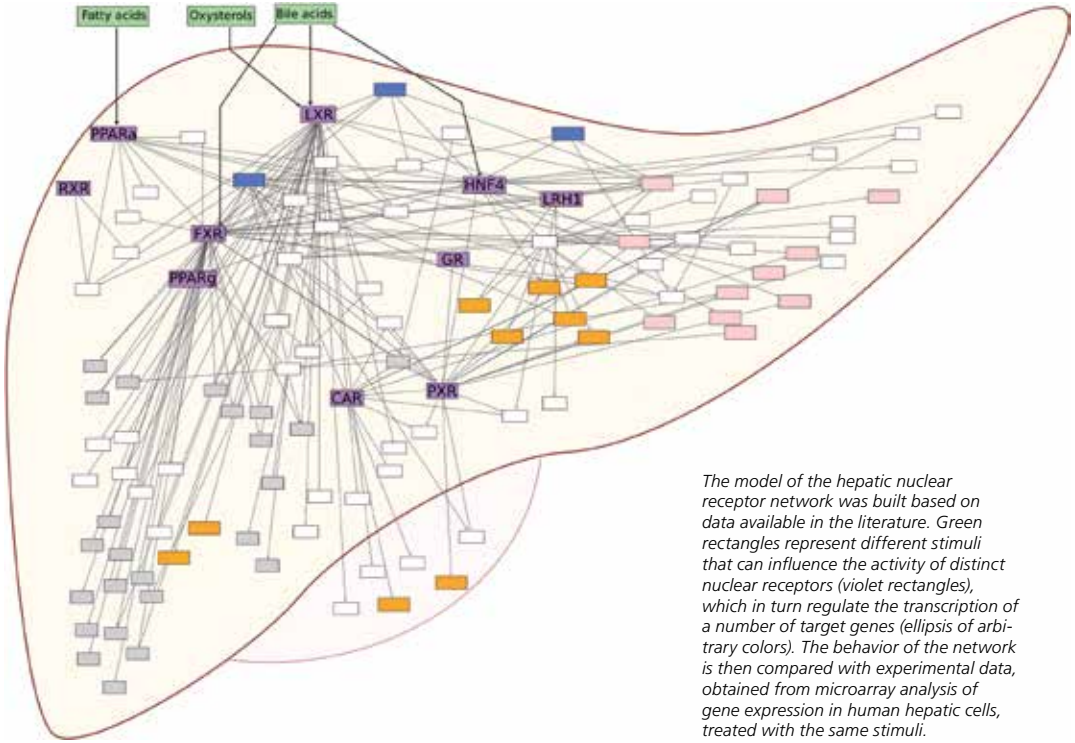

The model of the hepatic nuclear receptor network was built based on data available in the literature. Green rectangles represent different stimuli that can influence the activity of distinct nuclear receptors (violet rectangles), which in turn regulate the transcription of a number of target genes (ellipsis of arbitrary colors). The behavior of the network is then compared with experimental data, obtained from microarray analysis of gene expression in human hepatic cells, treated with the same stimuli.

Vincent Dion
SNSF Professor

Vincent Dion first experienced research life in 1999 as a summer student in Stanley L. Miller's laboratory at UCSD (USA) working on the prebiotic stability of 5-substituted pyrimidines. After that, he did research with David H. Evans at the University of Guelph (Canada) and with Benoît Chabot and Raymund J. Wellinger at the Université de Sherbrooke (Canada). In 2007, he obtained his PhD from Baylor College of Medicine (USA) under the supervision of John H. Wilson. There he defined the role of DNMT1, a DNA methyltransferase, in preventing disease-causing repeat expansions. This is when he became interested in the interplay between genome stability and chromatin. As a postdoctoral fellow with Susan M. Gasser at the Friedrich Miescher Institute (Basel, Switzerland), he discovered a novel role for chromatin remodeling enzymes in the repair of deleterious DNA double-strand breaks. He joined the CIG in 2013 as an Assistant Professor with the support of a SNSF professorship.

Chromatin, genome stability and the expansion of trinucleotide repeats

Because we breathe oxygen and because most of our body is composed of water, our DNA is being damaged at a rate of about 100'000 lesions per cell per day. This enormous amount of damage must be repaired efficiently and accurately if the genetic information contained in our genome is to be maintained. This fundamental process of DNA repair is the focus of our research.

Mutations in several DNA repair genes greatly increase cancer predisposition, while malfunction of several caretakers of the genome lead to neurological disorders. These observations highlight the importance of maintaining genome stability for human health.

Each cell in our body contains no less than 2 meters of DNA that needs to be packaged into a nucleus of about 20 to 50 micron in diameter (a micron is 1/1'000'000 of a meter). To achieve this, DNA is wrapped around histone octamers to form nucleosomes and higher-order chromatin structures. Chromatin therefore helps to package the genome. Additionally, it provides great opportunities for the regulation of DNA-based events since nucleosomes can mask the binding site of many DNA binding proteins. This interplay between chromatin structure and DNA metabolism has been extensively studied in the context of transcription, but much less is known about its impact on DNA repair.

To study how chromatin affects DNA repair events, our laboratory focuses on tandem repeats composed of pure stretches of CAG or CTG trinucleotides. These loci are hotspots for genome instability, and the size of the repeat can expand greatly, in some cases reaching thousands of trinucleotides at a single locus. As the repeat tract gets longer, it becomes more unstable and adopts chromatin configurations that bear many of the hallmarks of dense heterochromatin. The instability depends primarily on the normal activity of DNA repair on an unusual DNA sequence. These characteristics make trinucleotide repeats an ideal paradigm to explore the relationship between genome stability and chromatin structure at endogenous loci. We use a combination of cutting-edge microscopy, molecular biology, genetics, and genomics in cultured human cells to identify new players in trinucleotide repeat instability and to study the effects of chromatin structure and organization on DNA repair. Specifically, our projects deal with the following questions:

Do chromatin modifiers affect repeat instability directly by changing the local structure of the expanded repeat tract? Many chromatin modifying enzymes have been implicated in repeat instability but their exact role is unclear. This is because every study conducted so far includes loss of function experiments that do not permit the differentiation between direct or indirect causes such as changes in transcription genome-wide. Here we are designing a novel assay to address the molecular roles of chromatin modifying enzymes in repeat instability.

What is the role of chromatin remodeling enzymes in trinucleotide repeat instability? Here we are interested in defining the role of a family of enzymes, the SNF2-type ATPases, in trinucleotide repeat instability. We are therefore performing siRNA (small interfering RNA) screens for novel remodelers implicated in repeat instability. These are followed up using both biochemical and genetic approaches to understand the mechanism of action of these molecular machines.

What is the impact of nuclear organization on trinucleotide repeat instability? Here we aim to determine whether expanded trinucleotide repeats impact their 3D organization in the nucleus and whether this organization in turn influences their repair and thus their instability.

Can we induce repeat contractions in patients? Our last ongoing project is especially relevant to human health. Indeed, the expansion of trinucleotide repeats cause a number of neurological, neuromuscular and neurodegenerative disorders. Examples of these diseases include Huntington disease, myotonic dystrophy, Fragile X syndrome, Friedreich Ataxia, as well as several spinocerebellar ataxias, all of which remain without a cure. A long term goal of our research is to understand the mechanism of trinucleotide repeat instability such that we can manipulate it at will and induce repeat contractions in patients. This would, in theory, remove the underlying cause of the disease and provide a therapeutic avenue. This project, therefore, is focused on finding conditions or treatments that specifically contract the repeat tracts and would therefore alleviate the molecular symptoms.

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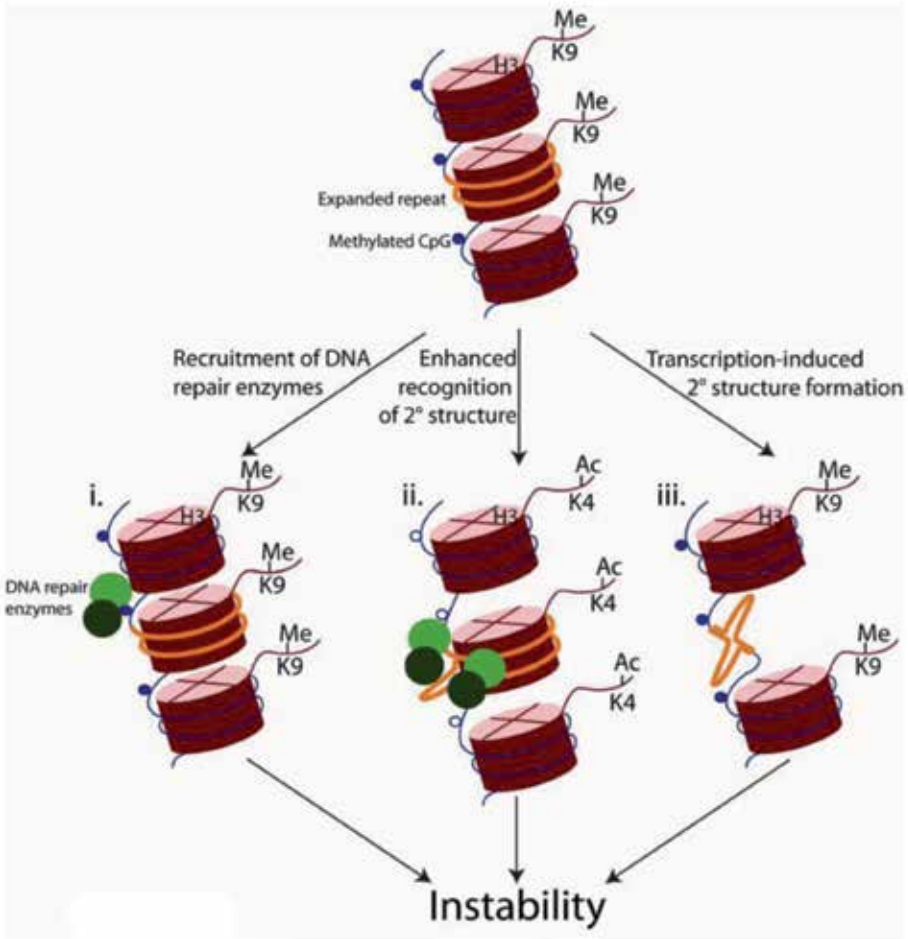


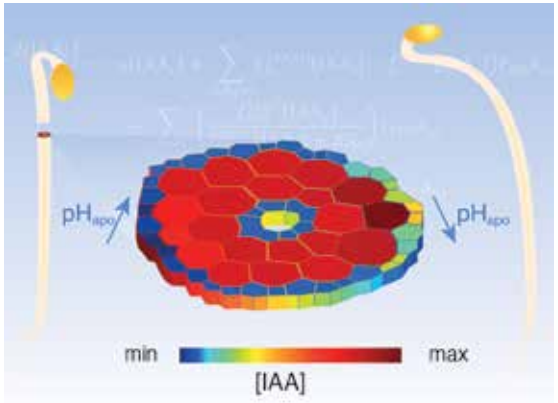
Repeat instability is thought to occur because of the formation of non-B-DNA structures that are misprocessed by the DNA repair machinery. Thus, chromatin could enhance the recruitment of repair proteins, enhancing the recognition or the formation of the unusual secondary structures.

Christian Fankhauser
Professor

Light regulation of plant growth and development

Christian Fankhauser received his PhD from the University of Lausanne in 1994 after carrying out his thesis at the 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. In 2011 he was promoted Professor.

Almost all our food, feed, fuel and fiber ultimately derive from plants. Plant growth depends on photosynthesis, the process in which light energy is harnessed for the synthesis of high-energy carbon compounds. In order to capture light, plants have evolved unique ways of building cells, tissues and organs, a highly diverse metabolism and a life-long continuation of versatile growth and development. Plants possess numerous photoreceptors enabling them to sense changes in the amount, spectral composition (color), photoperiod and direction of light. The central goal of our research is to understand how plants manage to gain access to direct sunlight when this resource becomes limiting. This situation occurs for example when a seedling develops in the shade of other plants. When facing such conditions plants deploy specific growth and developmental strategies: in particular the Shade Avoidance Syndrome and Phototropism. We use the model plant *Arabidopsis thaliana* to study the molecular events leading from light perception to the physiological responses elicited by this unfavorable light environment.



A model illustrating key steps leading to phototropism. Regulated change in apoplastic pH leads to the formation of a lateral auxin gradient, leading to asymmetric growth and resulting in growth towards the light source.

A distinguishing feature of foliar shade is the low R/FR ratio due to absorbance of red light by the photosynthetic pigments. Hence direct sunlight has a high R/FR ratio, while under vegetational shade this ratio is low. Plants use phytochrome (phy) photoreceptors to sense competitors. In *Arabidopsis* this response is primarily mediated by phyB, one member of this photoreceptor family. Phytochromes are synthesized as Pr (red-light absorbing). Upon light excitation they are photo-transformed into Pfr (far-red-light absorbing), which is the active conformer that is converted back into the inactive Pr by far-red light. Hence, in direct sunlight (high R/FR ratio) phyB is mainly in its active PfrB conformation while under foliar shade (low R/FR) phyB is mostly present as the inactive PrB conformer. A key step in this pathway is the conformation-specific interaction between PfrB and a family of bHLH class transcription factors known as PIFs (Phytochrome Interacting Factor). In sunlight, the interaction between PfrB and the PIFs leads to their inactivation, a process that is reversed by shade which leads to the conversion of phyB into its inactive conformer that does not inhibit the PIFs.

Using a combination of molecular genetics and genome-wide determination of PIF binding sites we identified PIF target genes that are central to the process of shade-induced elongation growth, enabling young seedlings to reach unfiltered sunlight. Of particular importance in this process is the plant growth hormone auxin. PIFs bind to the promoters and regulate the expression of genes coding for auxin biosynthesis enzymes, auxin transporters and auxin signaling components (reviewed in de Wit et al. *Physiol Plant* 2014). Using this information we combined modeling and experimental validation to further study the gene regulatory network underlying shade-induced hypocotyl elongation. Interestingly our study reveals interesting parallels between information transmission in plants and the "information theory" developed by Claude Shannon (Hersch et al. *Proc Natl Acad Sci USA* 2014).

Phototropism is a directional growth response enabling plants to optimally position their photosynthetic organs (leaves). Phototropin photoreceptors (phot1 and phot2 in *Arabidopsis*) sense light direction to initiate phototropism. These light sensors also control leaf flattening, chloroplast movements and opening of stomata (pores on leaves regulating gas exchange) and thereby contribute to the optimization of photosynthesis. Phototropins are blue-light activated protein kinases, composed of two light-sensing LOV (Light Oxygen Voltage) domains and a carboxyl-terminal protein kinase domain. We study signal transduction mechanisms leading from photoreceptor activation to phototropin-mediated growth responses (phototropism and leaf positioning).

By combining molecular genetics, cell biology, biochemistry and modeling we uncovered important aspects of phototropin signaling. First, we showed that, in contrast to a widely accepted model, in *Arabidopsis* light perception and the growth response coincide spatially (Preuten et al. *Curr Biol* 2013). This information allowed us to make a simplified 2D model of the steps leading from photoreceptor activation to the formation of an auxin gradient that drives asymmetric growth to enable the plant to grow towards the light. A central prediction from this model was validated experimentally leading to the discovery of a novel mechanism by which upon unilateral light perception phototropins lead to the formation of an auxin gradient (Hohm et al. *Mol Syst Biol* 2014).

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Genetics and energetics of sleep homeostasis and circadian rhythms

Paul Franken received his PhD from the University of Groningen, the Netherlands, in 1993 for his work on sleep homeostasis and thermoregulation at the University of Zürich, Switzerland, under the direction of Alexander A. Borbely. 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. 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. In 2005, he joined the CIG as a 'Maitre d'Enseignement et de Recherche' and was promoted Associate Professor in 2013.

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. Relative minor changes in this interaction lead to performance decrements and clinically significant sleep disruption. To gain insight in the molecular pathways underlying the sleep homeostat and its interaction with the circadian process, we apply a combination of forward, molecular, and reverse genetic approaches in the mouse.

SYSTEMS GENETICS OF SLEEP

In the past, we have used Quantitative Trait Loci (QTL) analysis to map genomic regions that regulate sleep and brain activity, using the electroencephalogram (EEG). These studies demonstrated that genetic factors do importantly affect sleep and yielded a number of significant QTLs. For two of these loci the responsible genes could be successfully traced, thereby implicating novel signaling pathways involved in rhythmic brain activity. We have continued this line of research with two large scale projects.

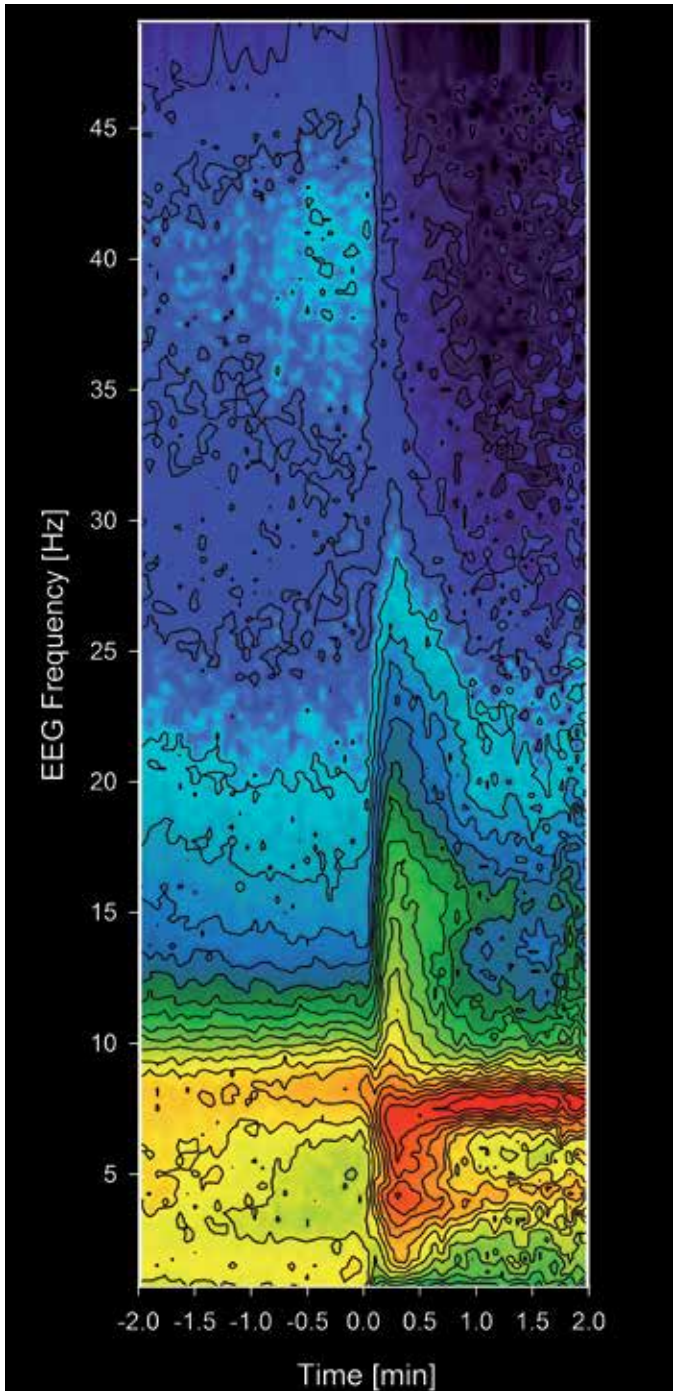
In a first project, we used the genetically diverse CFW-outbred mice to map genes implicated in sleep. We phenotyped 1316 male and female CFW mice using a novel, high throughput method to measure sleep. We identified a strong, genome-wide significant linkage signal for sleep quality that pointed to a promising candidate gene, which we are currently investigating further. In the second project, we used a genetic reference population, the BXD panel of recombinant inbred lines, to initiate a systems genetics approach aiming at elucidating the genes and gene pathways important for sleep, metabolism, and aging. This project aims at interrogating the DNA, chromatin, transcriptome and metabolome at the behavioral, tissue, and cellular levels to chart the core genetic networks important to sleep and its homeostatic regulation. Sleep and EEG phenotyping has been completed in 42 lines and initial mapping efforts revealed a large number of significant loci associated with the various aspects of sleep, including its amount and distribution over the day and the EEG response to enforced periods of wakefulness. Results for ongoing RNA-sequencing of peripheral (liver) and central (cerebral cortex) tissues and metabolome analyses of blood plasma of sleep deprived and control BXD mice will be correlated with these sleep phenotypes.

