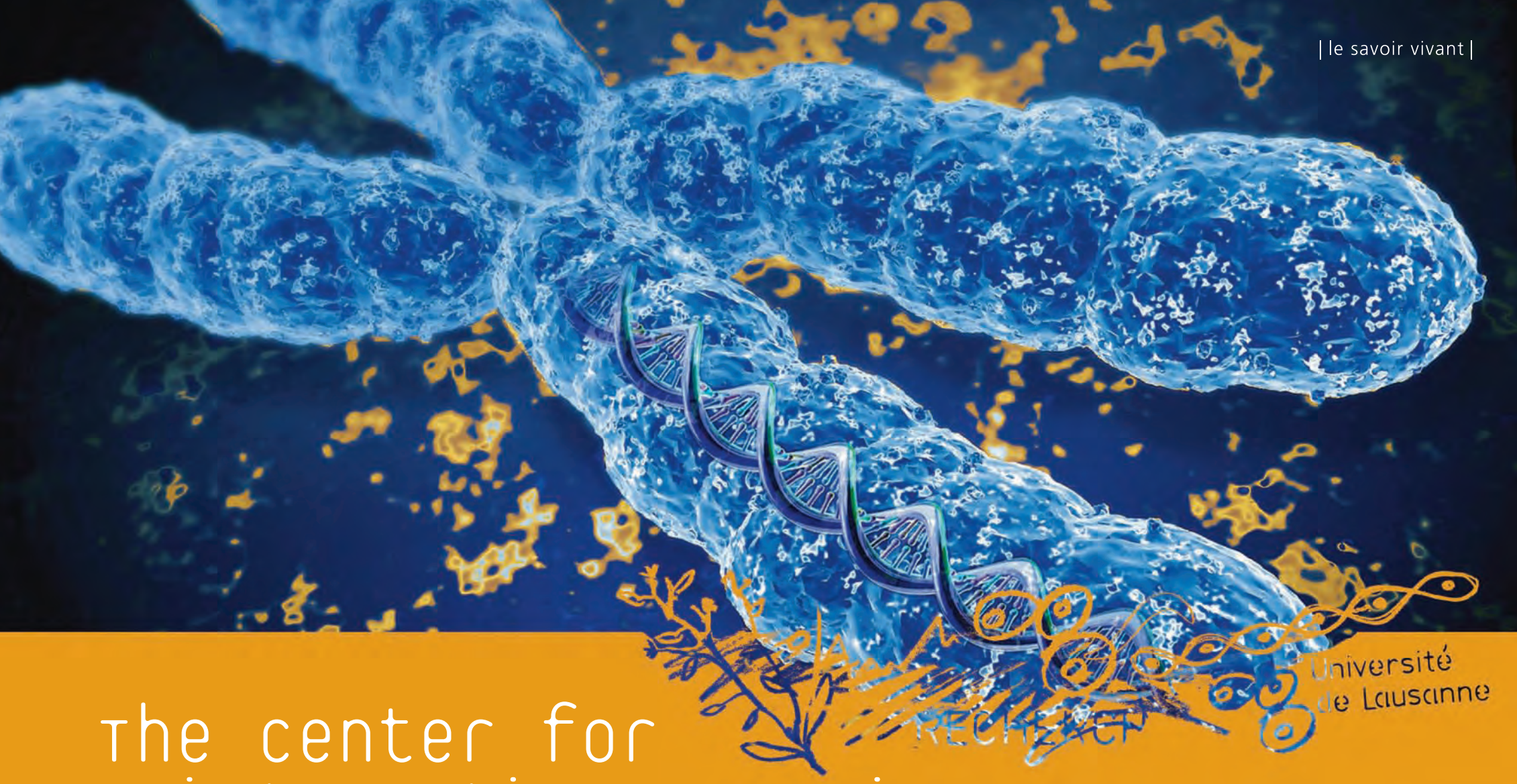


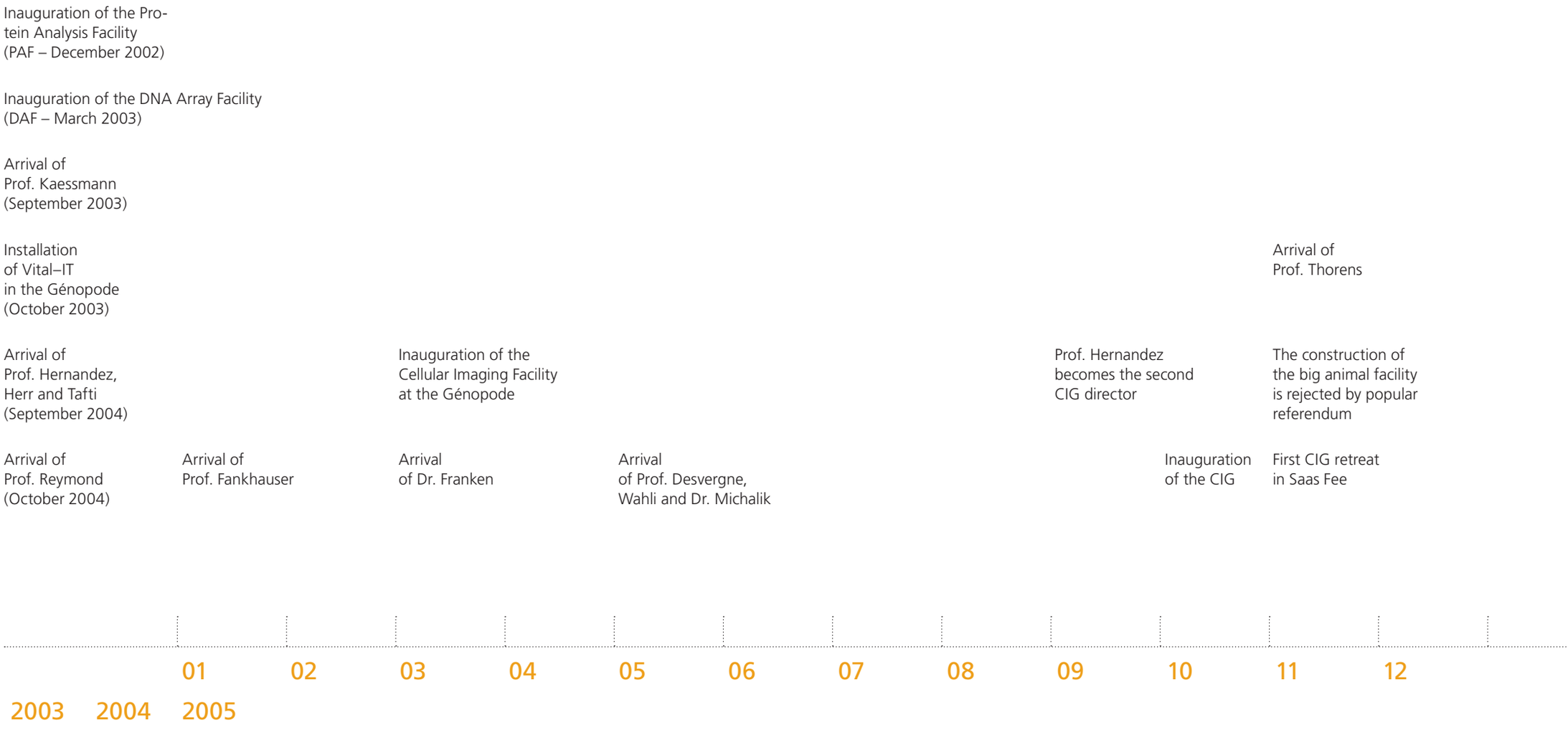
The center for integrative genomics

Report 2005-2006

UNIL | Université de Lausanne
Centre intégratif
de génomique

Index

CIG Timeline



Installation HeLa in the hall of the Génopode (until December 2006)

«Journées de la recherche en génétique»

«passeports vacances» (July and August)

Lectures «continuing education»

Inauguration of the Center for Investigation and Research on Sleep (CIRS)

UNIL open house days

Second CIG retreat in Saas Fee

Installation of the Mouse Metabolic Evaluation Facility (MEF)

01 2006 02 03 04 05 06 07 08 09 10 11 12 2007

Message from the Director

WE ARE IN THE MIDST OF A REVOLUTION IN THE BIOLOGICAL SCIENCES.