MICRO-RNAS & SLEEP HOMEOSTASIS

Micro-RNAs (miRNAs) receive increasing interest in neuroscience. Given that these non-coding transcripts importantly affect the mRNA levels of many coding genes, we have started investigating the role of miRNAs in sleep homeostasis, using two approaches. First, we made an inventory of miRNAs affected by sleep loss in various brain areas using miRNA expression arrays and identified one miRNA that is strongly and consistently up-regulated after sleep deprivation. We are currently assessing the functional involvement of this miRNA in sleep homeostasis. In a second approach, we assessed sleep homeostasis in mice lacking *Dicer*, encoding an enzyme critical for miRNA maturation. We used a conditional and inducible *Dicer* knock-out construct in which miRNAs can be down-regulated specifically in neurons of adult mice. Besides a profound homeostatic phenotype these mice also displayed an unexpected obesity phenotype. Thus besides their now established role in circadian rhythm generation, miRNAs also play a role in the homeostatic aspect of sleep regulation.

CLOCK GENES & SLEEP HOMEOSTASIS

We discovered 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, especially in the cerebral cortex, is tightly linked to the prior sleep-wake history. Thus contrary to the prevailing notion that circadian and homeostatic processes are separate, at the cellular level the same molecular circuitry seems to be implicated in both processes. We now focus on the mechanisms linking clock gene expression to time-spent-awake. The observation that the transcriptional activity of 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 have investigated this issue *in vitro* using redox-sensitive GFP probes and at level of the whole organism using *in vivo* imaging techniques to monitor PER2 protein levels in freely behaving mice. Previously, we established that the sleep-wake dependent changes in *Per1* and *Per2* are, in part, mediated by their transcriptional factor NPAS2. Using chromatin immunoprecipitation (ChIP) analyses we could demonstrate that sleep loss reduces the binding of NPAS2 to the E-boxes of specific target genes. Moreover, we discovered that the stress hormone corticosterone contributes to the transcriptome changes in the brain after sleep loss in mice 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 circulating corticosterone levels. Model predictions are useful in helping to design relevant experiments to unravel these non-linear relationships.



We discovered a novel, cataplexy-associated EEG state in mice lacking the neuropeptide orexin. The contour plot illustrates the changes in the spectral composition of the EEG at the transition from active wakefulness to cataplexy. The unique spectral signature of brain activity in the first 45 seconds after the onset of cataplexy (at time 0 minutes) is specific to deficiency in orexin neurotransmission and remained unnoticed during 14 years of EEG studies in this mouse model.

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David Gatfield
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RNA biology of circadian rhythms

David Gatfield earned a diploma in biochemistry from the University of Tübingen (Germany) in 2000. He then joined the group of Dr Elisa Izaurralde at the European Molecular Biology Laboratory (EMBL) in Heidelberg (Germany) to study mechanisms of mRNA transport and degradation in human and *Drosophila* cells and received his PhD in 2004. During his postdoctoral training 2004-2010 with Dr Ueli Schibler at the University of Geneva (Switzerland) he worked on mechanisms of biological timekeeping in mice and developed his dual interest in circadian clocks and RNA biology. He joined the CIG as a Swiss National Science Foundation Professor in November 2010. In 2012 he was awarded the *Prix Leenaards pour la Promotion de la Recherche Scientifique*.

Research in our group combines two main scientific themes: circadian rhythms and RNA biology.

A considerable proportion of mammalian gene expression undergoes rhythmic oscillations driven by circadian clocks, which coordinate the daily timing of behaviour, physiology and metabolism. It is commonly thought that the majority of mRNA and protein rhythms are generated through cyclic transcription. However, there is accumulating evidence that posttranscriptional regulation makes important contributions as well. Using mouse organs such as the liver and tissue culture cells as model systems, we investigate how mechanisms acting at the mRNA level participate in shaping the rhythmic transcriptome and proteome, and how the identified regulatory pathways impact on rhythmic functions in the organ and in the animal.

Since starting the group in November 2010, three main research lines have emerged:

INTERACTIONS BETWEEN THE MICRORNA PATHWAY AND THE CIRCADIAN CLOCK.

One focus of our research has been on the activity of miRNAs in the context of circadian gene expression. Using a genetic mouse model devoid of miRNAs in hepatocytes (*Dicer* knockout), we have recently defined the miRNA-dependent circadian liver transcriptome, identified miRNA-regulated core clock components, and shown how miRNAs tune the phases and amplitudes of rhythmic transcripts. In on-going projects we now wish to gain a deeper understanding of physiological functions of selected miRNA-mediated regulatory events that we discovered.

IDENTIFICATION OF NOVEL RNA-BASED REGULATORY MECHANISMS IN THE CORE CLOCK.

We are using the large group of RNA-binding proteins (RBPs) as entry points to identify novel regulatory mechanisms at any level of RNA metabolism – from transcription to splicing, nuclear export, translation and mRNA degradation – that impact on core clock functions. We have thus performed a small siRNA screen for circadian phenotypes in cultured cells and, from several RBPs whose knockdown engenders altered circadian parameters, are mechanistically following up one of the hits, a splicing factor that is involved in setting the period length of free-running rhythms.

PRINCIPLES OF DAYTIME-DEPENDENT TRANSLATION IDENTIFIED BY RIBOSOME PROFILING.

We have adapted the technique of ribosome profiling (RPF-seq), which relies on the deep sequencing of ribosome-protected mRNA footprints to quantify translation in a transcriptome-wide fashion, to solid mouse tissues. We find that for hundreds of mRNAs, ribosome occupancy shows daily rhythms and, for the cases investigated, leads to protein oscillations from non-oscillating transcripts. Many of the novel rhythmic events concern transcripts with links to metabolism. We are thus particularly interested in dissecting how translational regulation is involved in integrating metabolic and core clock signals to give rise to the correct gene expression output.

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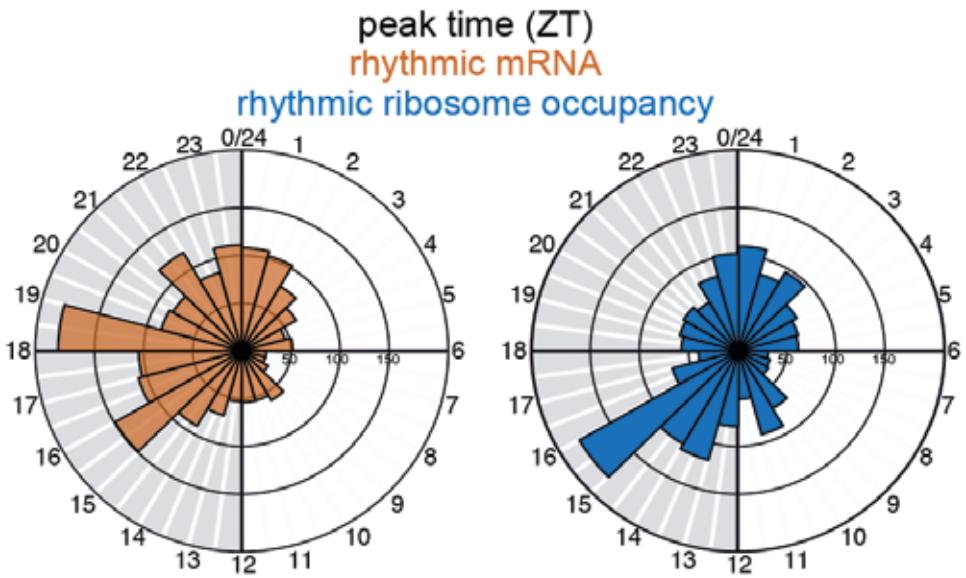

Comparison of phase distribution of rhythmic gene expression detected in mouse liver at the level of mRNA abundance (left, orange; RNA-seq data) and ribosomal occupancy (blue, right; RPF-seq data), the latter can be interpreted as translation. Many translational rhythms peak around the light-dark transition and at the beginning of the night, around Zeitgeber *Time 12-16, which coincides with activity and feeding onset in mice. The length of each radial sector indicates the number of transcripts found at this phase.*

Fisun Hamaratoglu
SNSF Professor

Growth control and patterning in *Drosophila*

Fisun Hamaratoglu received her PhD in 2007 from the Baylor College of Medicine, for her work in the group of Georg Halder at the MD Anderson Cancer Center in Houston, USA. During that period, she identified several upstream regulators, including the first receptor, of the Hippo tumor suppressor pathway. Her interest in growth control stems from those days spent in Houston. In 2008, she joined Markus Affolter's laboratory at the Biozentrum, University of Basel, for her post-doctoral training, funded by HFSP, Marie Curie and Roche postdoctoral fellowships. In Basel, as part of the WingX.ch initiative, she established the fly wing as a model system to study scaling quantitatively and at a molecular level. Her experience in Basel enabled her to take a more quantitative approach to classical developmental biology questions. She joined the CIG in October 2013 as a "Maître Assistant suppléant" and became a Swiss National Science Foundation Professor in April 2014.

What are the molecules that give animals their final size and shape? Over the years, developmental biologists have identified many molecules with key roles in pattern formation and size control. Several signaling pathways have emerged from this work, including the Hippo and the Bone Morphogenetic Protein (BMP) pathways. Research in our laboratory focuses on these two key signaling cascades and aims at a better understanding of each pathway individually (with quantitative resolution) and how their activities are coordinated during development. The developing *Drosophila* wing tissue, the wing imaginal disc, is an ideal organ for performing such experiments, as it is a single cell-thick epithelium (hence, it is practically two-dimensional), easy to image.

GENERATING LIVE-IMAGING READ-OUTS FOR THE HIPPO PATHWAY ACTIVITY

The Hippo signalling pathway was discovered at the turn of the 21st century via EMS mutagenesis screens in *Drosophila*. The components and – meanwhile, experiments have provided increasing confidence – the mechanisms of signal transduction of Hippo signalling are highly conserved. This pathway functions as a critical regulator of tissue size in flies and vertebrates. Evidence indicating the involvement of this pathway in human cancer is also rapidly accumulating.

Hippo signalling restricts growth and interacts genetically with other known growth regulators, such as Myc, and the TOR and Epidermal Growth Factor Receptor (EGFR) pathways. Moreover, cell polarity, contact inhibition, cell-cell adhesion, cellular architecture and mechanical forces, all regulate Hippo activity. Hence – integrating information from all these extracellular and intracellular cues and linking them to the regulation of cell cycle and survival – Hippo acts as a major decision hub.

We have learned a great deal about the components and the signalling mechanisms of this pathway over the last decade, but we have no information about the pathway dynamics. Current pathway activity reporters depend on immunostaining of fixed tissue and thus cannot capture dynamic events. To overcome this shortcoming, we are developing live read-outs of Hippo signalling which can be tracked in real time. Our approach is to fluorescently tag pathway components in their endogenous loci using the recent CRISPR technology. Careful spatial and temporal examination of Hippo activity in the wing disc will help us in reaching a unifying model of how this tissue obtains its final size and shape.

USING MULTI-COLOUR LINEAGE TRACING TO QUANTIFY GROWTH PARAMETERS

Growth and patterning occur concurrently in the developing organs of all multi-cellular organisms, from flies to humans. Their coordination is of paramount importance to yield functional organs of proper size and shape. How this coordination is achieved is a long-standing question. Careful quantification of growth parameters is the key to answering this question and until recently tools necessary for such quantification were not available.

We use a new tool, called Raeppli (named after the confetti used in the Basel Carnival), a lineage tracing method that permanently marks a cell with one of 4 different fluorescent markers at the desired time point. Importantly, all progeny of the first cell inherits the colour-code forming a "clone". Since all clones are induced simultaneously, differences in clone sizes reflect differential growth rates. Therefore, cell division rates can be inferred from clone sizes. Using multiple copies of the construct, cells can be labelled with up to 20 different colours providing an impressive level of spatial resolution. These images pose a formidable image analysis challenge that we are undertaking in collaboration with the Bioimaging and Optics Platform at the EPFL. We developed a new algorithm that enables the automated detection of Raeppli clones using sophisticated image analysis software. Our long-term aim is to determine spatial and temporal growth dynamics after simple genetic modifications to Dpp and Hippo pathways.

INVESTIGATION OF THE COOPERATION BETWEEN EGFR AND HIPPO PATHWAYS IN GROWTH CONTROL

Epidermal Growth Factor Receptor (EGFR) signalling is another major player in organ size determination and differentiation in many vertebrate tissues as well in *Drosophila* imaginal discs. Gain-of-function mutations in Ras and Raf (transducers of the activated EGFR signal) are arguably the most common lesions in human cancer.

We have uncovered an unexpected synergy between the gain-of-function mutations in the EGFR pathway and loss-of-function mutations in Hippo signalling. This synergy seems to stem from nuclear interactions between both pathways, since we were able to recapitulate this synergy by combining modulations at different levels of the two signalling pathways. For example, activating mutations in the EGFR as well as inactivating mutations in the transcriptional factor Capicua synergize with loss-of-function mutations in the Hippo pathway. Similarly, inactivating mutations in one of the most upstream components in the Hippo pathway, Expanded, as well as activating mutations in the transcriptional effector of the pathway, Yorkie, synergize with gain-of-function mutations in the EGFR pathway. Currently, we are conducting RNA-seq experiments to pinpoint potential common targets of the two pathways that may explain the observed synergy.

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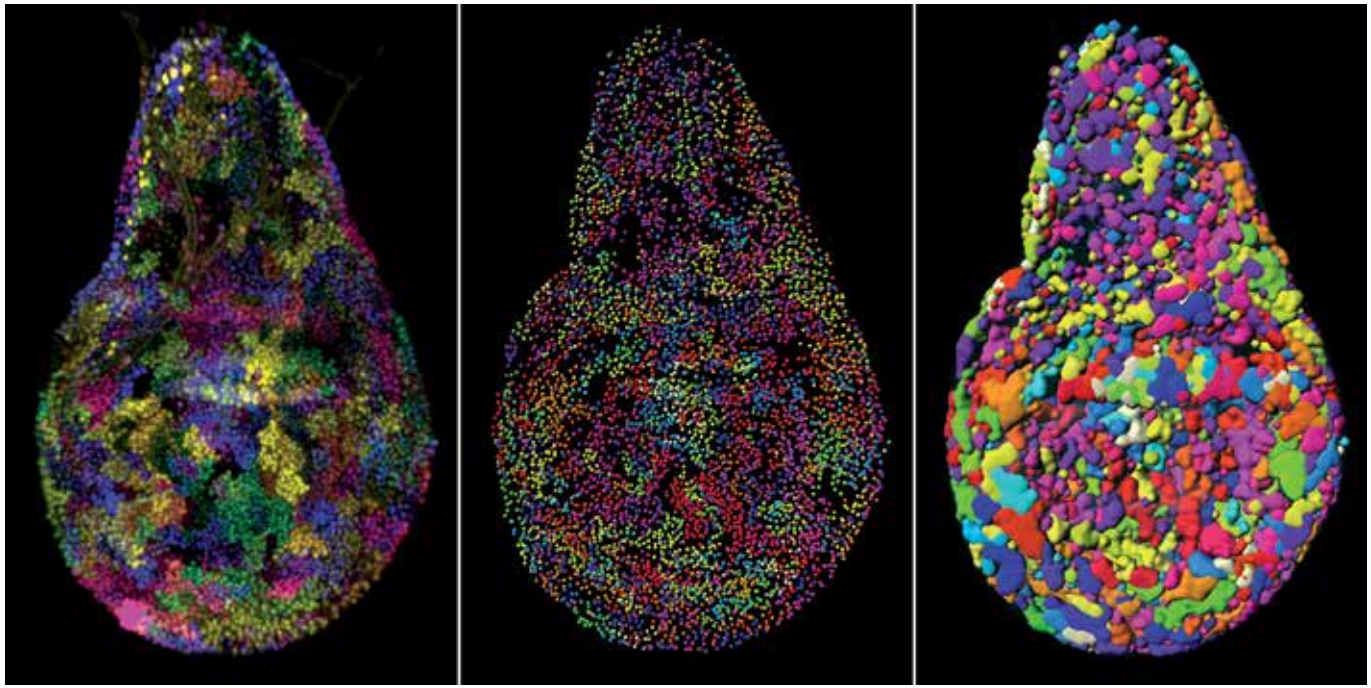


Automatization of detection of the Raeppli clones. *The left panel shows a raw image of an 80h-old wing imaginal disc, 30h after Raeppli activation, acquired using confocal microscopy. Using Imaris XT and Matlab, we first detect all the nuclei and then cluster them according to their signal intensities in different channels, using K-means (middle). The last step is to convert the clusters into 3D surfaces for obtaining volume and spatial position information (right).*

Nouria Hernandez
Professor

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

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 human 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.

RNA polymerase III (pol III) synthesizes small RNAs, all tRNAs and the ribosomal 5S RNA essential for protein translation as well as a number of other RNAs required for the control of RNA polymerase II transcription elongation, maturation of various types of RNA molecules, and other functions. Pol III genes harbor three main types of promoters: type 1 and 2 promoters direct the synthesis of the 5S RNAs and most tRNAs, respectively, and are located downstream of the 5' end of the genes, within the RNA coding region. Type 3 promoters direct the synthesis of a small collection of mostly catalytic RNAs and are located upstream of the 5' end of the genes. Type 3 promoters are very similar to the RNA polymerase II promoters of small nuclear RNA genes. Like them, type 3 pol III promoters contain a "distal sequence element" or DSE, which serves as a transcriptional enhancer, and a "proximal sequence element" or PSE, which constitutes the core promoter. Type 3 pol III core promoters contain in addition a TATA box downstream of the PSE. Type 2 and 3 promoters use common transcription factors, in particular Oct-1, binding to the DSE, the multisubunit complex SNAPc, binding to the PSE, and the TATA box binding protein TBP, which in the case of the pol III type 3 promoters binds to the TATA box. However, whereas the pol II snRNA promoters recruit TFIIB and RNA polymerase II, the type 3 pol III promoters recruit a TFIIB-related factor called Brf2, a SANT domain protein called Bdp1, and RNA polymerase III. One of our research focuses is to understand how the pol II snRNA promoters and the type 3 pol III promoters achieve specific recruitment of the correct RNA polymerase.

Pol III products are abundant and stable. Accordingly, pol III activity is high in proliferating cells, which have to synthesize an entire set of tRNAs and other pol III products at each generation, and lower in quiescent cells, which only have to replace mostly slowly degrading pol III products. Indeed, a hallmark of cancer cells is increased pol III activity. Various regulators of pol III transcription have been identified over the years, but how these regulators interplay with each other, and which of them play a role in various *in vivo* situations, is poorly understood.

A second research focus is to understand how pol III is regulated under various conditions (for example, during the circadian cycle or in response to nutrients) and what the consequences are of pol III deregulation.

In the past two years, we have continued our work along these two main research lines. Completed projects are summarized below.

TWO FORMS OF CELLULAR POLYMERASE III

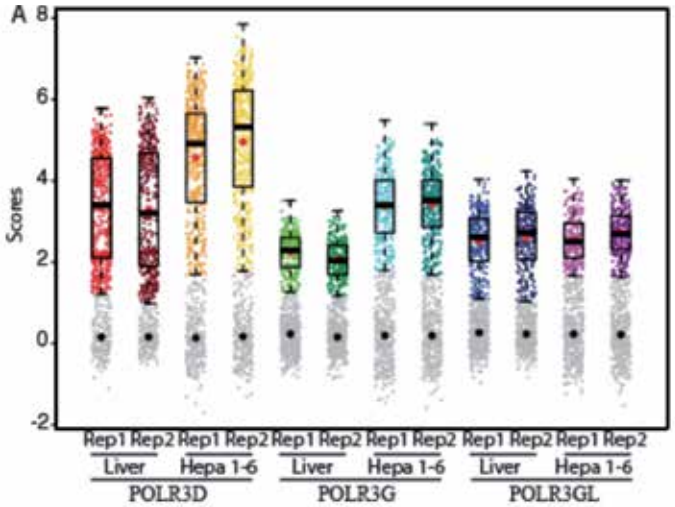
A mass spectrometry analysis of pol III, highly purified from cultured human cells identified all known pol III subunits, as expected, as well as some other proteins, one of them highly similar to the POLR3G pol III subunit but encoded by a different gene. This suggested the possibility that two forms of pol III exist in the cell. Indeed, we and others (Haurie et al. *Proc Natl Acad Sci USA* 2010) could detect these two forms in cells and show that both were transcriptionally active *in vitro*. This in turn raised the possibility that these two forms may have different functions.

We established that the POLR3G and POLR3G-like (POLR3GL) genes arose from a DNA duplication in a common ancestor of vertebrates. We then examined whether the two forms of pol III might target different genes, for example with different types of promoters. We localized, genome-wide, POLR3D, a pol III subunit common to the two forms, as well as POLR3G and POLR3GL, in human cultured cells. We found that the two forms occupied the very same genes and that the proportion of each form was mostly constant from gene to gene, suggesting that the two forms share largely the same targets. Nevertheless, it remained possible that the two forms occupy different genes in different types of cells or tissues, in particular if one of the pol III forms were much more abundant than the other.

We observed that mouse liver and the mouse hepatocarcinoma cell line Hepa 1-6 contain very different ratios of POLR3G over POLR3GL, with liver displaying a low ratio and Hepa 1-6 cells a high ratio. We thus localized POLR3D, POLR3G, and POLR3GL in these two systems and observed that, like in human cells, POLR3G and POLR3GL-containing pol III occupied the same loci. However, pol III genes showed general higher pol III occupancy in Hepa 1-6 cells as compared to liver cells, consistent with pol III transcription being upregulated in cancer cells, and this increased occupancy cold be attributed to POLR3G-containing pol III. Indeed, whereas the levels of POLR3GL were quite similar in normal and cancer cells, the levels of POLR3G were higher in cancer cells. Consistent with this observation, the POLR3G promoter, like the promoters of genes encoding the other pol III subunits, bound the trans-activator MYC, whereas the *POLR3GL* promoter did not. These results suggest that duplication of the POLR3G gene did not lead to two pol III types with different specificities for target genes but rather to two transcription units with different regulation potentials. The POLR3GL gene provides a relatively low but constant amount of protein whereas the POLR3G gene serves to provide increased levels of the subunit when needed, for example upon rapid cellular proliferation.

QUANTIFYING CHIP-SEQ DATA

Chromatin immunoprecipitation followed by deep sequencing (ChIP-seq) experiments are widely used to determine, within entire genomes, the occupancy sites of any protein of interest. In addition, the method allows, in principle, the establishment and comparison of occupancy maps in various cell types, tissues, and conditions. Such comparisons require, however, that samples be normalized. Widely used normalization methods that include a quantile normalization step perform well when factor occupancy varies at a subset of sites, but may miss uniform genome-wide increases or decreases in site occupancy such as may happen for pol III. We developed a spike adjustment procedure (SAP) in which a constant, low amount from a single batch of chromatin of a foreign genome is added to the experimental chromatin. This "spike" chromatin then serves as an internal control to which the experimental signals can be adjusted. We showed that the method improved similarity between replicates and could reveal biological differences, including global and largely uniform changes.



Box plots showing occupancy scores for the POLR3D subunit, common to the two forms of pol III, and the POLR3G and POLR3GL subunits. Replicates (Rep1 and Rep2) samples from liver or Hepa 1-6 cells are shown, as indicated on the x-axis. The y-axis shows scores in log2. Genes considered not occupied are represented by gray dots. The median is indicated by the black horizontal bar, the mean of the pol III occupied genes by the red dot, the mean of the genes not occupied by the black dot. Pol III occupancy is higher in cancer cells as determined from the POLR3D scores and this can be attributed to increased POLR3G-containing pol III.

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Mammalian transcriptional regulation

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, UK 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 was elected member of the European Molecular Biology Organization (EMBO) in 2008. He arrived at the CIG in September 2004 as Full Professor and was named director of the FBM's School of Biology in 2009.

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 called HCF-1 for herpes simplex virus (HSV) host-cell factor-1. It serves as an adaptor protein that links a large number of site-specific DNA-binding proteins with a plethora of chromatin-modifying activities, resulting in both activation and repression of transcription. It also undergoes an unusual proteolytic maturation process that generates two associated HCF-1 subunits that regulate different phases of the human cell cycle: An N-terminal subunit permits cells to progress into S phase for genome replication, and a C-terminal subunit promotes proper segregation of the replicated genome in M phase.

HCF-1 IS CLEAVED IN THE ACTIVE SITE OF O-GLCNAC TRANSFERASE.

HCF-1 is cleaved at a critical glutamate residue located within any one of six 26 amino acid repeated sequences called the HCF-1PRO-repeat. We discovered previously that the enzyme responsible for HCF-1 cleavage is *O*-linked beta-N-acetylglucosamine transferase (OGT), an enzyme previously known only for modification of a large number of cytoplasmic and nuclear proteins by the addition of the sugar N-acetylglucosamine (GlcNAc) to serine or threonine residues in the form of *O*-GlcNAc. OGT not only cleaves but also heavily glycosylates HCF-1. Thus, a single enzyme can both cleave and chemically modify a protein substrate. How an enzyme can achieve such diversity remained unanswered.

In collaboration with Prof. Suzanne Walker of Harvard Medical School, we determined the OGT–HCF-1_{PRO} repeat co-crystal structure. OGT possesses two major domains – a globular glycosylation catalytic domain and a structure containing 13.5 tandem copies of the 34 aa tetratricopeptide repeat (TPR). The co-crystal structure revealed that the TPR domain binds the C-terminal portion of the HCF-1_{PRO} repeat positioning the glutamate cleavage site in the glycosyltransferase active site – a conformation essentially identical to that of a glycosylation-competent peptide substrate. Indeed, conversion of the glutamate cleavage site into serine converts an HCF-1_{PRO} repeat into a glycosylation substrate. Thus, protein glycosylation and HCF-1 cleavage occur in the same active site.

HCF-1 RESIDES ON OVER 5000 PROMOTERS IN HELA CELLS COINCIDING WITH ZNF143, THAP11, YY1 AND GABP TRANSCRIPTION FACTOR OCCUPANCY

HCF-1 was discovered in the 1980's because it associates with the HSV transcriptional activator VP16 and stabilizes the VP16-induced transcriptional regulatory complex for activation of the HSV immediate-early promoters. Since then, we have been interested in understanding its cellular role. In 2013, we had a major advance in this understanding.

Using high-throughput DNA sequencing in combination with chromatin immunoprecipitation (ChIP-seq), we examined the genomic residency of HCF-1 in human HeLa cancer cells. We discovered – to our surprise – that HCF-1 is bound close to over 5000 start sites of transcription of generally active promoters, the majority in a HeLa cell. Examination of the DNA sequences underlying the many HCF-1-binding sites revealed three sequence motifs associated with the binding of site-specific DNA-binding transcription factors: (i) ZNF143 and THAP11, (ii) GABP, and (iii) YY1. Indeed, HCF-1 was located with these four transcription factors at approximately 90% of the more than 5000 HCF-1-bound promoters. These studies have suggested that a relatively small number of transcription factors play a major role in HeLa-cell transcriptional regulation in association with HCF-1.

HIGHLY SYNCHRONOUS TRANSCRIPTIONAL PROGRAMMES DURING MOUSE LIVER REGNERATION

Despite the advent of DNA sequencing in the 1970s, the study of mammalian genome expression remained largely inaccessible owing to the genome's enormous size. Immediate advances came instead from the study of viruses, which display exquisite gene-expression cascades upon infection — thus, the origins of our work on HCF-1.

Today, ChIP-seq can reveal genome-wide mammalian transcriptional programs, but, to rival viruses, well-synchronized programs of gene expression are required. The cascade of gene transcription during the rapid regeneration, within days, of the mammalian liver following its two-thirds resection represents such a synchronized cellular gene expression program. The combination of ChIP-seq and liver regeneration with computational biology is an ideal system to study mammalian genome-wide transcriptional regulation.

We have initiated such a research program. Indeed, the response to partial hepatectomy is rapid and very synchronous. The figure shows the RNA polymerase II (pol II) profiles on three selected cell-cycle genes: the broadly expressed cyclin-dependent kinase Cdk2, the G1-to-S regulator Cyclin D1, and the S-to-M regulator Cyclin A2. The pol II profiles reveal transcription patterns that are consistent with their regulatory

roles. Significantly, not only does pol II appear on the Cyclin D1 and Cyclin A2 genes at the expected times, it also disappears in each case at different points, indicating that all cells transcribing these two genes are shutting off transcription synchronously. We will be pursuing this very robust transcriptional response in future years.

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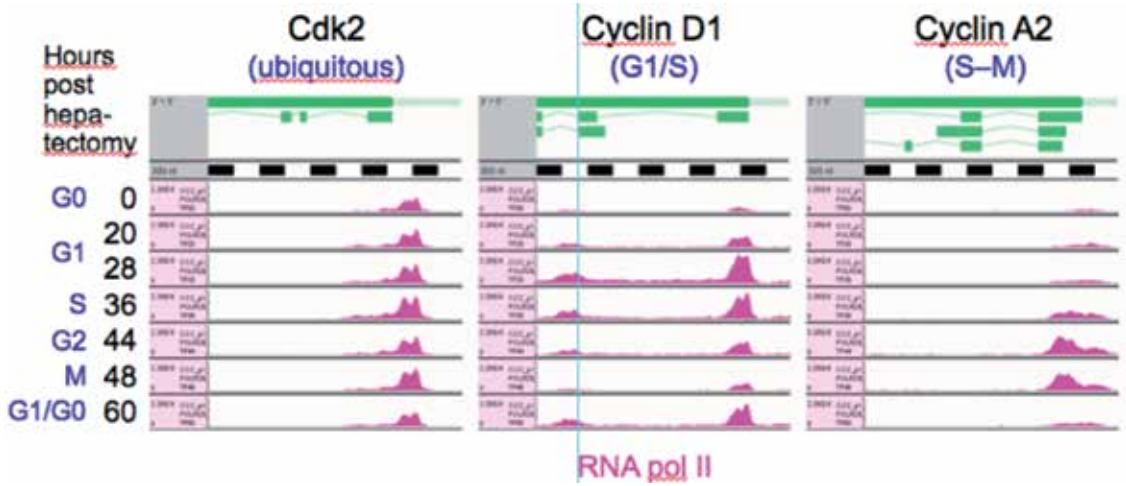
Pol II distribution on three cell-division cycle regulatory genes during mouse liver regeneration, indicating robust entry into and synchrony of the cell-division cycle post partial hepatectomy. Pol II distribution (pink) of the time points and cell-cycle phases indicated to the left is shown.



Henrik Kaessmann
Professor

Functional evolutionary genomics in mammals

Henrik Kaessmann received his PhD in 2001 from the University of Leipzig, for work performed at the Max Planck Institute for Evolutionary Anthropology (Leipzig), and was an EMBO/Emmy Noether postdoctoral fellow at the University of Chicago. He joined the Center for Integrative Genomics as an Assistant Professor in 2003, and was promoted Associate Professor in 2007 and full Professor in 2014. For the research of his group he has received various awards and honors, including the EMBO Young investigator Award (2005), the Friedrich Miescher Award (2010), the Jürg Tschopp Life Science Prize (2014), full EMBO Membership (2014), and the Prix Cloëtta (2014). He has also been awarded with prestigious funding, such as European Research Council (ERC) Starting (2009) and Consolidator (2013) Grants. Since 2010 he has also been an elected group leader and member of the Swiss Institute of Bioinformatics (SIB).

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

In 2009, the Kaessmann group embarked on a major new series of projects that are related to various aspects of gene expression evolution in mammals and center around integrated comparative analyses of large-scale transcriptomic and genomic data for organs from a wide range of mammalian species and vertebrate "outgroup" species (e.g. birds and amphibians). Following initial major studies on protein coding gene expression evolution (Brawand et al. *Nature* 2011; Julien et al. *PLoS Biol* 2012), we published several new transcriptome evolution studies in the past two years. For example, we recently performed the first large-scale evolutionary study of long noncoding RNAs (lncRNAs), an abundant yet overall poorly characterized class of transcripts, and their expression patterns in eleven tetrapod species (Necsulea et al. *Nature* 2014). This work revealed many conserved lncRNAs of different ages, suggested various functions of lncRNAs in different tissues, and highlighted their potentially major contribution to mammalian phenotypic evolution (e.g. in the emergence of the placenta). Our work on small RNAs unraveled the functional evolution of mammalian microRNAs and mechanisms underlying their origination (Meunier et al. *Genome Res* 2013; Warnefors et al. *Genome Biol* 2014).

We have also continued our efforts to unravel the origins and functional evolution of mammalian sex chromosomes using our large-scale datasets. In particular, to understand the functional evolution of Y chromosomes, we traced in detail the evolution of the Y chromosome across 15 representative mammals based on high-throughput genome and transcriptome data (Cortez et al. *Nature* 2014). We thus un-covered the independent (yet concomitant) origins of two different sex determination systems in mammals, the evolutionary dyna-mics of Y gene repertoires and chromosomal regions, and that many Y genes have regulatory functions and were preserved because of dosage constraints. Finally, we have also unraveled the mechanisms and cellular source underlying the widespread "promiscuous" transcription in the mammalian testis (Soumillon et al. *Cell Rep* 2013), lending strong support to the hypothesis that the peculiar chromatin environment in the testis facilitated the emergence of new genes (the "out of testis" scenario). Given our contributions to the field of gene expression evolution, we were invited to write a reference review on this topic (Necsulea & Kaessmann *Nat Rev Genet* 2014).

In addition to these major themes, we have been working on several other key aspects of mammalian gene expression evolution, including the functional evolution of alternative splicing (Bilican et al. *in preparation*), untranslated regions (UTRs), and circular RNAs. Finally, we have also begun to open up major new research avenues. For example, facilitated by a newly awarded ERC Consolidator Grant, we have begun to add the developmental dimension to our work by gene-rating and analyzing extensive transcriptome data for dense ontogenetic time course sample series from representative mammals and tetrapod outgroup species. We will thus be able to go beyond the analysis of the molecular evolution of (adult) organ physiologies and begin to investigate the molecular basis of the evolution of organ anatomies.

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Liliane Michalik
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Transcriptional control of tissue repair, carcinogenesis and vascular functions by PPARs

Liliane Michalik received her PhD from the University Louis Pasteur of Strasbourg in 1993, for work on microtubule-associated proteins in the group of Jean-François Launay, INSERM. In 1994, she joined the group of Walter Wahli at UNIL for her post-doctoral training, during which she initiated a research project aimed at elucidating the roles of the nuclear hormone receptors PPARs in skin homeostasis and repair. Between 1996 and 2002, she persued her research in the same field as "Maître Assistant", then "Maître d'Enseignement et de Recherche" at UNIL. She arrived at the Center for Integrative Genomics in 2003 as "Maître d'Enseignement et de Recherche", is MER-privat docent since 2008 and also Vice-director of the "Ecole de biologie" since November 1st, 2011.

The skin offers an effective permeability barrier and provides protection against harmful conditions such as microbial invasion, mechanical damage, xenobiotic poisoning or solar radiation. In response to an injury, a cascade of events is initiated, which is aimed at repairing the damage in a life saving process, but which does not lead to complete regeneration. The response of the skin to excessive UV exposure includes inflammation, disruption of the epidermal barrier function, premature aging and UV-induced carcinogenesis. Murine skin is a valuable model, widely used to study organ repair and tumor development: two situations that share many cellular and molecular similarities.

PPARα,β and γ are nuclear hormone receptors discovered in the early 1990's. PPARα major functions are the regulation of energy homeostasis, of cholesterol, amino acid and urea metabolism, and of inflammatory reactions. PPARβ is involved in the control of energy homeostasis and in the functions of skeletal and heart muscle. PPARγ is mostly known as a major actor in adipose tissue differentiation and metabolic functions. It is also involved in the regulation of glucose and cholesterol metabolism, heart functions and it has anti-inflammatory functions.

In collaboration with the group of Prof. Walter Wahli, we have described a number of roles for PPARβ in skin homeostasis and repair. We showed that PPARβ promoted keratinocyte differentiation, controlled their proliferation, favored their resistance to apoptosis, and promoted their directional migration towards the damaged area. Consistent with these observations, experimentally prolonged expression of PPARβ accelerated skin wound closure, whereas premature down-regulation of PPARβ expression resulted in a transient but significant delay in wound closure. We also described that PPARβ regulated the interactions between epidermal and dermal compartments in healing wounds, through controlling the activity of the IL-1 pathway. More recently, we unveiled that ultraviolet (UV)-induced PPARβ activity stimulated the expression and activity of the oncogene cSrc in mouse epidermis. Increased Src kinase activity enhanced the EGFR/Erk1/2 signaling pathway, promoting epithelial-to-mesenchymal transition (EMT) marker expression in keratinocytes. Consistent with this procarcinogenic function of PPARβ, *PPARβ*-null mice developed fewer and smaller skin carcinomas (skin tumors of keratinocyte origin), and inhibition of PPARβ by an antagonist prevented UV-dependent Src stimulation. Importantly, bioinformatics analysis suggested that the expression of PPARβ correlated with the expression of Src and EMT markers in human skin squamous cell carcinoma. Moreover, linear models applied to several human epithelial cancers revealed an interaction between PPARβ and Src at the transcriptional level in human tumors.

Whether PPARs are also involved in the development of melanoma, a skin tumor of melanocyte origin, is under current investigation. We i) explore the therapeutic potential of PPARγ activation in melanoma, as a monotherapy but also as adjuvant therapy with the BRAF/MEK kinase inhibitors, ii) investigate the molecular cascades by which PPARγ ligands exert their effect in melanoma cells and tumors, iii) analyze PPARγ specific expression profiles in the course of tumor progression in patient nevi and melanoma samples, in order to evaluate its potential as a diagnosis marker and as a therapeutic target.

In addition to orchestrating keratinocyte functions, PPARβ also regulates blood vessel homeostasis. The remodeling of quiescent vessels, associated with an increase in permeability, vasodilatation and edema, are hallmarks of inflammatory disorders. Using a combination of wildtype, germline and conditional PPARβ mutant mice, as well as human endothelial cells, we have investigated whether the nuclear hormone receptor PPARβ was involved in the regulation of this type of remodeling. Acute vascular hyperpermeability (AVH) and dilatation of dermal microvessels were severely compromised in *PPARβ*-deficient mice. Selective deletion of the PPARβ-encoding gene in endothelial cells *in vivo* similarly limits dermal AVH and vasodilatation, providing evidence that endothelial PPARβ is the major player in regulating acute dermal microvessel remodeling. Furthermore, endothelial PPARβ deletion – but not smooth muscle cell deletion – lead to reduced systemic anaphylaxis, the most severe form of allergic reaction, in which acute vascular response plays a key role. PPARβ-dependent AVH activation likely involves the activation of MAPK and Akt pathways, and lead to downstream destabilization of endothelial cell-to-cell junctions. These results unveiled a novel function of PPARβ as a direct regulator of acute vessel permeability and dilatation, but also provide evidence that antagonizing PPARβ represents an important strategy to consider for moderating acute diseases with altered endothelial integrity, such as acute inflammatory and allergic disorders.

These results benefit to basic research by deepening our understanding of PPAR functions, and by providing insights into the molecular mechanisms underlying skin responses to UV and to injuries, as well as in the vasculature. Besides these fundamental aspects, our work is of preclinical interest by investigating novel pathways that may inspire future development of more efficient therapeutics for skin diseases and allergic reactions.