This revolution, started with the sequencing of the human genome and then that of a number of other organisms, continues with the spectacular development of technologies that allow the interrogation of thousands of molecules in one experiment. We can now not only compare the genome structures of, for example, a normal cell and a cancer cell, but also the expression pattern of an entire genome in different cells, at different times, and under different conditions. Any molecule of interest can be analyzed in such a global manner, from mRNAs, small RNAs, and proteins to metabolites and other compounds. The techniques that allow these types of experiments are powerful, but they offer a challenge to the individual research laboratory: they rely on costly instruments, unaffordable for the typical research group, and on highly specialized know–how, and this not only for the generation of the data but also for their analysis.

It is in the context of this biological revolution that the Center for Integrative Genomics was created, a center combining research groups working on functional genomics with core facilities offering, not only to the Center itself but to the entire surrounding region, the latest technologies in genome analyses. The Center was officially inaugurated on the 27th of October 2005. The inauguration was followed on the 28th by the inaugural CIG Symposium "Genomics, a new road for science and society". These public events that marked the birth of the CIG were the culmination of an enormous amount of work that involved many scientists in the Lemanic region.

The conception of the CIG was intimately linked to the project "Science, Vie, Société" (SVS), in which, in an unprecedented collaborative effort, the Universities of Lausanne (UNIL) and Geneva (UNIGE), and the EPFL (Ecole Polytechnique Fédérale de Lausanne) agreed to redistribute some of their competences to avoid redundancies and optimize the use of resources. The SVS project was developed in the years 2000 and 2001 and resulted in the transfer of the UNIL sections of Chemistry, Mathematics, and Physics to the EPFL, in the fusion of the UNIL School of Pharmacy with that of the UNIGE, and in the fusion of the UNIL Biology section with the UNIL Faculty of Medicine to create the first Faculty of Biology and Medicine in Switzerland. It also resulted in the creation of two research axes, one focused on functional genomics and the other on human and social sciences.

What form the functional genomics axis of the SVS program would take was of great interest to W. Wahli (UNIL) and D. Duboule (UNIGE) who composed, as early as 1999, a first document describing a "Swiss Center of Genetics/Genomics". The missions of this proposed center included cutting–edge research and teaching in genomics, data collection and analysis, the development of core facilities, the development of interactions between fundamental and biomedical research, and the facilitation of technology transfer, an ambitious set of goals indeed!

In the following year, the project was further studied by two committees, the "groupe de réflexion stratégique lausannois" on the one hand, and a group of three people representing the three SVS program institutions and charged with developing its genomic aspect on the other hand. These documents already mentioned the Center by its present name, the Center for Integrative Genomics, and mentioned its location in the Pharmacy Building of the UNIL. The CIG was viewed as a place where genetic models then absent at the UNIL would be introduced, where bioinformatics would be developed, and where core facilities would be established. The second document described the CIG as a new type of structure, perhaps a foundation, co–owned by the three SVS members.

In 2001, a final report was presented to the Rectorate of the UNIL by a group composed of professors from the Faculty of Sciences and from the Faculty of Medicine. One of the important points of this report was the realization that the financing of the CIG, originally imagined as provided by the three SVS institutions, would in fact be provided by the UNIL; this led to the eventual incorporation of the CIG into the UNIL as a department of its Faculty of Biology and Medicine.

In 2002, Walter Wahli was appointed the founding director of the CIG, and in Autumn 2004, work started in the building now known as the Génopode to prepare it for the move of the first CIG groups. Several people gave a lot of their time to the transformation of the Pharmacy Building into the Génopode, in particular Liliane Michalik, the delegate of the Rectorate to the renovation of the building, who worked closely with the architect Guido Cocchi and with the coordinator of the work on the site, Stéphane Porchet. Béatrice Desvergne contributed her knowledge of mouse work to help in the design of the CIG animal house. The renovation was officially completed in May 2005, and the last group to move in, that of Bernard Thorens, arrived in October 2005, just in time for the inauguration!

After several years of relentless work to see the CIG evolve from an idea, formulated in early 1999, to a reality, Walter Wahli resigned as CIG Director as of September 2005, having decided, I think, that it was time for the CIG to "fly with its own wings", and that it was time for him to go back to teaching and research. We at the CIG are all indebted to Walter and it is fitting that he be thanked here, in this first biennial report of CIG, for having devoted so much effort and energy to the development of this very unique center! And on my part, I thank him for having helped immensely the next CIG director learn the ropes!

The CIG inauguration was closely followed by the success of the popular referendum against the construction of a large animal house, the last piece of the CIG project, that was to be built underground on the south side of the Génopode. This was indeed a depressing moment for the just inaugurated CIG and was to have profound long–term consequences for the UNIL at large, all of which have yet to be fully grasped. One consequence was the impossibility for the CIG to develop further research using the mouse as an animal model, and another was the greatly increased difficulty to regroup basic research on the Dorigny campus. It is with these new elements that the CIG completed its first year in the Génopode.

With all its groups now in a single building, the CIG could start taking care of recruiting new colleagues. One of the first undertakings was the organization, in large part through the efforts of C. Fankhauser, A. Reymond, and B. Thorens, of a seminar series in which we invited a number of young people eligible to apply for a "professeur boursier" position to present their work and meet CIG faculty. A few months after this recruitment effort, a second recruitment was launched to fill our last CIG faculty position. The recruiting committee included professors S. Antonarakis (UNIGE), M. Swartz (EPFL), J. Beckmann, L. Keller, P. Moreillon, J. Tschopp, and myself, as well as M. Haenni who represented the "corps intermédiaire" and L. Baratali who represented the students (all UNIL). The committee was presided by I. Stamenkovic (UNIL). Thanks to the enthusiasm and energy of its president and the dedication of committee members, progress was fast. As a result of these combined efforts, by the end of 2006 the CIG had recruited

a candidate professeur boursier, Dr. Sophie Martin, and an assistant professor, Dr. Richard Benton. Sophie Martin is presently a post–doctoral fellow in the Department of Microbiology at Columbia University in New York, USA, working with Fred Chang on cell polarization in the fission yeast Schizosaccharomyces pombe. Richard Benton is a post–doctoral fellow at the Rockefeller University in New York, USA, working with Dr. Leslie Vosshall on olfaction in the fruit fly, *Drosophila melanogaster*. We look forward to welcoming them in 2007!

Another type of recruiting effort was that of the CIG scientific advisory committee. We were fortunate to convince a group of exceptional scientists to be part of this committee; their guidance will be invaluable in helping us achieve our missions. Their first visit will take place in June of 2007 and they should find a fully functional CIG!

The CIG cannot easily be dissociated from the other "inhabitants" of the Génopode building. The Génopode with all its research groups, including not only the CIG and the Unité CIG Sciences (UCS) but also groups from the Swiss Institute of Bioinformatics, the Ludwig Institute, and the group of Olivier Michielin from the Multidisciplinary Oncology Center (CePO), and with its core facilities including the DNA Array and Protein Analysis Facilities (DAF and PAF), the Cellular Imaging Facility (CIF), the Vital-IT facility, the Mouse Metabolic Evaluation Facility (MEF), is well prepared for the challenges of modern biology. The highly interactive environment of the Génopode, together with its location on the Dorigny campus, close to its SVS partners, indeed neighbor to the EPFL, and less than an hour away from the University of Geneva, makes it an exciting place to work.

The genomic revolution, with its new tools and the knowledge of entire genome sequences, is greatly accelerating the rapidity with which we can decipher the mechanisms of life. The magnitude and speed of biological research today are having an ever increasing impact on society. Given the individuals involved and given the facilities available, there is no doubt in my mind that the CIG will develop into a major player in international biology research. It will be all the more important, then, that it develops its mission of education and teaching, not only of students in biology, but also of the public at large.