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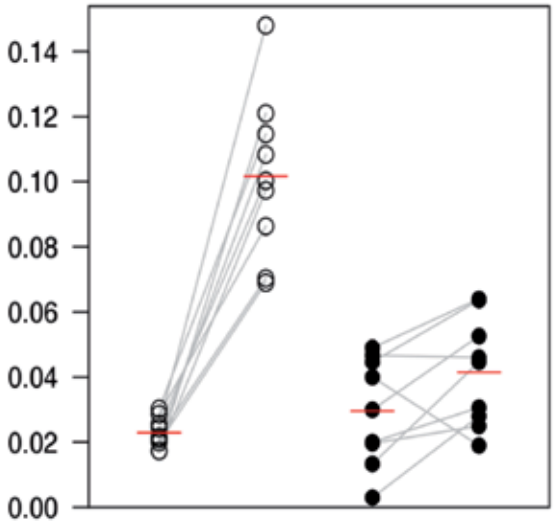

PPARβ/δ loss-of-function severely compromises acute vascular hyperpermeability in PPARβv/δ-/- mice, despite normal microvessel density and architecture. *An acute response of dermal microvessels was induced by injecting vasoactive agents (VEGF-A, Not shown: Thrombin, Histamine) in the dermis of PPARβ/δ$^{-/-}$ and PPARβ/δ$^{+/+}$ mice. Acute hyperpermeability was quantified by Evans blue extravasation. Dots: individual animals; Black lines: individual responses to treatment; Red lines: mean per group.*

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Assessing the Impact of Copy Number Variants

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 University of Lausanne in 1993. After postdoctoral, scientist and "maître-assistant" positions at Harvard Medical School in Boston, the Telethon Institute of Genetics and Medicine (TIGEM) in Milan and the University of Geneva Medical School, respectively, he joined the Center for Integrative Genomics at its creation in October 2004. He heads this Institute since January 1st, 2015.

THE 16p11.2 REARRANGEMENTS

Copy number variants (CNVs) significantly contribute to phenotypic variation and disease predisposition in humans. For example, the last 15 million years of hominoid evolution have seen a rapid integration of segmental duplications or low-copy repeats in two of the most proximal bands of the short arm of human chromosome 16 (chromosomal bands 16p11.2 and 16p12.1). While we showed that these evolutionary novelties support the emergence of new regulatory elements (Giannuzzi et al. *Genome Res* 2014), these genome reconfigurations also set these regions at risk of recurrent pathogenic rearrangements through non-allelic homologous recombination. Different recurrent rearrangements have been described within this interval, including a proximal ~600 kb (kilobase) BP4-BP5 (breakpoint) deletion. With a prevalence of ~0.05% in the general population this CNV is one of the most frequent known etiologies of autism spectrum disorder (ASD). Others and we have demonstrated that it also predisposes to a highly penetrant form of obesity and macrocephaly. A mirror phenotype is observed in carriers of the reciprocal duplication, who present a high risk of being underweight, microcephalic and/or schizophrenic. We investigated the variation in brain anatomy of 16p11.2 BP4-BP5 deletion and duplication carriers. Beyond gene dosage effects on global brain metrics, we showed that the number of genomic copies negatively correlated to the gray matter volume and white matter tissue properties in cortico-subcortical regions implicated in reward, language and social cognition. Despite the near absence of ASD or schizophrenia (SCZ) diagnoses in our 16p11.2 cohort, the pattern of brain anatomy changes in carriers spatially overlaps with the well-established structural abnormalities in ASD and SCZ. Using measures of peripheral mRNA levels, we confirm our genomic copy number findings. This combined molecular, neuroimaging and clinical approach, applied to larger datasets, will help interpret the relative contributions of genes to neuropsychiatric conditions by measuring their effect on local brain anatomy (Maillard *Mol Psy* 2014).

Rolandic Epilepsy (RE) is the most common idiopathic focal childhood epilepsy. Its molecular basis is largely unknown and a complex genetic etiology is assumed in the majority of affected individuals. We revealed a significant excess of the 600 kb BP4-BP5 duplication in patients with typical and atypical RE compared with the prevalence in European population controls ($P = 4.5 \times 10^{-9}$; OR 35.5). In contrast, the 16p11.2 duplication was not detected in 1738 European epilepsy patients with either temporal lobe epilepsy and genetic generalized epilepsies, suggesting a selective enrichment of the 16p11.2 duplication in idiopathic focal childhood epilepsies (Fisher's exact test P = 2.1 x 10-4). In a subsequent screen among children carrying 16p11.2 600 kb BP4-BP5 rearrangements we identified three patients with RE-spectrum epilepsies in 117 duplication carriers (2.6%) but none in 202 carriers of the reciprocal deletion. Our results suggest that the 16p11.2 duplication represents a significant genetic risk factor for typical and atypical Rolandic epilepsy.

We then explored the transcriptome-wide effect of the reciprocal 16p11.2 structural rearrangements. We profiled the genome-wide transcriptome of 81 individuals carrying reciprocal 16p11.2 BP4-BP5 CNVs, as well as 29 control individuals. Transcript perturbations correlated with clinical endophenotypes and were enriched for genes associated with ASD and ciliopathies. Ciliary genes expression was also perturbed in orthologous mouse models, raising the possibility that ciliary dysfunction contributes to 16p11.2 pathologies. In support of this hypothesis, we found structural ciliary defects in the CA1 hippocampal region of 16p11.2 duplication mice. Moreover, using an established zebrafish model we show genetic interaction between *KCTD13*, a key driver of the mirrored neuroanatomical phenotypes of the 16p11.2 CNV and ciliopathy-causing genes. Strikingly, overexpression of BBS7 rescues head size and neuroanatomical defects of *kctd13* morphants, while suppression or overexpression of *CEP290* rescues phenotypes induced by *KCTD13* under- or overexpression, respectively. Our data suggest that dysregulation of ciliopathy genes contributes to the clinical phenotypes of this CNV.

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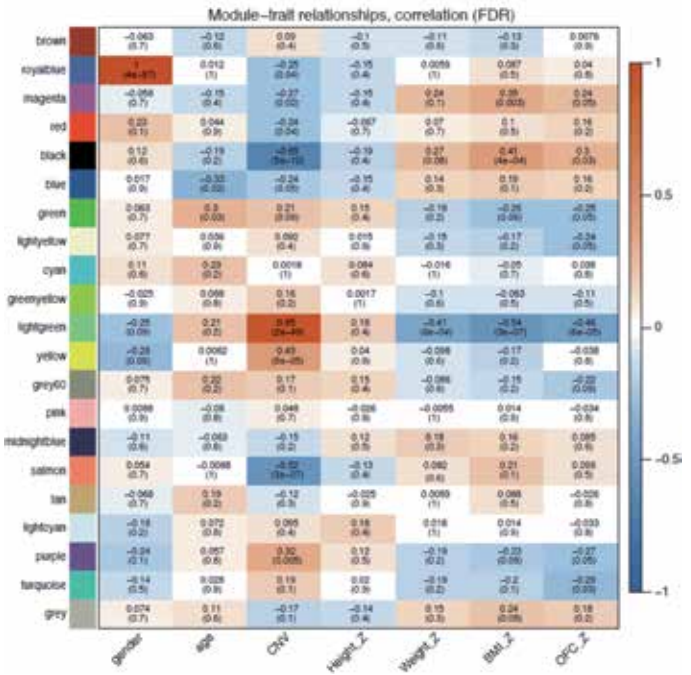

16p11.2 transcriptome expression modules and traits. *Relationships between weighted gene co-expression module (each color coded line) and gender, age, number of copies of the 16p11.2 CNV (CNV) and Z scores for height, weight, BMI and HC (OFC). Both the Pearson correlation coefficient (top) and FDR (bottom in bracket) estimated as Benjamini-Hochberg adjusted p-value are indicated. The "light-green module" (51 genes) is anticorrelated with weight, BMI and HC and includes all 22 imbalanced 16p11.2 genes expressed in LCLs. The "black" module (264) groups genes involved in RNA biosynthesis/ regulation, gene expression/transcription and cilium morphogenesis. The "purple" and "salmon" modules are enriched in genes regulating RNA splicing (191 and 131 genes), while gene expression regulation by chromatin modification/organization characterizes the "yellow module" (444 genes including* CEP290*). Among these, the purple module is also anticorrelated with HC.*

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Functional transitions of DNA structure

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

The main interest of our group is directed towards understanding underlying physical reasons responsible for the organization of genomes, starting with bacterial nucleoids and ending with topological domains in interphase chromosomes of higher eukaryotes. We are especially interested in topological effects resulting from the trivial fact that long polymer chains cannot freely pass through each other. Numerical simulations constitute the main method applied by our group. During the last two years (2013-2014) we addressed the following aspects of genome organization:

CONSEQUENCES OF DOUBLE-STRANDED BREAKS FOR THE INTERACTIONS BETWEEN SISTER CHROMOSOMES IN BACTERIAL CELLS

Several earlier studies have shown that due to entropic reasons sister chromosomes in bacterial cells spontaneously segregate from each other, which is the necessary step before bacterial division. However, this spontaneous segregation should be abolished for the process of double-strand breaks by homologous recombination, since the efficient search of homology requires that broken ends can freely contact all regions in the undamaged sister chromosome. To elucidate this problem, we tested by numerical simulations what happens when one of circular sister chromosomes is linearized as a consequence of double-strand break. Our numerical simulations revealed that as long as the two sister chromosomes in bacterial nucleoids maintain their circular topology they very effectively exclude each other and there is very little of intermingling between them. However, when one of the chromosomes is linearized due to X-ray irradiation, for example, the entropy starts to favour intermingling of ends of linearized chromosome with the intact circular homologous chromosome. Of course the possibility of intermingling is the necessary prerequisite enabling DNA repair of double strand breaks by homologous recombination between broken ends and intact sister chromosome. We believe that our simulations solved the apparent paradox, where two sister chromosomes need to efficiently segregate to permit division yet after a double-strand break they do need to have the possibility to intermingle (Dorier & Stasiak *Nucleic Acids Res* 2013).

UNDERSTANDING FORMATION OF TOPOLOGICAL DOMAINS IN INTERPHASE CHROMOSOMES OF HIGHER EUKARYOTES

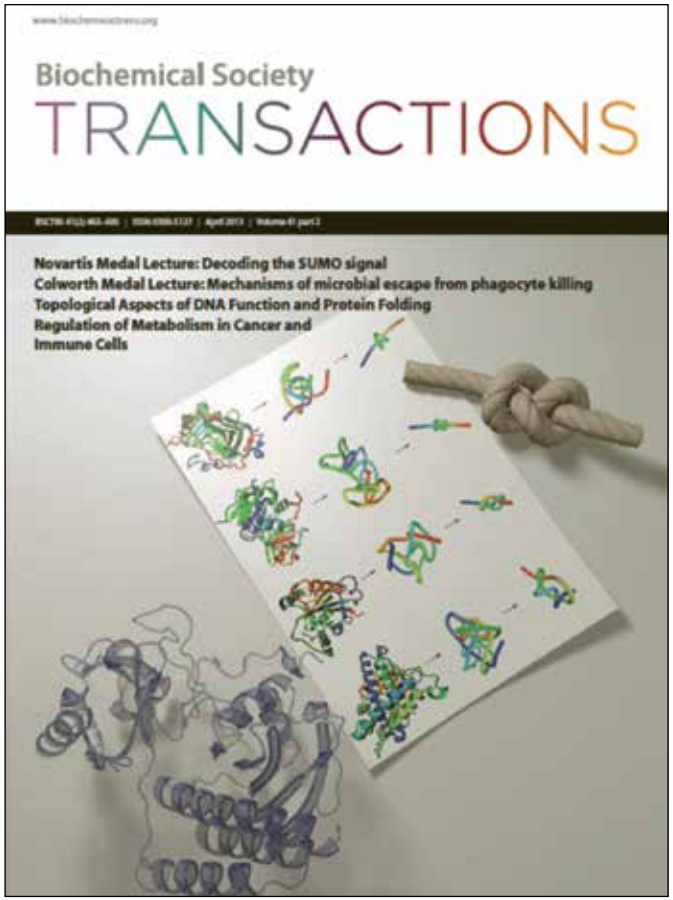
Thanks to the progress of high-resolution 3C (Chromosome Conformation Capture) methods it was revealed in 2012 that interphase chromosomes of higher eukaryotes are composed of sequential blocks with high frequency of internal contacts. The average sizes of these blocks, known also as topological domains, are of about 1 Mb. It is not known yet what is the arrangement of chromatin fibres in these blocks and what is the mechanism responsible for their formation. Inspired by the known fact that bacterial chromosomes are composed of supercoiled topological domains we have performed Brownian dynamics simulations of the situation where chromatin fibres between borders of individual topological domains are supercoiled. Our simulations revealed that transcription-induced supercoiling very well explains formation and all known properties of topological domains (Benedetti et al. *Nucleic Acids Res* 2014).

EFFECTS OF SUPERCOILING ON ENHANCER-PROMOTER INTERACTION

The discovery of topological domains was followed by the observation that enhancer-promoter interactions involve almost exclusively enhancers and promoters located within the same topological domain. This observation was somewhat surprising since enhancers can interact with many promoters, such as these located in neighboring topological domains. We decided to test whether supercoiling assures that enhancers interact almost exclusively with promoters located in the same topological domain. Our Brownian dynamics simulations revealed that when neighbouring chromatin loops in modelled chromosomes were not supercoiled, then enhancers were frequently interacting with promoters located in neighbouring loops. However, when the chromatin loops were supercoiled the enhancers contacted almost exclusively promoters located in the same chromatin loop. These results additionally supported our proposal that topological domains in interphase chromosomes are supercoiled (Benedetti et al. *Nucleic Acids Res* 2014).

STUDIES OF PROTEIN KNOTTING

The polypeptide chain of some proteins is knotted. In a collaborative project, involving mathematicians and biophysicists, we have analyzed all deposited protein structures for the presence of knots. Our novel form of analysis permitted us to obtain knotting fingerprints of various proteins. We observed that, despite large sequence variance, the precise knotting pattern is highly conserved within the same protein family and sometimes the conservation involves separate families. High conservation of knotting patterns naturally suggests that knots in proteins have a specific function. We continue our studies aimed at understanding the function of knotted regions in some proteins (Millett *Biochem Soc Trans* 2013; Rawdon et al. *Biochem Soc Trans* 2013; Jamroz et al. *Nucleic Acids Res* 2014).



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Genetics of sleep and sleep disorders

Mehdi Tafti received his PhD from the University of Montpellier (France) in 1991 and spent 3 years as 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, where he is a Full Professor since 2011. He also co-directs the Center for Investigation and Research in Sleep (CIG-CHUV) since 2006.

MOLECULAR 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 have established an in vitro model of sleep amenable to cellular and molecular analyses of sleep. Primary cortical cultures are used in electrophysiology and molecular studies. Finally, we are interested in the pharmacology of vigilance states in mice as a model to understand the mode of action of drugs used to treat various sleep disorders in humans.

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. 5064 subjects from the Lausanne population have been screened by sleep-related questionnaires and 2160 of them underwent the standard polysomographic recording. All subjects have been genotyped with hundred of thousands of genetic variants and have 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, genome-wide associations, and exome sequencing. 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. We have also reported the first mutation causing a familial form of narcolepsy. Future plans include genome-wide association study in sleepwalking and large exome sequencing in narcolepsy.

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Physiological genomics of energy homeostasis

Bernard Thorens received his PhD from the University of Geneva for studies on the biosynthesis of immunoglobulins in pre-B lymphocytes. He did a first postdoctoral fellowship in Geneva, working on hematopoietic growth factors with Pierre Vassalli. In 1986 he joined the group of Harvey F. Lodish at the Whitehead Institute for Biomedical Research in Cambridge (USA) as a postdoctoral fellow. In 1991 he came back to Switzerland to take a Career Development award from the Swiss National Science Foundation and to establish his laboratory at the Department of Pharmacology and Toxicology. Since 2002 he is Professor of Physiology and joined the Center for Integrative Genomics in 2005. His work has been recognized by several awards, including the Friedrich Miescher award, the Cloëtta award, and the Albert Renold award of the European Association for the Study of Diabetes. His work is supported by Swiss and European grants, including an advanced research grant from the European Research Council.

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 number; impairment of these processes underlie the pathogenesis of type 2 diabetes.

IGF-2/IGF-1R AUTOCRINE LOOP

We are continuing the study of an IGF2/IGF-1R autocrine loop that operates in beta-cells to control their proliferation and their secretion capacity, and to protect them against apoptosis. The activity of this autocrine loop is controlled by the gluco-incretin hormones GLP-1 and GIP, which increase IGF-1R expression, and by nutrients (in particular glutamine) which increase IGF-2 biosynthesis and secretion. This autocrine loop is therefore well designed to control beta-cell mass in response to nutrition-related cues, glutamine and gluco-incretin hormones.

The physiological role of this autocrine loop is being studied, using mice with beta-cell-specific inactivation of the IGF-2 gene (ßIGF2KO mice). Our data show that IGF-2 is required to preserve beta-cell mass and function during ageing and for normal beta-cell mass expansion during pregnancy, a defect caused by impaired estrogen action, which involves down-regulation of miR388-3p and de-repression of IGF-1R expression. We also showed that beta-cells from ßIGF2KO mice displayed a markedly reduced expansion in response to pharmacologically induced insulin resistance.

A SYSTEMS BIOLOGY APPROACH TO BETA-CELL FUNCTIONAL ARCHITECTURE

As part of a European program (IMIDIA), we are performing a Systems Biology investigation of beta-cell plasticity in response to metabolic stress. This involved the study of 6 different strains of mice, which were fed two different diets for 4 different periods of time. The mice were then extensively phenotyped for glucose homeostasis, islet transcriptomic (RNASeq), and islets and plasma lipidomic analysis. Bioinformatic analysis has now generated a new view of the functional modules underlying the adaptation – or failure to adapt – of beta-cells in response to metabolic stress. This new beta-cell functional map forms the basis of the identification of novel mechanisms that control beta-cell function and number, and could constitute new intervention sites for the treatment of diabetes. We are currently focusing our investigation on two genes from a gene module that is strongly correlated with *in vivo* insulin secretion.

BRAIN GLUCOSE SENSING AND THE CONTROL OF GLUCOSE HOMEOSTASIS

The brain critically depends on glucose as a source of metabolic energy and several brain areas, in particular the hypothalamus and brainstem, contain glucose sensitive neurons that control glucose and energy homeostasis. Identifying these glucose sensing cells, the molecular mechanisms they use to sense glucose, and the circuits they form to control these homeostatic functions may lead to a better understanding of the pathogenesis of obesity and diabetes.

Glut2 neurons and glucodetection

The glucose transporter isoform Glut2 is involved in central glucose sensing and the control of glucose and energy homeostasis. We are investigating the physiology of mice with brain-specific Glut2 inactivation (NG2KO mice). We showed that Glut2 in the nervous system is required for the control by glucose of both the sympathetic and parasympathetic nerve activities. We showed that absence of glucose-stimulated parasympathetic activity prevents normal beta-cell expansion in the postnatal period in NG2KO mice leading to reduced beta-cell mass in adult mice. This leads to late-onset glucose intolerance due to a defect in glucose-stimulated insulin secretion. We have thus identified a functional link between central glucose-dependent control of autonomic innervation and the long-term control of glucose homeostasis through a regulation of beta-cell mass in the perinatal period.

Using mice that express a fluorescent protein under the control of the Glut2 promoter, we identified and functionally characterized Glut2 neurons of the nucleus tractus solitarius (NTS). These are GABAergic interneurons that are activated by hypoglycemia, and which project to the dorsal motor nucleus of the vagus. Using mice which express channelrhodopsin2 in Glut2 neurons, we showed that pulses of blue light activate the firing of these neurons in acute brain slices. When these neurons are similarly activated in living mice, they increase parasympathetic nerve activity and glucagon secretion. These studies demonstrate that the NTS Glut2 neurons participate in the response to hypoglycemia and the triggering of counterregulatory hormone secretion. This may represent an important site involved in hypoglycemia-associated autonomic failure (HAAF), a major problem linked to the insulin treatment of type 1 and type 2 diabetes.

BXD mice to identify QTL controlling counterregulatory response

To identify novel genes controlling the response to hypoglycemia, we screened forty strains of recombinant inbred BXD mice for their

response to 2-deoxyglucose-induced neuroglucopenia. Plasma glucagon, corticosterone, epinephrine and norepinephrine levels were measured as well as total pancreatic insulin and glucagon levels. Hypothalamus and brainstem from the same forty non-treated BXD mice were prepared for RNA extraction and RNASeq analysis. Genetic and genomic data were combined to identify QTL and single genes controlling glucagon, corticosterone, and catecholamine secretion. Physiological studies are ongoing to finalize the characterization of a novel gene, expressed in the hypothalamus, which regulates glucagon secretion.

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NCCR Frontiers in Genetics
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ERC Advanced Grant (PI)
Project IMIDIA
Project BetaBat

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Walter Wahli
Professor emeritus

The multifaceted roles of PPARS and micronutrients in health and disease

Walter Wahli is Professor emeritus at the University of Lausanne and Professor of Metabolic Disease in Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore. He obtained his PhD in 1977 at the University of Bern. He has been postdoctoral fellow at the Department of Embryology, Carnegie Institution of Washington in Baltimore, USA, and Visiting Associate at the National Institutes of Health (NIH), Bethesda, USA. He was appointed Full Professor and Director of the Institute of Animal Biology of the University of Lausanne in 1980. He is also the Founder Director of the Center for Integrative Genomics at Lausanne. He co-discovered the medically relevant PPARs and has demonstrated their central physiological significance. He has received several awards for his findings, the more recent being the Lifetime Achievement Award from the Faculty of Biology and Medicine, University of Lausanne (2011) and the *Chaire d'Excellence Pierre de Fermat*, Toulouse France (2014).

We are deepening our understanding about how the nuclear receptors Peroxisome Proliferator-Activated Receptors (PPARs) control genes that regulate metabolism, in the hope of developing therapeutic targets for metabolic diseases. PPARs, which are activated by fatty acids, have emerged as moderators of systemic and cellular metabolic functions, and as links between lipid signaling and inflammation, both involved in metabolic diseases.

PPARα-DEPENDENT TRANSCRIPTIONAL REGULATION OF MILK LIPID CATABOLISM

Most of our knowledge on the role of the three PPAR isotypes (α, β/δ, γ) in lipid catabolism is based on studies conducted with adult mouse models, which limits our understanding of perinatal energy metabolism in the not yet completely differentiated young liver. Insofar, whether lipid catabolism at birth is developmentally programmed or is an adaptive response requiring an external stimulus (i.e. milk suckling) remains an open question. While testing if milk fatty acid oxidation is regulated via PPARs in response to postnatal milk suckling, we observed a stronger PPARα activity at labor, before exposure of the pups to milk. This finding suggests that PPARα governs a developmental, anticipatory control of milk lipid metabolism already in the fetus. The knowledge gained from this study may provide novel interventional opportunities to alleviate the metabolic perturbations associated with preterm births, and may offer new clues to understand the fetal origin of metabolic diseases.

HOW IS PPARβ/δ IMPLICATED IN NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

We propose to evaluate the role of inter-organ signalling that takes place between the liver and other metabolic organs to elucidate the impact of liver dysfunctions (NAFLD and NASH) on whole body physiology. To dissect this interplay, we use a mouse model that lacks the expression of PPARβ/δ and, in the near future, whose PPARβ/δ expression is suppressed specifically in the liver (hepatocytes) only. These mice will be fed diets (high fat, high fat & high sucrose) that induce the accumulation of lipids in the liver (fatty liver). Based on preliminary data, we anticipate that control mice will develop a 'classical' NAFLD/NASH (nonalcoholic steatohepatitis) phenotype that may evolve into hepatocellular carcinoma (HCC), whereas PPARβ/δ liver knockouts will be protected. Using this model, we hope to unveil mechanisms that participate in the development of hepatic steatosis and HCC, which may suggest novel targets for interventions.

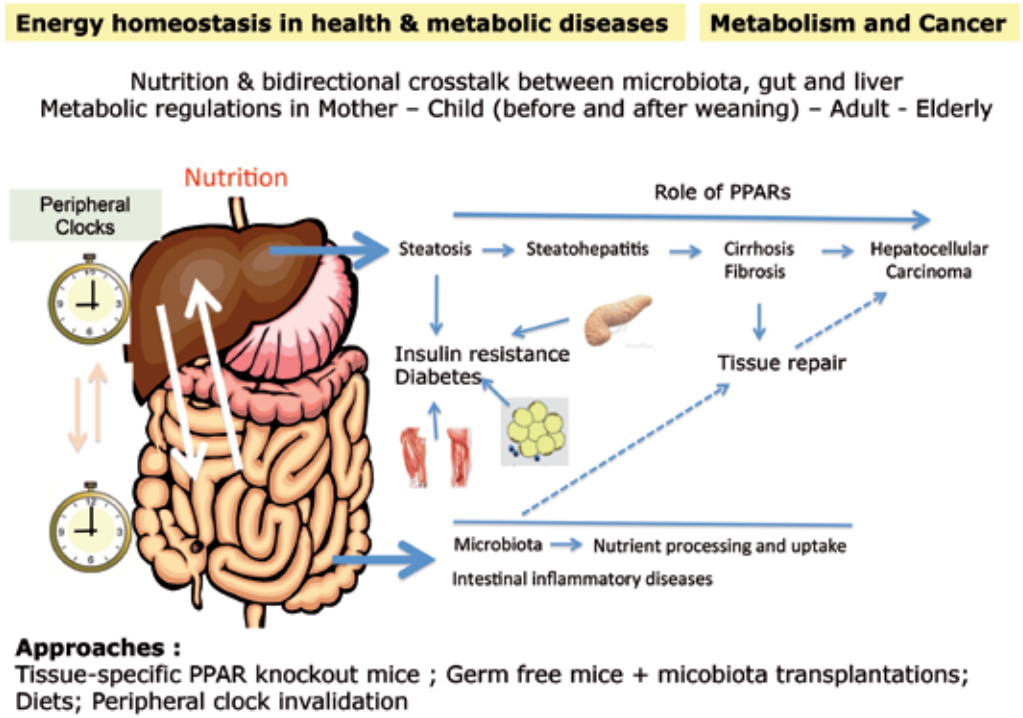
ENTEROCYTE LIPID METABOLISM AND HOST-MEDIATED CHANGES IN GUT MICROBIOTA COMPOSITION

Using mouse models, we aim to address intestinal functions related to lipid absorption and metabolism in health and diseases. We investigate the effects of intestine-specific null mutations of PPARs on the gut microbiota composition, thereby elucidating the mechanisms by which PPARs contribute to the host-to-microbe crosstalk. We hypothesize that dietary conditions would impact the gut microbiota landscape corresponding with a distinctive intestinal gene expression signature and that PPARs play a central role in connecting diet-microbe-host communication by functioning as lipid and environment sensors. This research addresses important questions related to good health-promoting nutrition with the potential to cause paradigm shifts in our understanding of host-microbe crosstalk. We will seek translation into the clinics along with the development of microbiota-based diagnostic and therapeutic options for obesity and type 2 diabetes.

CIRCADIAN CLOCKS AND REGULATION OF THE CROSSTALK BETWEEN ORGANS

The circadian clock is a cell-intrinsic molecular mechanism that regulates the expression of physiologically important genes in a 24-hour daily cycle in response to external timing cues.

The central clock in the brain is responsible for receiving light input, whereupon it synchronizes peripheral clocks in other tissues, including liver, intestines and skeletal muscle. Using mouse models with organ-specific knockout of the clock function, we study the consequences of deregulating peripheral "clock" genes in intestine or liver. We want to deepen our understanding of the role of liver and intestine clocks and how aging and diet impact whole body physiology when the clock dysfunctions in a single specific organ/tissue. Does the failure of the clock in the gut affect liver physiology and vice versa, does the liver clock influence intestinal functions? Using tissue-specific invalidation of PPARs, this research will also address how these transcription factors interact with the clock and whether this interaction is tissue-specific. It should also unveil whether disruption of the crosstalk between the clock and PPARs promotes metabolic alterations and associated diseases.



Nutrition and the crosstalk between metabolic organs. Nutritional excesses are recognized as causes of health problems worldwide. They result into dysfunctioning of metabolic organs and how they communicate between each other, which can result in metabolic diseases.

Publications

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Ioannis Xenarios
Professor ad Personam

Ioannis Xenarios is the Director of two groups within the SIB (Swiss Institute of Bioinformatics): the Vital-IT Group in Lausanne as well as the Swiss-Prot Group in Geneva. He is Full Professor ad Personam at the University of Lausanne since August 2010, affiliated with the CIG of the University of Lausanne, and Professor titulaire at the UNIGE Chemistry and Biochemistry Department since August 2014. He received a PhD in immunology at the Ludwig Institute of Cancer Research and the Institute of Biochemistry from the University of Lausanne. He worked on the development of the Database of Interacting Proteins (DIP) under the supervision of Prof. David Eisenberg at the University of California Los Angeles. He then became the head of Translational Bioinformatics at Serono (now Merck Serono) where his group developed computational methodologies in the area of proteomics, microarray and genetics. He was one of the Principal Investigators of the EU-funded ENFIN project aiming at providing methods in dynamical systems modeling. During the last six years, Prof. Xenarios and his team have been involved in several systems biology research projects for providing the basic supporting functions and infrastructure, as well as research activity in the area of network and predictive biology function. His team contributes to collaborative projects funded at the national, European and international level, by SystemsX.ch, IMI-JU (IMIDIA), the FNS, the NIH through the UniProtKB/Swiss-Prot activities, amongst others.

Vital-IT

His group is composed of 56 FTE in Vital-IT and 63 FTE in Swiss-Prot that help shaping the future of research in both biology and medicine.

VITAL-IT

Vital-IT maintains a competency centre in bioinformatics and computational biology, composed of 58 multidisciplinary scientists and technical staff, including 14 bioinformaticians embedded in experimental laboratories. A collegium of 8 senior scientists maintains and structures the different departments of Vital-IT.

Vital-IT's mission

Operate high-productivity computational and storage resources for the UNIL, EPFL, UNIGE, UNIFR, UNIBE

Provide high-quality access to computational expertise and bioinformatics competencies

Train life/biomedical scientists and embedded bioinformaticians in the use of HPC and in bioinformatics software development

Maintain and develop computer algorithms for life and medical sciences

Perform research within Vital-IT and with other research groups on both computing and advanced algorithmic design.

Computational infrastructure

Vital-IT maintained in 2013 a total storage capacity of over 2.3 Peta-bytes, with more than 5500 CPUs. In 2014 Vital-IT maintains a storage capacity of 5 Petabytes and 5000 CPUs.

Access

The number of Vital-IT users has increased from 546 in 2012 to 671 in 2013, and to 760 until November 2014, including users from UNIL, EPFL, UNIGE, UNIFR and UNIBE.

Training activity

Vital-IT coordinated and/or delivered in coordination with other groups 27 training courses in 2013 and 34 in 2014, to research groups in Switzerland through the SIB network.

Scientific contribution

Vital-IT provides a wealth of IT hardware resources and software services to partners and users. Per year, Vital-IT users run more than 10 million jobs and consume more than 5 million CPU hours.

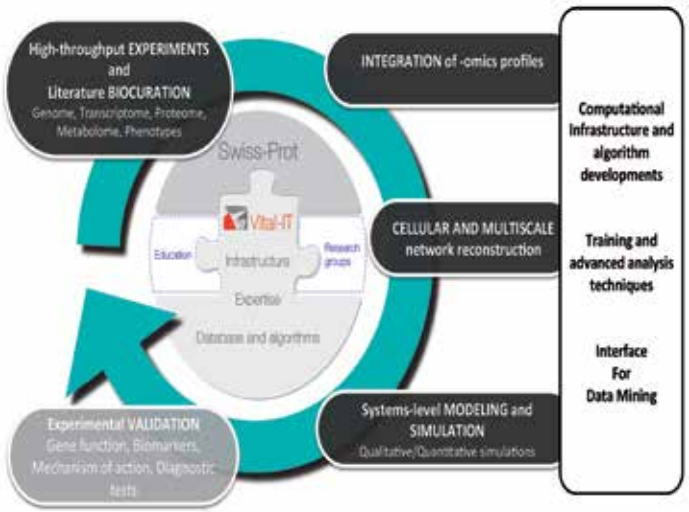
Vital-IT bioinformatics services and support were provided to various collaborators in Swiss universities and international research groups through joint research projects. Vital-IT enables and supports life and medical science research in multiple domains such as behavior, ecology, genetics, genomics, metagenomics, pharmacodynamics, phylogeny, population genetics, proteomics, structural biology, systems biology, amongst others. Some of the on-going projects are listed on **Vital-IT's web site:**

http://www.vital-it.ch/projects/project_list.php

Vital-IT has authored and/or was acknowledged in 96 publications in 2013 and in more than 90 by November 2014, most of them in high-impact journals such as Nature, Nat Genet, Cell, Science, Nat Methods, NAR, Plos One, BMC SysBiol, MBio, Plos Genet, Nat Chem Biol, Clin Genet, Genome Res, Clin Cancer Res, PNAS, Am J Hum Genet, amongst others.

Perspectives

Given the increasing amount and complexity of biological data generated among the different scientific groups, there is a growing need for training highly qualified personnel and for developing, coordinating and maintaining high-performance level computational resources enabling (Big Data) large-scale data analysis and management. Through its active participation to the European infrastructure for biological information ELIXIR, Vital-IT will contribute with all the SIB groups to building a sustainable support for life and medical science research in Europe, building the highway for research and innovation.



Frédéric Schütz

Maître d'Enseignement
et de Recherche

Frédéric Schütz studied Mathematics and Computer Science as an undergrad at the University of Geneva. He received a PhD in 2005 from the University of Melbourne (Australia) for work on statistical analysis of Mass Spectrometry data with Terry Speed at the Walter and Eliza Hall Institute of Medical Research in Melbourne. He then joined the Bioinformatics Core Facility led my Mauro Delorenzi at the "Institut Suisse de Recherche Expérimentale sur le Cancer" (ISREC) and the Swiss Institute of Bioinformatics (SIB) in Lausanne, as a postdoctoral researcher in statistics. In 2009, he led the creation of a Biostatistics Service within the Swiss Institute of Bioinformatics (SIB), providing expert consulting and training in biostatistics to Swiss life science researchers, for academic institutions and the industry. In 2014, he joined the Center of Integrative Genomics as a "Maître d'enseignement et de recherche" (senior scientist). His main responsabilities include training in statistics and related topics for bachelor and master students. In parallel, he remains responsible for the SIB Biostatistics Service; his current tasks include training in statistics as well as providing consulting on all aspects linked to data analysis. He is particularly interested in aspects linked to "reproducible research", the principles that allow researchers to set up analysis processes preventing incorrect results.

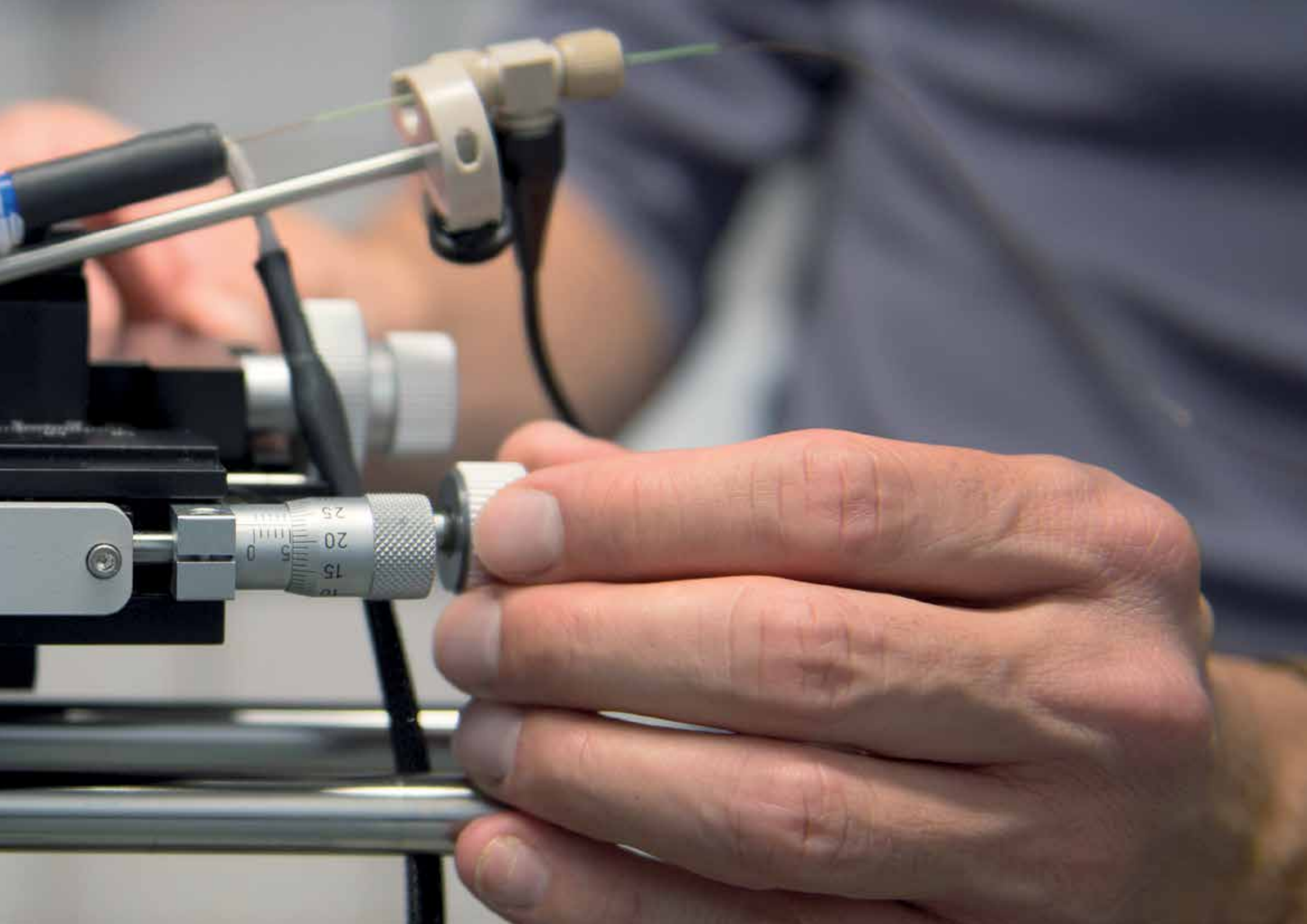
Frédéric Preitner

Maître d'Enseignement
et de Recherche

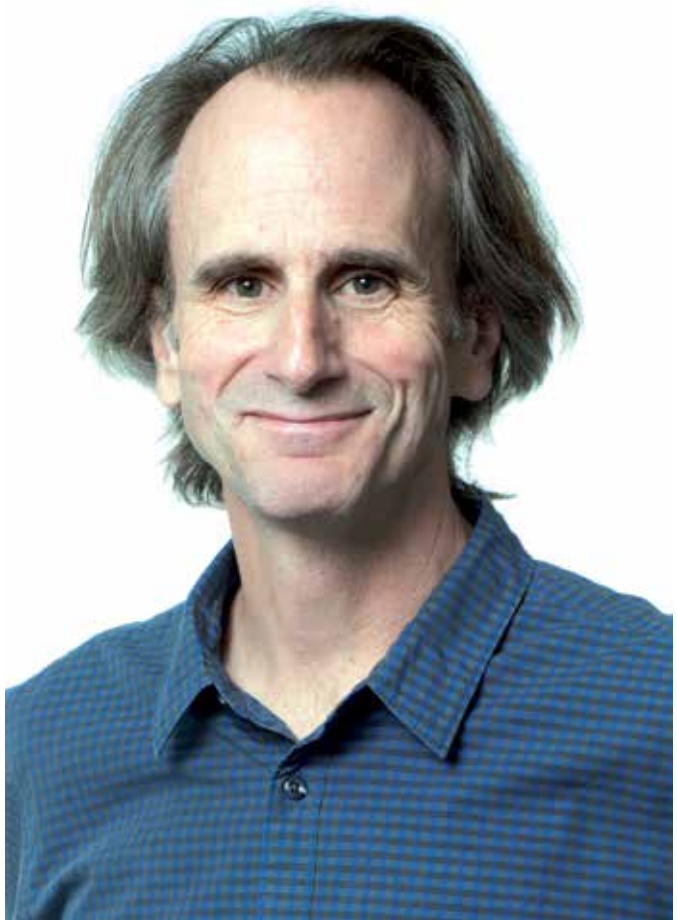
Supervisor of the Mouse Metabolic Facility (MEF) from UNIL-CHUV

Frédéric Preitner received his PhD in 2000 for his study on the role of beta-adrenergic receptor signalling in the control of body weight in mice, performed in Jean-Paul Giacobino's laboratory at the Department of Medical Biochemistry, University of Geneva. He then joined Bernard Thorens at the University of Lausanne, DPT, for a post-doctoral research on the role of incretin receptor signalling in insulin secretion in mice. In 2003, he received a SNF fellowship to join Barbara Kahn at Beth Israel Deaconess Medical Center, Harvard Medical School (Boston, MA, USA) for a post-doctoral research on the role of an adipokine in the control of insulin action in mice. In September 2006 he joined the Center for Integrative Genomics to develop and coordinate the activites of the Mouse Metabolic Facility. In 2010 he was promoted Maître d'Enseignement et Recherche.

CORE FACILITIES



Keith Harshman
Maître d'Enseignement et de Recherche



Keith Harshman received his PhD in biochemistry from the California Institute of Technology in 1990, working in the laboratory of Carl Parker on the isolation and characterization of eukaryotic transcription factors. Following postdoctoral fellowships with Walter Schaffner at the University of Zurich and Dennis Ballinger at the Sloan-Kettering Cancer Center, he joined Myriad Genetics Inc. in 1993, 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 goal of the Lausanne Genomic Technologies Facility (GTF) is to provide users with access to *State of the Art* technologies used to detect and measure quantitative and qualitative variations in nucleic acids. The principal technology and service platforms supported by the GTF are:

- Illumina HiSeq and MiSeq as well as the Pacific Biosciences RSII high throughput DNA
- Sequencing instruments
- Nanostring nCounter Analysis system
- Fluidigm C1 Single-Cell Auto Prep System
- Affymetrix GeneChip oligonucleotide arrays
- Agilent oligonucleotide arrays
- Applied Biosystems QuantStudio 6 and 7900HT instruments for quantitative real-time PCR analyses
- PerkinElmer/Caliper and Tecan liquid handling robots for the preparation of high throughput sequencing libraries and qPCR reaction plates
- Bioinformatics support and consultation at the stages of experimental design, data collection and storage as well as higher level data analysis

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

EXPANDING AND IMPROVING THE GTF SERVICE BASE

The period 2013-2014 saw a continued expansion of the GTF's service base, in particular by increasing and improving its high throughput DNA sequencing platform. In the fall of 2014, the facility's sequencing platform includes Illumina HiSeq (2x 2500 and 1x 2000) and MiSeq instruments as well the Pacific Biosciences RSII. Additionally, the GTF added the capability of processing nucleic acids from single cells by implementing the Fluidigm C1 Single-Cell Auto Prep System and improved its support of medium throughput RNA expression profiling by implementing a Nanostring nCounter instrument. Finally, the facility significantly improved its bioinformatic support of NGS sequencing projects in this period by developing pipelines for exome sequencing (together with Vital-IT) and RNA-seq data analysis.

ACKNOWLEDGEMENTS IN PUBLICATIONS

As a core facility, the GTF receives acknowledgement, but not authorship, on publications containing results obtained through regular services. Authorships reflect extensive collaborations beyond regular services. In 2013 and 2014 the GTF was acknowledged in more than 100 publications that appeared in a wide variety of journals.

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Publications in which GTF staff appeared as co-authors

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Manfredo Quadroni
Maître d'Enseignement et de Recherche

Protein Analysis Facility (PAF)

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

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 the main analytical tool.

IMPROVED OFFER OF SERVICES

Starting in 2010, the facility has reoriented its activity even further towards large scale proteomics analyses. We offer quantitative, comparative proteome analysis by SILAC (Stable Isotope Labeling with Amino Acids in Culture) or multiplex isobaric labelling using iTRAQ/TMT reagents. When both of these techniques cannot be used, label-free analyses can also be performed. All these workflows allow to quantitatively probe the proteome at a depth of up to 4000-6000 proteins. Through appropriate biochemical enrichment, large scale analyses can also be designed to map changes in post-translational modifications (PTM) such as phosphorylation or ubiquitination. In addition to proteome-wide assays, we still perform in-depth characterization of sequence or modifications on individual proteins. All the above mentioned workflows include extended support to users during experiment design and planning as well as data analysis and statistical evaluation of results. Last but not least, in 2014 the facility underwent a major restructuration and renewal and is now equipped with two State of the Art high resolution mass spectrometers (Orbitrap Fusion and QExactive Plus).

INDEPENDENT R&D PROJECTS

We have continued our exploration of cellular stress response mechanisms, using as a model system the inhibition of the molecular chaperone Hsp90 by geldanamycin. In a previous project we had developed a strategy to measure the profound changes in both protein synthesis and decay rates induced by such a perturbation of cellular protein metabolism[1,2]. Since the ubiquitin–proteasome system is one of the major pathways responsible for responding to folding stress, we mapped and quantified changes in protein ubiquitination induced by a blockade of Hsp90. The results (article submitted) revealed a mixture of (probably direct) effects on Hsp90 targets but also far reaching changes in the cellular ubiquitinome due to the perturbation of the cellular proteostasis.

COLLABORATIVE PROTEOMICS STUDIES

We collaborated with the group of F. Gachon (formerly UNIL, now Nestlé Research Centre, Lausanne) to carry out the first large scale measurement of protein levels in mouse liver as a function of circadian rhythms. The results highlighted sets of proteins that oscillate rhythmically in close correlation with mRNA levels, but also others whose levels vary independently of transcripts[3]. This study is being continued with the analysis of subcellular fractions.

Further on, we continued our collaboration with the group of Darius Moradpour at the UNIL Medical Microbiology Institute (IMUL) aimed at determining the cellular substrates of proteases from the Hepatitis C virus[4].We also started a collaboration with the group of Andreas Conzelmann (University of Fribourg) on a project aimed at developing and applying methods for determining the topology and orientation of inte gral membrane proteins in yeast. Finally, with the group of N. Chevre (UNIL Earth Surface Dynamics Institute) we studied the impact of anticancer drugs on the proteome of *Daphnia pulex*, a model for aquatic ecotoxicology (Borgatta M et al. *J Proteome Res* accepted).

1. Fierro-Monti I, Racle J, Hernandez C, Waridel P, Hatzimanikatis V, Quadroni M A novel pulse-chase SILAC strategy measures changes in protein decay and synthesis rates induced by perturbation of proteostasis with an Hsp90 inhibitor. PLoS One (2013) 8(11):e80423

2. Fierro-Monti I, Echeverria P,Racle J, Hernandez C, Picard D, Quadroni M Dynamic impacts of the inhibition of the molecular chaperone Hsp90 on the T-cell proteome have implications for anti-cancer therapy. PLoS One (2013) 8(11):e80425

3. Mauvoisin D, Wang J, Jouffe C, Martin E, Atger F, Waridel P, Quadroni M, Gachon F, Naef F Circadian clock-dependent and -independent rhythmic proteomes implement distinct diurnal functions in mouse liver. Proc. Natl. Acad. Sci. U. S. A. (2014) 111(1):167–72

4. Morikawa K, Gouttenoire J, Hernandez C, Dao Thi VL, Tran HT, Lange CM, Dill MT, Heim MH, Donzé O, Penin F, Quadroni M, Moradpour D Quantitative proteomics identifies the membrane-associated peroxidase GPx8 as a cellular substrate of the hepatitis C virus NS3-4A protease. Hepatology (2014) 59(2):423-33

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Publications

Fierro-Monti I, Echeverria P, Racle J, Hernandez C, Picard D, Quadroni M *Dynamic impacts of the inhibition of the molecular chaperone Hsp90 on the T-cell proteome have implications for anti-cancer therapy.* **PloS One** (2013) 8(11):e80425

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Barrera C, Millon L, Rognon B, Quadroni M, Roussel S, Dalphin J-C, Monod M *Immunoreactive proteins of Saccharopolyspora rectivirgula for farmer's lung serodiagnosis.* **Proteomics Clin Appl** (2014) 8(11-12):971–81.

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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 Center for Investigation and Research in Sleep (CIRS)

The Center of investigation and research on sleep (CIRS) aims to study and treat different forms of sleep disorders and represents a multidisciplinary research center (UNIL - CHUV) co-led by Dr Raphael Heinzer and Prof. Mehdi Tafti.

His main areas of research include the evaluation of sleep and its disorders in the general population: sleep over 2000 persons has been studied as part of the HypnoLaus study.

Research on sleep disordered breathing and cardiovascular consequences of sleep and study in extreme conditions (mountain climbers, sailors, airmen) are other important areas of specialization of the center.

More information:
www.chuv.ch/sommeil

The Cellular Imaging Facility - CIF

The Cellular Imaging Facility (CIF) assists researchers with imaging needs such as widefield fluorescence and transmission optical microscopy, confocal microscopy, time-lapse and ion imaging, to digital image processing and analysis.

The facility is located on the Bugnon, Dorigny, and Epalinges campuses of the University of Lausanne.

The CIF is organized around primary missions of providing access to a wide panel of State of the Art imaging equipment and technology, and of diffusing and sharing the practical and theoretical know-how on these approaches through teaching and training.

More information:
www.unil.ch/fbm/home/menuinst/la-recherche/plates-formes/cellular-imaging-facility-ci.html

The Bioinformatics Core Facility (BCF)

The Bioinformatics Core Facility (BCF) is active at the interface of statistics, biology and genomics. It performs:

- teaching and training
- consulting
- statistics and data analysis support at all steps of the scientific process:
- grant writing
- project planning (experimental design)
- result generation and representation (tables, figures)
- interpretation and report (paper writing)

It thus bridges gaps between medicine, genomics technologies and statistics and aims at catalyzing the discovery process by supporting excellence in the application of high-throughput laboratory approaches through high quality data analysis.

This service is aimed at all people active in life sciences.

INTRODUCTION

Genomic technologies allow the simultaneous measurement of thousands or millions of molecular variants and have uncountable applications. Data analysis is a key step, but few groups in Switzerland have the full range of statistics and bioinformatics skills required.

PROJECTS AND SERVICES

Statistical consulting

The BCF provides consultancy services on biostatistics matters, for the planning, experimental design and analysis of projects. It also supports grant proposal writing.

Education and practical training

The BCF provides researchers with educational support and practical training in the use of software and analysis methods. This includes the organization of seminars, workshops and training courses.

Data analysis services

The BCF performs computationally intensive analysis using suitably chosen or in-home developed computational tools. It also offers joint analysis of researcher's data with a specifically curated version of publicly available clinical and genomics datasets.

Personal embedding

A data analyst funded by the project who requires support can be coached by BCF team members, participates to internal meetings, use the BCF infrastructures and resources and work either in the BCF or at the site of the supported group, or can share time between the two. This allows data analysts to be exposed to both sides (laboratory and data analysis) of the project.

Scientific collaborations

The BCF provides support to help achieve the goals of biomedical projects, no matter how big or small, through a wide range of activities. The BCF has acquired in-depth expertise in a broad range of studies and techniques, including cancer subtype discovery, biomarkers selection, class discrimination, cross-platform analysis, meta-analysis of multiple datasets. The group participates in various research efforts, where it performs advanced data analysis tasks and methodological development or evaluation.

Recent examples:

Method development / evaluation:
Bonhoure et al. , Genome Res. 2014 , PMID: 24709819 (collaboration with Hernandez group, CIG)
Soneson et al. , BMC Bioinformatics. 2013, PMID: 23497356 (internal project)

Biomedical project, exploratory analyses for research applications:
Ragusa et al. , Cell Rep. 2014, PMID: 25242332 (collaboration with Petrova group, UniL-CHUV)
Bady et al. , Acta Neuropathol 2012, PMID: 22810491 (collaboration with Hegi group, CHUV)

Biomedical project, epidemiological-statistical analyses for clinical applications:
Roth et al. , J Natl Cancer Inst. 2012, PMID: 25246611 (international cancer collaboration)
Popovici et al. , J Clin Oncol, 2012, PMID: 25246611 (international cancer collaboration)

Website for Further Information
Bioinformatics Core Facility: *http://bcf.isb-sib.ch/*

The Mouse Metabolic Facility (MEF)

The MEF proposes a wide repertoire of State-of-the-Art metabolic analyses in the areas of energy metabolism, glucose homeostasis and lipid metabolism, to phenotype murine models of obesity and diabetes and to test the therapeutic efficacy of new pharmacological agents.

The MEF is directed by Frédéric Preitner (see page 45).

More information:
www.unil.ch/fbm/fr/home/menuinst/la-recherche/plates-formes/mef.html

Vital-IT

Vital-IT is also a core facility associated with the CIG. It is directed by Ioannis Xenarios (see page 44).

EDUCATION


Analysis of brains lacking NOPCI expression in glia and neurons
WT (A1-A3)
A1
A2
A3
Anterior Commissure
GFAP
NOPCI
Hoechst

EDUCATION: AN ESSENTIAL MISSION OF THE CIG

Becoming a scientist starts, before anything else, with gaining knowledge: knowing the relevant facts and being able to put them into their proper context, understanding mechanisms and their interplay and gaining insight into complex relationships between – more often than not in the genomics field – an overwhelming amount of seemingly unrelated data. This is basically a lifelong process, but very few will deny that teaching offers a first and basic step towards gaining these skills and, as such, cannot be overestimated. Consequently, it will come hardly as a surprise that the CIG, since the beginning years, has displayed a strong commitment towards academic education in the field of biological sciences, as part of the teaching mission of the University of Lausanne. A lot of members of the CIG, whether research group leaders or members of core facilities, give courses at the bachelor, master and PhD level, give lectures, seminars and organize practical courses at the Faculty of Biology and Medicine (UNIL) or at other institutions. Moreover, advanced doctoral students and postdoctoral fellows actively participate in teaching activities, mainly at the level of laboratory courses for students.

The CIG participates not only in teaching *per se*, but is also strongly involved in the organization of teaching programs: Winship Herr is director and Liliane Michalik vice-director of the UNIL School of Biology, Christian Fankhauser heads the master "Molecular Life Sciences" (MLS), Keith Harshman the doctoral program "Integrated Experimental and Computational Biology" (IECB), while Nouria Hernandez heads the CUSO (Academic Conference of Western Switzerland) doctoral program StarOmics.

Obviously, learning is not the privilege of bachelor, master or PhD student. All scientists continually seek to improve their knowledge through reading scientific publications, attending seminars and lectures and interacting with colleagues. The CIG would not be an institute worth that name if it did not create constellations where such essential "researcher's needs" can be actively pursued. In practice, this means that the CIG organizes numerous internal and external seminars and symposia where internationally reputed scientists come to the Génopode building to present their latest results in workshops or in plenary sessions, allowing participants the pleasure of an informal discussion. In addition, many *ad hoc* seminars and journal clubs are organized independently by CIG faculty members.

Over the years, the CIG annual retreat – where all CIG members, whether students, postdoctoral fellows, professors and group leaders, technical and administrative staff, are invited – has become immensely popular, as it provides an unmatched opportunity for researchers to exchange on their work progress and future plans, as each group presents an update of its research to the full Génopode scientific community. Of no less importance during this retreat are the social gatherings – elsewhere in this biennial report, former CIG director Prof. Nouria Hernandez explains how highly she values team spirit – bringing all people from every research team together in a relaxed atmosphere.

Courses and lectures given by CIG Faculty members at the UNIL

RICHARD BENTON
- Génétique des modèles eucaryotes
- Molecular basis of development and evolution module: body patterning
- Dynamic cell module: cilia, cellular antennae in health and disease
- Chemosensory perception in minibrains: from gene to behaviour
- Evolution and development of insects and plants
- Write a review, write a fellowship request

VINCENT DION
- Topics in genomics
- From clinic to basics and back
- Genomics, proteomics, and quantitative genetics

CHRISTIAN FANKHAUSER
- Génétique de modèles eucaryotes
- Circadian clocks
- Transposable elements
- Origine, division et dynamique des chloroplasts
- Perception et réponse à la lumière chez les plantes
- Write a review, write a fellowship request
- Perception of environmental signals in plants
- MSc MLS Organizer of the Master program
- Circadian clocks

PAUL FRANKEN
- Sleep and circadian rhythms: from molecules to performance
- Physiology of complex systems: neuroscience
- Understanding & interpretation of scientific literature
- Sleep physiology
- Genomics, proteomics, and quantitative genetics
- Problem based learning in biological modeling
- Circadian clocks
- Molecules for good sleep, molecules for bad sleep: from animal models to human sleep disorders

DAVID GATFIELD
- Topics in RNA biology
- Topics in genomics
- Circadian rhythms and metabolism
- Introductory course in animal science: circadian clocks

FISUN HAMARATOGLU
- Organizer of the practical course on animal developmental biology

NOURIA HERNANDEZ
- Regulation of eukaryotic gene expression
- Practical course in molecular biology
- Writing a review

WINSHIP HERR
- Biologie cellulaire et moléculaire
- Epigénétique
- Génétique générale
- Viral regulation of the cell division cycle
- Directionnalité du cycle cellulaire et points de contrôle
- Lecture critique de la littérature scientifique

HENRIK KAESSMANN
- Introduction into molecular evolution
- Molecular evolution
- Evolutionary nutritional genomics
- Next generation sequencing and evolution

LILIANE MICHALIK
- Génomique comparative
- Raisonnement et logique en biologie expérimentale et computationnelle
- Molecular evolution
- Molecular and cellular biology
- Introduction to animal embryology
- Genetics today, genetics for non-scientists

ALEXANDRE REYMOND
- Genetics and genome evolution
- Structural genomics and mutation
- Evolutionary and comparative genomics
- Genetics today: societal and scientific challenge
- Reasoning & logic in experimental and computational biology
- Write a review
- Biology & Society
- Genomics in medicine
- Evolution and genomes

ANDRZEJ STASIAK
- Défauts et réparation de l'ADN
- Structure et topologie de l'ADN
- Cycle cellulaire, réplication et recombinaison de l'ADN
- Compréhension et interprétation de la littérature scientifique

MEHDI TAFTI
- Genetics of eukaryote models
- Genetics and genome evolution
- Genomics, proteomics, and quantitative genetics: quantitative genetics
- Sleep physiology: genetics of sleep

BERNARD THORENS
- Métabolisme : homéostasie glucidique
- Régulation du métabolisme Régulation du cycle cellulaire
- Le glucose comme signal dans la régulation métabolique
- Adaptation métabolique au jeûne : rôle des senseurs métaboliques

DOING A PhD AT THE CIG

Why study and work at the CIG?

The integrative nature of the CIG, harboring 15 research teams – using different model organisms and a wide variety of technologies in exploring the mechanisms and laws that rule within the fields of molecular biology, genetics and genomics – as well as its location in the immediate vicinity of other first rate research institutions (EPFL, CHUV, ISREC) make the center an excellent place to study the biological sciences. Not only its proximity to research and intellectual resources contribute to making it a premier centre, the CIG is also an exceptionally attractive place to study and work for other reasons: the institute is not only located in a stunningly beautiful natural environment (with sailing, skiing and hiking opportunities) but benefits from the rich cultural life of Lausanne and Geneva.

A PhD training: an essential step towards a science career

The CIG is committed to the success of its doctoral students and heavily invests in the training of tomorrow's scientists. To promote a high level of student achievement, the faculty and administration take an active role in mentoring and supervising the students. All PhD students at the CIG 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.

- PhD students are integrated in one of the CIG groups, to pursue a research project in the laboratory. Doctoral students, as well as postdoctoral fellows, actively participate in seminars and journal clubs, organized by the individual groups, allowing them the opportunity to present their work (thereby training their presentation skills) and discuss their research project with other lab members.
- PhD students at the CIG benefit from a mentoring program. Through this program, each student is assigned to a mentor, in general a faculty member working in a different field than the one pursued by the student. This mentor is available for scientific or non-scientific discussions and advice.
- The CIG has been instrumental in launching the StarOmics program, an inter-institutional program funded by the *Conférence Universitaire de Suisse Occidentale* (CUSO), offering a wide variety of courses and study programs to PhD students.
- Modern Biology and *a fortiori* the fields of molecular genetics and genomics rely more and more on computational techniques for the analysis of large data sets and students and scientists alike have to acquire the necessary skills to meet those challenges. To that end, the CIG has established a new thematic doctoral program, entitled "Integrated Experimental and Computational Biology" (IECB). This program is integrated within the FBM doctoral school and has become established through support of the Swiss Institute of Bioinformatics. Students within this program can also apply to the "Fund for Research and Education in Genetics" for funding to participate in an international conference or course.
- The CIG seminars program brings every week leading scientists from all over the world to Lausanne, presenting their work and/or commenting on the latest progress within their field and discussing with interested PhD students and postdoctoral fellows.

DOING A POSTDOC AT THE CIG

Over the years, the number of postdoctoral fellows at the CIG has considerably increased and their expertise has been one of the main factors that contribute to the success of individual research groups and to the worldwide fame of the institute. Several initiatives have been launched and are implemented to provide support to postdocs and offer them the best chances for a successful career development. For example, following advice from the CIG Scientific Advisory Committee (SAC), an "ombudsman for postdoctoral fellows" has been appointed, offering advice and support in all issues that may arise during a postdoctoral training. The CIG is proud that Prof. Jacques Dubochet, Professor emeritus (UNIL) with a broad background in the life sciences, has taken up this function and has substantially contributed to the enrichment of the "Life of a postdoc" at the institute.

THE MENTORING PROGRAM

The CIG has organized a support program for PhD students: soon after commencement of his or her studies, each doctoral student selects, by mutual agreement, a CIG faculty member (Professor or Maître d' Enseignement et de Recherche) as an academic mentor. As such, a PhD student at the CIG receives guidance from both a research mentor (the thesis advisor) and an academic mentor, an interested and impartial faculty member chosen to provide diversity in the student's education.

The academic mentor closely follows the student's academic and research progress and remains available for support and advice, for the entire duration of the doctoral study period. In principle, the academic mentor belongs to another research team than the student and as such is working on a different research topic. By getting to know their mentees well, the academic mentor is able to promote the student's further career and can provide a well-informed letter of recommendation. Thus, with dual research and academic mentoring, the CIG support program ensures diversity of complementary support, thereby maximizing the chances of a productive PhD training, as an essential step towards a successful career. Another important role of the academic mentor is to offer advice in case of any conflicts that may arise between the student and his/her PhD thesis advisor. As such, the role of the academic mentor is to:

- enable PhD students having close contact with a senior member of the CIG community, other than his group leader
- provide PhD students with a faculty member, whose primary concern is their academic development
- provide PhD students with a letter of reference
- act as a guide

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

THE STAROMICS DOCTORAL PROGRAM

Genomics, transcriptomics, proteomics and other large scale data generating technologies are confronting PhD students with a new spectrum of challenges: analyzing large data sets, which will become an everyday task for a lot of biologists in the not too distant future, thereby necessitating the need for appropriate training programs. The StarOmics inter-institutional doctoral program, supported by the universities of Lausanne, Bern, Fribourg, Geneva and Neuchâtel fills this niche and covers quantitative aspects of modern biology, integrating novel biological strategies and reasoning. Students attending this program are offered training in genome-wide and proteome-wide data analysis, biological modeling, quantitative image analysis, programming and statistics through a didactic program that complements both their individual research topic and background. Consequently, PhD students enrolled in the StarOmics program will become conversant in both experimental and computational approaches and acquire the ability to integrate quantitative and experimental methods in their own research.

Website: *www.biologie.cuso.ch/staromics/welcome/*

THE IECB DOCTORAL PROGRAM

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

PhD theses obtained at the CIG (2013-2014)

Ali Alfaiz
(groups Reymond & Xenarios)
Isolation of genetic mutations leading to abnormal phenotype in human through ultra-high-throughput sequencing (UHTS)

Rati Bell
(group Benton)
Molecular and physiological characterisation of ionotropic receptors in the sacculus in *Drosophila*

Vincent Croset
(group Benton)
Evolution and functional characterisation of the IR chemosensory receptors in the Drosophila larval gustatory system

Gwendoline Degueurce
(group Michalik)
PPAR-Beta and miR-Star in the UV irradiated skin regulation / PPAR-Beta et miR-Star dans la régulation de la peau irradiée aux UVS

Francesco La Spada
(group Franken)
On the role of Periode2 in the circadian and homeostatic regulation of sleep

Géraldine Mang
(group Franken)
Uncovering a role for microRNAs in sleep homeostasis and energy metabolism

Honey Mody
(group Thorens)
Autocrine secretion of IGF2 regulates adult beta cell functional plasticity

Dhaval Patel
(group Thorens)
Clic4, a novel protein that sensitizes β-cells to apoptosis

Marianne Renaud
(group Hernandez)
RNA Polymerase III regulation in mammals

Gianina Luca Rusu
(group Tafti)
Sleep, metabolism and aging

Doing a PhD at the CIG

Ana Claudia Marques is an SNSF assistant professor at the Department of Physiology at the University of Lausanne. Her research combines molecular genetics with computational biology and aims to understand the function and biological significance of long intergenic non-coding RNAs. Prof. Marques was among the first persons to start a PhD training at the newly founded Centre for Integrative Genomics. Now, what could be a better reason for luring her into an interview?

Marques… a typical Swiss name.

Prof. Marques (laughs): I am Portuguese. I grew up in Sintra, a town in the Lisbon region. I studied at the *Instituto Superior Técnico in Lisbon* – the Portuguese equivalent of the EPFL, you might say – and obtained a degree in chemical engineering and biotechnology. After that, I became research assistant at the *Instituto Gulbenkian de Ciencia*, a biomedical and graduate training institute in Oeiras; I had become interested in genome evolution and started to work on prokaroytes, trying to understand the evolution of mutation rates in bacteria. This was a stepping stone towards what I really wanted to do: I wanted to work on human evolution.

You mean stepping into the footsteps of Richard Leaky? Hunting for fossil skulls and bones from Australopithecines in Ethiopia, in search for Lucy's brother?

Prof. Marques: No, no, I wanted to understand human evolution from a molecular genetics and genomics perspective. I particularly wanted to find out how our ancestral and evolutionary history is imprinted in our genome. At that time, I hoped it might be possible to find remnants of early vertebrate genomes – dinosaurs, so to speak – in the DNA of *Homo sapiens*. In retrospect a somewhat naive concept, I would say. And then, one day, I saw an advertisement from Henrik Kaessmann, who was at that time setting up his own group at the Max Planck Institute for Evolutionary Anthropology in Leipzig. He accepted me as a PhD student, but before I moved to Leipzig, to join his team, Henrik got an "offer you can't refuse" as one says, from the newly founded Center for Integrative Genomics. So, I started my PhD training with him at the CIG.

When was this?

Prof. Marques: This was in September 2003.

In a nutshell: what were you doing in Henrik Kaessmann's laboratory, during those early days?

Prof. Marques: At that time, our team was studying how new gene functions arise in mammals, through gene duplication events. I was trying to understand how retrotransposition, an RNA based gene duplication mechanism, contributes to the emergence of primate specific genes in the human genome. Later – more towards the end of my doctoral thesis – I got interested in how differences in subcellular localization between parental and duplicated gene products might contribute to creating new biological functions for duplicated genes.

What was the title of your PhD thesis?

Prof. Marques: I obtained my PhD degree in February 2008 with a doctoral thesis, entitled *"The role of gene duplication in the origin and evolution of new biological functions"*.

What was your impression of the CIG? Did you like it there?

Prof. Marques: I loved it! These were still the early days of the CIG and one could feel the positive vibrations. People were highly motivated and keen on setting things into motion. We shared the lab space with the group from Alex Reymond and in both teams there was a lot of genetics and molecular biology going on. So, there were a lot of interactions and we had a common journal club. In Henrik's group, I learned how to get your equipment, how to organize your experiments and contacting other scientists for collaborations. As a matter of fact – setting up my own research group – I now came to realize how well I've been prepared for that task.

What would you consider the strengths of the CIG?

Prof. Marques: Apart from the things I just came to mention, one of the great advantages of the CIG has always been its diversity, even within the field of genomics. According to my opinion, this is a quality of the institute which can hardly be overestimated. You had the opportunity to go to a seminar on plant genomics, and the next day you could listen to a research report on physiological genomics of energy homeostasis or a State of the Art lecture on the genetics of sleep and sleep disorders. And even if it was not your topic – or maybe I should say: *because* it was not your topic – you could pick up new ideas. People from different fields talked a lot to one another and these discussions quite often made one perceive things in a somewhat different perspective. For example, I remember becoming aware of a technique being used in the group of Nouria, which could be helpful for my work. So, I moved over to the Hernandez' lab and watched over the shoulders of a postdoc for a couple of days. You know, I have to admit that at that

" I have to admit that at that time – I was young and standing at the beginning of my career – I did not realize how special the CIG really was. I believed it was like that everywhere. Now, I know better."

Prof. Ana Claudia Marques

Prof. Ana Claudia Marques, among the first to have started a PhD traing at the CIG

time – I was young and standing at the beginning of my career – I did not realize how special the CIG really was: the individual qualities of the group leaders as excellent scientists, the level of the technical platforms, the interactions among people – not only scientifically, but also socially – not to mention the solid financial situation of the institute. I believed it was like that everywhere. Now, I know better.

So, we are writing February 2008 and Ana Claudia Marques is allowed to call herself "Philosophiae Doctor".

Prof. Marques: Right.

What happened next?

Prof. Marques: I wanted to be trained as a computational biologist in order to gain more insight in genomics, and went for a postdoctoral training to the laboratory of Chris Ponting at the University of Oxford. His group was doing research in the field of comparative genomics and people were doing a lot of bioinformatics and computational biology. During those days it became apparent, mainly through transcriptome-wide expression studies, that a lot of RNA species where non-coding. I became interested in so called lincRNAs: long intergenic non-coding RNAs. I remained for 6,5 years in Oxford: 4 years as a postdoc and 2,5 years I had a semi-independent position. I came back to Lausanne in October 2014, to set up my own group.

Why did you come back to Lausanne?

Prof. Marques: There were several reasons. For instance, my husband is Swiss and we have two kids, meaning that also non-scientific issues infiltrated the discussion and influenced my decision. On the other hand, Switzerland is a great country to do science…

…you could have gone to Bern or Geneva…

Prof. Marques: … and Lausanne is not only a very nice place to live, but an excellent place to do research in the genomics field.

What is your research topic?

Prof. Marques: Our research aims to increase the functional repertoire of lincRNAs and understand their contributions to cellular homeostasis and disease.

Looking back, not being naive anymore…

Prof. Marques: …I would not be too sure about that…

…would you say that you received a good training at the CIG?

Prof. Marques: Oh yes, there is no question about that. I can recommend a PhD training at the CIG to anyone who wants to understand genomes and their evolution, in its broadest sense.

CIG SEMINARS PROGRAM SPRING 2013

Thursday January 17, 2013
Félix HAUSER
University of California at San Diego, La Jolla, USA
A genomic scale artifical micro RNA library as a tool to investigate the redundant gene space in Arabidopsis thaliana
Host: Christian Fankhauser

Monday January 21, 2013
Erik VAN NIMWEGEN
Biozentrum, University of Basel, Switzerland
A democracy of transcription factors: automatically inferring the key regulators of chromatin and gene expression dynamics from high-throughput data
Host: Winship Herr

Monday February 11, 2013
Edward E. FARMER
DBMV, University of Lausanne, Switzerland
How leaves defend themselves
Host: Christian Fankhauser

Thursday February 28, 2013
Ronald PIERIK
Utrecht University, The Netherlands
Plant signaling and multi-tasking in crowded environments
Host: Christian Fankhauser

Monday March 11, 2013
Bertram GERBER
Leibniz Institute for Neurobiology, Magdeburg, Germany
Decision-making in larval Drosophila
Host: Richard Benton

Monday March 18, 2013
Bart DEPLANCKE
EPFL, Lausanne, Switzerland
Systems-based, quantitative analysis of gene regulation during fat cell differentiation
Host: Nouria Hernandez

Monday April 15, 2013
Bruno LEMAITRE
EPFL, Lausanne, Switzerland
The Drosophila gut: a new paradigm for epithelial immune response
Host: Richard Benton

Thursday April 18, 2013
Michael NEFF
Washington State University, Pullman, USA
Functional analysis of the AT-hook motif containing nuclear localization (AHL) gene family in Arabidopsis thaliana
Host: Christian Fankhauser

Monday April 22, 2013
Andrzej STASIAK
CIG, University of Lausanne, Switzerland
Numerical simulations shed light on the organization of topological domains in interphase chromosomes
Host: Nouria Hernandez

Monday April 29, 2013
Margriet OUWENS
German Diabetes Center, Düsseldorf, Germany
The impact of epicardial adipokines on cardiac function in type 2 diabetes: from molecular biology to clinical biomarkers
Host: CIG Students & Postdocs

Monday May 13, 2013
Julie AHRINGER
University of Cambridge, UK
Chromatin regulation and the landscape of RNA polymerase II transcription in C. elegans
Host: Richard Benton

Monday May 27, 2013
Alexandre REYMOND
CIG, University of Lausanne, Switzerland
Genome structure and gene expression
Host: Christian Fankhauser

Monday June 17, 2013
Harry NOLLER
University of California, Santa Cruz, USA
Structure and Dynamics of the Ribosome During Translation
Host: Winship Herr

CIG SEMINARS PROGRAM SPRING 2014

Monday January 13, 2014
Sophie POLO
Université Paris Diderot, France
Chromatin bookmarking for transcription restart in response to DNA damage
Host: Vincent Dion

Monday January 20, 2014
Raffaella SANTORO
University of Zurich, Switzerland
The epigenetic of the nucleolus
Host: Vincent Dion

Monday January 27, 2014
Aoife MCLYSAGHT
University of Dublin, Ireland
Gene dosage sensitivity in evolution and disease
Host: Alexandre Reymond

Monday February 10, 2014
John MARKO
Northwestern University, Evanston, USA
Structure, mechanics and topological self-organization of chromosomes
Host: Andrzej Stasiak

Monday February 24, 2014
Jørgen KJEMS
Aarhus University, Denmark
Circular RNA - a novel regulator of gene expression
Host: David Gatfield

Monday March 10, 2014
Greta GUARDA
University of Lausanne, Switzerland
NLRC5 - a novel transcriptional regulator of MHC class I
Host: Winship Herr

Monday March 17, 2014
Anne-Claude GINGRAS
University of Toronto, Canada
Signaling interactomes in health and disease
Host: Manfredo Quadroni

Monday March 31, 2014
Mehdi TAFTI
CIG, University of Lausanne, Switzerland
Sleep in a dish
Host: Paul Franken

Monday April 7, 2014
Alexandre REYMOND
CIG, University of Lausanne, Switzerland
Genome rearrangements and mirror phenotypes
Host: Nouria Hernandez

Monday April 14, 2014
Luis MENDOZA
Universidad Nacional Autonoma de México, Mexico
Modeling the regulatory network that controls lymphopoiesis
Host: Ioannis Xenarios

Monday April 28, 2014
Eran MESHORER
The Hebrew University of Jerusalem, Israel
Fluorescent libraries in embryonic stem cells in search of novel regulators of pluripotency
Host: Christian Fankhauser

Monday May 12, 2014
Steve WEST
London Research Institute, Potters Bar, UK
Defective DNA strand break repair, and links to genome instability and cancer
Host: Andrzej Stasiak

Monday May 26, 2014
Nadine VASTENHOUW
Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany
The role of chromatin structure in zygotic genome activation
Host: David Gatfield

CIG SEMINARS PROGRAM FALL 2014

Monday September 29, 2014
Lluis FAJAS COLL
University of Lausanne, Switzerland
The E2F abd CDKç cell cycle regulators are key effectos of metabolic signaling in normal and in cancer cells
HOST: Liliane Michalik

Monday October 20, 2014
Brigitee GAILLOT
University of Geneva, Switzerland
Hydra, a model of epithalial plasticity
Host: Nouria Hernandez

Monday October 27, 2014
Markus AFFOLTER
University of Basel, Switzerland
Live imaging and beyond: a deep look at vascular development in a living organism
Host: Vincent Dion

Monday November 17, 2014
Geneviève GOURDON
Institut Imagine, INSERM, Paris, France
ICTG repeat expansions and myontonic dystrophy: deciphering the complex mecanisms involved towards therapeutics development
Host: Vincent Dion

Monday November 24, 2014
Olivier MICHIELIN
University of Lausanne, Switzerland
Rational design of new therapeutic strategies in stage IV melanoma
Host: Liliane Michalik

Monday December 8, 2014
Benjamin PRUD'HOMME
CNRS, Marseille, France
Evolution of wing pigementation patterns and reproductve behaviors in Drosophila
Host: Richard Benton

CIG Symposium 2013: Genome, Disease and Evolution

ORGANIZERS
H. Kaessmann
A. Reymond

Leif ANDERSSON
Uppsala University, Sweden
How domestic animal genomics can teach human medicine and evolutionary biology

Gil BEJERANO
Stanford University, USA
Forward genomics and the prospects of cure models for human disease

Laurent DURET
Université de Lyon et CNRS, France
The dynamics of recombination hotspots in the human genome: Insights from ancient DNA

Evan E. EICHLER
University of Washington, USA
Human genome structural variation, disease and evolution

Paul FLICEK
Wellcome Trust Sanger Institute, UK
Human genome structural variation, disease and evolution

Svante PÄÄBO
Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany
Archaic genomics

Catherine L.PEICHEL
Fred Hutchinson Cancer Research Center, Seattle, USA
The genomic architecture of speciation in sticklebacks

Katherine S. POLLARD
University of California, San Francisco, USA
Many human accelerated regions are human-specific developmental enhancers

Gunter P. WAGNER
Yale University, USA
Transposable element saturation and the tunable genome

Robert K. WAYNE
University of California, Los Angeles, USA
Genomic studies of wild and domestic canids

Eske WILLERSLEV
University of Copenhagen, Denmark
Hunting the molecular past

Patricia J. WITTKOPP
University of Michigan, Ann Arbor, USA
Genomic sources of regulatory variation: from mutation to polymorphism to divergence

CIG Symposium 2014: Rhythms in Biology

ORGANIZERS
P. Franken
D. Gatfield
D. Duboule (EPFL/UNIGE)

Bruce EDGAR
Heidelberg Universität, Germany
A novel oscillator that controls cycles of DNA replication

Ying-Hui FU
University of California, San Francisco, USA
Journey into the molecular machinery of sleep

Helge GROSSHANS
Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland
Large-scale gene expression oscillations as a timer for worm development

Craig HELLER
Stanford University, USA
Adaptive and pathological inhibition of neuroplasticity associated with circadian rhythms and sleep

Lisa MARSHALL
Universität Lübeck, Germany
Human genome structural variation, disease and evolution

Sophie MARTIN
Université de Lausanne, Suisse
Spatial regulation of cell cycle progression

Bela NOVAK
University of Oxford, UK
Cell cycle regulation by systems-level feedback controls

Olivier POURQUIE
Université de Strasbourg et CNRS, France
The segmentation clock: generation of periodic patterns in embryos

Akhilesh REDDY
Yale University, USA
Transposable element saturation and the tunable genome

Ueli SCHIBLER
Université de Genève, Switzerland
Systemic regulation of circadian gene expression

Joseph TAKAHASHI
University of Texas Southwestern Medical Center, Dallas, USA
Molecular architecture of the circadian clock in mammals

Benjamin TU
University of Texas Southwestern Medical Center, Dallas, USA
Logic of a metabolic cycle

CIG AND THE PUBLIC

Science communication: a responsibility

Since the discovery of the DNA double helix by James Watson and Francis Crick, biology has undergone a transformation – a continuing process, proceeding at a vast pace – and has faced the birth of a wide array of new disciplines: molecular genetics, proteomics, computational biology, genomics and systems biology, to name but a few. Nobody can refute that science (including the medical and biological sciences) and technology play an ever increasing role in our society and often have a direct impact on our daily lives. That process does not come without responsibility for those who create science: scientists.

Indeed, in an era where ordering one's personal genome sequence is but a mouse click away and where words, such as *"transgenic flies"*, *"genetically modified crops"*, *"cancer genes"* and *"knock-out mice"* are prominently present in the media, and sometimes give rise to concern – not seldom as a result of spreading misinformation – with the general public and policy makers alike, it is of little surprise that there is a genuine need for clarification. Within this discourse, the CIG has taken up its responsibility and considers it part of its mission to establish a link with the public at large and communicate what is happening behind its walls, in a transparent fashion.

Communication projects at the CIG

During the open doors at the University of Lausanne (*"Les Mystères de l'UNIL"*) and on other occasions, everyone is more than welcome to stop by at the CIG and visit the laboratories and the facilities. These activities are not only an opportunity for the scientists to inform the public about the research done at the CIG, but also offer them a unique chance to discuss with non-scientists about different research-related issues raised in today's society. In particular, these open doors constitute an opportunity for PhD students and postdoctoral fellows to talk with the general public about their work and gain experience in describing their research projects and explaining the meaning of their experiments to the layman, whether it be children, teenagers or adults. Each year, many non-specialists visit the institute on these different occasions.

Needles to say that science communication with the public can also take the form of features in the media: during the past years, CIG members and their research have been commented on the radio, TV and in the written press.

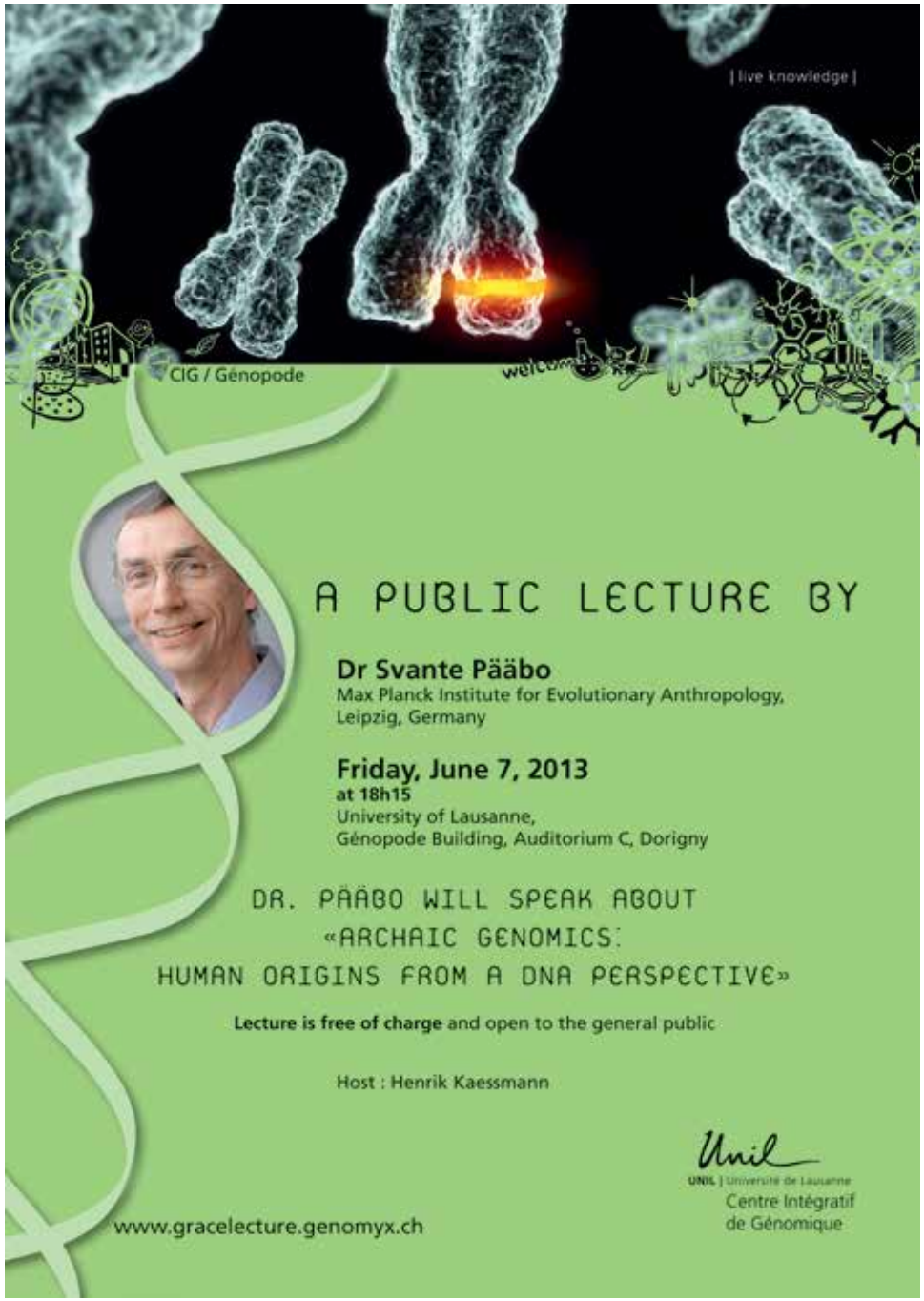
The next generation of scientists: always welcome at the CIG

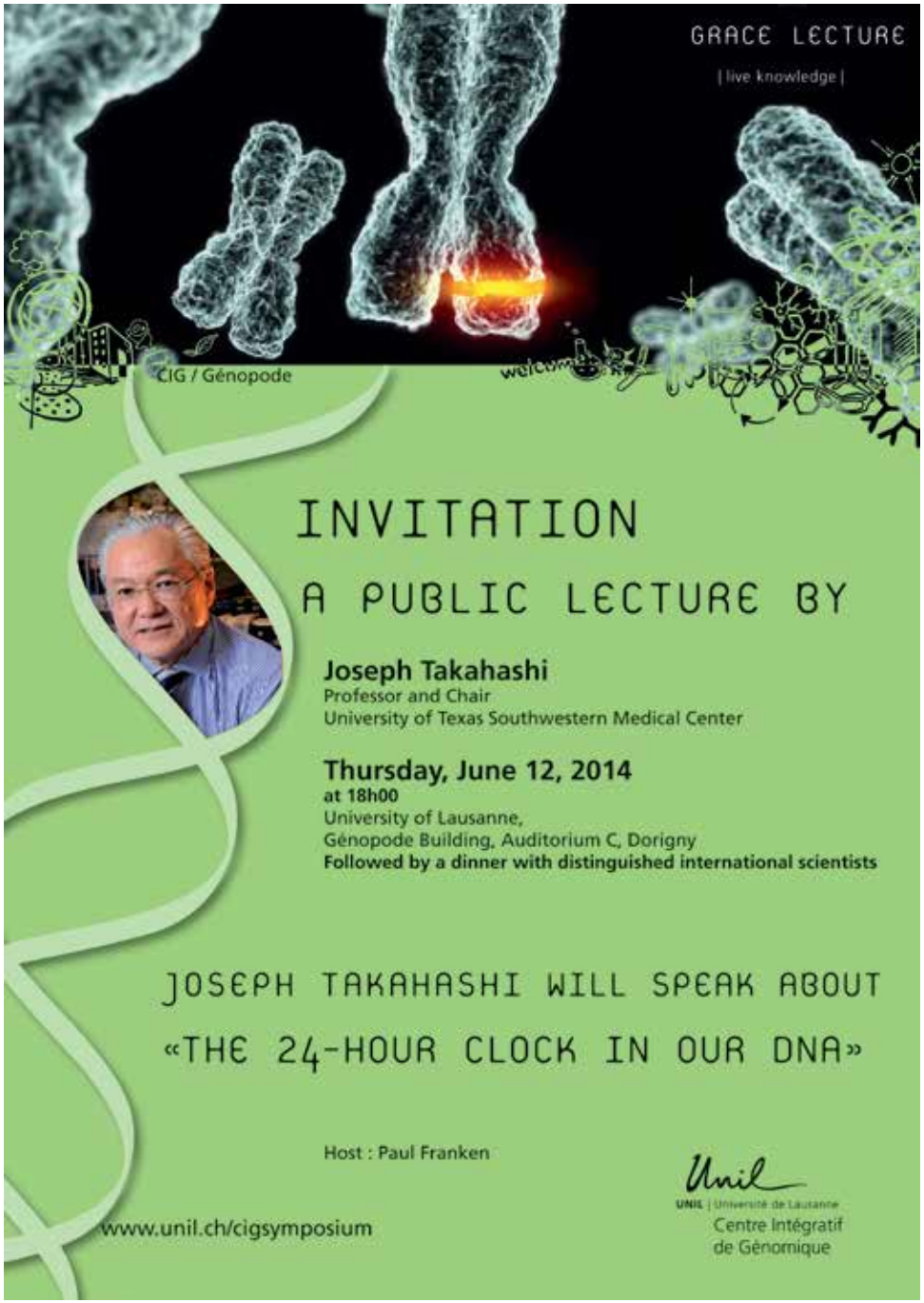
The CIG attaches great value to science communication with children and organizes every year a visit to the institute, within the framework of *"Passeport Vacances"*, a program that organizes activities for children and teenagers during their holidays. Likewise, the Center welcomes pupils, visiting with their school teacher. On those occasions, they get the chance to participate in the day-to-day life at the laboratory: become involved in simple experiments, learn to appreciate the miraculous world as experienced through the microscope and get an answer to all their questions. It would be a gross distortion of facts to claim that only the children benefit from these discussions with scientists. Professors, PhD students, postdocs and technicians alike can vouch for that, being more than just a little bit challenged in answering questions put from, let's say a "different angle". Not a few CIG members come to realize, after such visits, that children – displaying that charming mix of shyness and everlasting inquisitiveness – possess the most precious gift every scientist should cherish: a never ending "sense of wonder"…

John Grace lectures

The CIG is very fortunate to be able to host the famous "John Grace Lectures", made possible through generous support from the "Fund for Research and Education in Genetics", established in 2010 following a donation from the Grace family. These State of the Art lectures constitute a unique opportunity, both for specialists and non-specialists alike, to hear world-renowned scientists present the latest findings and concepts within their research field. In 2013, the John Grace Lecture was held by Prof. Svante Pääbo (Max Planck Institute for Evolutionary Anthroplogy, Lepzig, Germany) and the following year by Prof. Joseph Takahashi (University of Texas Southwestern Medical Center, USA).

The fund is dedicated to supporting, educating, and inspiring current and future genetic researchers and to making science more accessible to the community. It achieves this mission by supporting activities at the CIG and at *L'Eprouvette*, the public laboratory of the University of Lausanne.


| live knowledge |
CIG / Génopode
A PUBLIC LECTURE BY
Dr Svante Pääbo
Max Planck Institute for Evolutionary Anthropology,
Leipzig, Germany
Friday, June 7, 2013
at 18h15
University of Lausanne,
Génopode Building, Auditorium C, Dorigny
DR. PÄÄBO WILL SPEAK ABOUT
«ARCHAIC GENOMICS:
HUMAN ORIGINS FROM A DNA PERSPECTIVE»
Lecture is free of charge and open to the general public
Host : Henrik Kaessmann
Unil
UNIL | Université de Lausanne
Centre Intégratif
de Génomique
www.gracelecture.genomyx.ch


GRACE LECTURE
| live knowledge |
CIG / Génopode
INVITATION
A PUBLIC LECTURE BY
Joseph Takahashi
Professor and Chair
University of Texas Southwestern Medical Center
Thursday, June 12, 2014
at 18h00
University of Lausanne,
Génopode Building, Auditorium C, Dorigny
Followed by a dinner with distinguished international scientists
JOSEPH TAKAHASHI WILL SPEAK ABOUT
«THE 24-HOUR CLOCK IN OUR DNA»
Host : Paul Franken
Unil
UNIL | Université de Lausanne
Centre Intégratif
de Génomique
www.unil.ch/cigsymposium

PEOPLE AT THE CIG

Science is not only about doing science, it is also about enabling scientists to do science. The reproducibility of experiments in a biological laboratory would (and should) become rather questionable if the quality of products and materials would be less than impeccable – or not available because someone forgot to order them in time – or if technical assistants would not take care of and/or did not know how to handle equipment. Doing experiments with *Drosophila* could get tedious if the fly rooms could not be kept at the correct temperature, and the knock-out mice would be knocked out for sure if people from the animal facility would not take proper care of them. And who dares to imagine a CIG where there is no IT support if the computer makes "Beep" – and nothing else but that – or wants to contemplate over a scenario without administrative assistants within the walls of the institute? And surely, the Center for Genomics would be far less Integrative if people from the genotyping, phenotyping and sequencing facilities would not guarantee the highest experimental standards. Working together in the field of experimental and/or computational biology allows scientists to create success in a way that would be difficult, if not impossible, as compared to working alone. Indeed: "If you want to go fast, walk alone. If you want to go far, walk together". As such, it comes hardly as a surprise to state that the strength of the CIG, like every other research institute, comes from team work among its members. All of them.
At present, there are more than 220 people working at the CIG, originating from more than 25 countries.

CIG members in 2013-2014

Liliane Abuin Laboratory Technician Lorène Aeschbach Laboratory Technician Emilie Ait Yahya Graison Post-doctoral Fellow Ali Alfaiz PhD Student Waad Al-Bawardi Undergraduate Student Laure Allenbach Petrolati Laboratory Technician Flavio Angei Master Student Roman Arguello Post-doctoral Fellow Jan Armida PhD Student Bulak Arpat Bioinformatician Kelly Ascencao Laboratory Technician Catia Attanasio Post-doctoral Fellow Julie Baker Visiting Professor Suresh Balsiger Washing Facility Rebecca Balz Trainee Jachen Barblan Laboratory Technician Benoîte Bargeton Post-doctoral Fellow Michaël Baruchet Laboratory Technician Davide Basco Post-doctoral Fellow Armelle Bauduret Laboratory Technician Emmanuel Beaudoing Bioinformatician Rati Bell PhD Student Fabrizio Benedetti Post-doctoral Fellow Richard Benton Group Leader Dassine Berdous PhD Student Anouk Berger Apprentice Animal Keeper Marlyne Berger Stocks, Maintenance and Ordering Xavier Berney Laboratory Technician Tanja Bhuiyan PhD Student Adem Bilican PhD Student Jérôme Blanc Apprentice Technician Akash Boda Summer Trainee Karolina Bojkowska Laboratory Technician Marta Bombardo PhD Student Nicolas Bonhoure PhD Student Marion Bonnet Post-doctoral Fellow Naomi Borel PhD Student Gilles Boss Laboratory Technician Gergana Bounova Post-doctoral Fellow Frédéric Brun PhD Student Manuel Bueno Laboratory Technician Yannis Burnier civilist Sandra Calderon Copete Bioinformatician Donatella Canella Post-doctoral Fellow Danielle Canepa Del Canto-Perri Administrative Assistant Tiziana Caputo PhD Student Margarida Cardoso Moreira Post-doctoral Fellow Francesco Nicola Carelli PhD Student Marianne Carrard Laboratory Technician Violeta Castelo-Székely PhD Student Phing Chian Chai Post-doctoral Fellow Jacqueline Chrast Laboratory Technician Cinzia Cinesi Master Student Daniela Cisterna Administrative Assistant Catherine Clément Master Student Nathalie Clerc Administrative Assistant Elodie Colonello Apprentice Laboratory Technician Floriane Consales Laboratory Technician Diego Claudio Cortez Quezada Post-doctoral Fellow Nicoletta Corti Master Student Vinicius Costa Galvao Post-doctoral Fellow Violeta Castelo Székely PhD Student Pascal Cousin Laboratory Technician Jaime Humberto Copete Reina Laboratory Technician Annick Crevoisier Administrative Assistant Vincent Croset PhD Student Steeve Cruchet Laboratory Technician Thomas Curie Post-doctoral Fellow Sylvie Dafflon Washing Facility Gwendoline Degueurce PhD Student Maude Delacombaz Laboratory Technician Mauro Delorenzi BCF Coordinator Emilie Demarsy Post-doctoral Fellow Mara De Matos Laboratory Technician Corinne Dentan Administrative Assistant Oleksandr Dergai Post-doctoral Fellow Ilena D'Errico Post-doctoral Fellow Béatrice Desvergne Group Leader Mieke De Wit Post-doctoral Fellow Shanaz Diessler PhD Student Vincent Dion Group Leader Jun Ding Post-doctoral Fellow Wanda Dolci Laboratory Technician

Central services in 2013-2014

Chief operating officer
Nicole Vouilloz

Administration
Corinne Dentan
Kyle Marshall
Fabienne Sauvain

IT service
Fanny Gex
Corinne Hänggeli

Washing facility
Suresh Balsiger
Sylvie Dafflon
Joan Justiniano

Stock, maintenance and ordering
Marlyne Berger
Noura Egger
Christiane Freymond

Animal facility
Patrick Gouait
Alain Guéniot
José Luis Huaman Larios
Fabienne Junod Fontoillet
Martha Justiniano
Ridge Mafuala
Senda-N'ton Mafuala-Manua
Brigitte Lagnel
Cynthia Liardon
Marie-France Piguet
Mathieu Piguet
Caroline Ravy

Phenotyping facility
Catherine Moret

Genotyping facility
Armelle Bauduret
Marianne Carrard
Katharina Hausherr

Sequencing facility
Marina Pronina

Workshop
Gilles Boss

Apprentices
Anouk Berger
Jérôme Blanc
Elodie Colonello
Nathalie Fares
Lisa Haerri
Marc Lietti
Noélie Rochat

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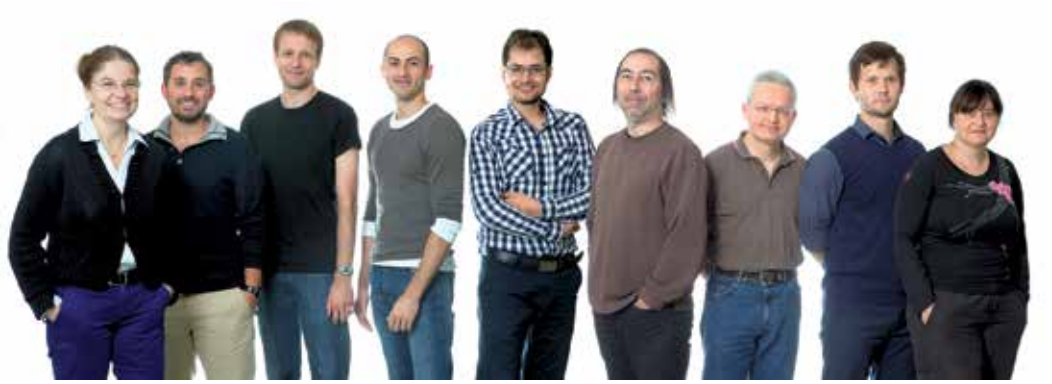

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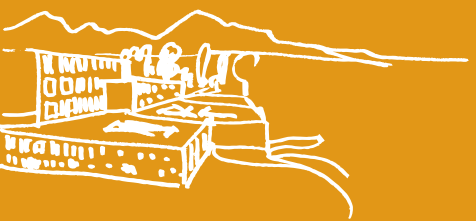

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