Nouri Hernandez, Director

Landmarks of the development of the Center for Integrative Genomics

THE SCIENCE, VIE, SOCIÉTÉ (SVS) PROGRAM	THE CIG
• **22–10–1998:** first outline of a tripartite (UNIL, UNIGE, EPFL) coordination project	
	• **Spring 1999:** W. Wahli and D. Duboule author a first document describing a "Swiss Center of Genetics/Genomics"
• **22–02–2000:** founding document describing the SVS project	
	• **16–08–2000:** the "groupe de réflexion stratégique lausannois", chaired by H. Diggelmann and composed of M. Aguet, J. Dubochet, L. Keller, N. Mermod, G. Pantaleo, B. Rossier, presents a report entitled "Centre intégratif de génomique et pôle de génomique fonctionnelle" to the Rector of the UNIL.
• **30–06–2000:** the cantons of Vaud and Geneva as well as the Swiss Confederation sign a common declaration of intent.	
	• **25–11–2000:** H. Diggelmann (UNIL), D. Duboule (UNIGE), and H. Vogel (EPFL) write a document titled "Pôle de génomique fonctionnelle".
	• **08–06–2001:** report on the CIG to the UNIL Rectorate by N. Mermod, J. Dubochet, B. Desvergne, L. Keller, P. Mangin, J.P. Kraehenbuhl, M. Aguet and G. Pantaleo.
• **03–07–2001:** the Universities of Lausanne and Geneva, and the EPFL sign the SVS convention.	
	• **01–01–2002:** W. Wahli is appointed founding director of the CIG
	• **01–09–2005:** N. Hernandez becomes 2nd CIG director
	• **27–10–2005:** CIG inauguration
	• **28–10–2005:** inaugural CIG symposium

CIG – Scientific Advisory Committee

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

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

The SAC will meet for the first time in June 2007 at the CIG.

The CIG is particularly honored that the following persons accepted to join the committee:

Dr Laurent DURET
Laboratory of Biometry and Evolutionary Biology
Université Claude Bernard – Lyon I
Villeurbanne, France

Prof. Robert EISENMAN
Fred Hutchinson Cancer Research Center
Department of Biochemistry
University of Washington
Seattle, USA

Prof. Susan GASSER
Director, Friedrich Miescher Institute for Biomedical Research (FMI)
Basel, Switzerland

Prof. Ueli GROSSNIKLAUS
Department of Developmental Genetics
University of Zurich
Zurich, Switzerland

Prof. Jacques SAMARUT
Director of the research, Ecole Normale Supérieure (ENS) de Lyon
Laboratory of Molecular Cell Biology
Lyon, France
and
Université Claude Bernard Lyon I
Villeurbanne, France

Prof. Ueli SCHIBLER
Member of the National Center of Competence in Research Frontiers in Genetics
Department of Molecular Biology
University of Geneva
Geneva, Switzerland

Prof. Ivan STAMENKOVIC
Director, Department of Experimental Pathology
University of Lausanne
Lausanne, Switzerland

Prof. Markus STOFFEL
Institute of Molecular Systems Biology
Swiss Federal Institute of Technology Zurich (ETHZ)
Zurich, Switzerland

Prof. Gisou VAN DER GOOT
Global Health Institute
EPFL (Ecole Polytechnique Fédérale de Lausanne)
Lausanne, Switzerland

Organigram of the CIG

Scientific Advisory Committee

University of Lausanne, Faculty of Biology and Medicine

Center for Integrative Genomics

- **Director: Nouria Hernandez**
  Directing Committee: CIG faculty members,
  representative of the administrative and technical staff

Research

CIG research groups

- **The structure and function of genomes and their evolution**
  Alexandre Reymond / Henrik Kaessmann / Victor Jongeneel
- **The regulation of gene expression**
  Nouria Hernandez / Winship Herr / Christian Fankhauser
- **The genomics of complex functions**
  Mehdi Tafti / Paul Franken / Bernard Thorens / Walter Wahli / Liliane Michalik / Béatrice Desvergne

Associated research groups

Core Facilities

CIG Core Facilities

- DNA Array Facility – DAF
- Protein Analysis Facility – PAF

Associated Core Facilities

- Vital-IT
- Cellular imaging facility – CIF
- Bioinformatics core facility – BCF
- Mouse metabolic evaluation facility – MEF
- Centre for Investigation and Research on Sleep – CIRS

Central Services

- Central administration
- Animal facility
- Genotyping
- Phenotyping
- Sequencing
- Common equipment lab
- Washing facility
- Workshop
- Informatic support
- Stocks and ordering

research

Alexandre Reymond

Assistant Professor

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

Genome Structure and Expression

The completion of the human genome sequence, as well as recent technological advances have demonstrated that our genome is much more fluid than we had thought and that variations can be of any scale. Inversions and copy number polymorphisms (CNPs), i.e. large stretches of genomic DNA that vary considerably in copy number, appear so abundant that it is conceivable that they play a major role in functional variation. Consistently, genomic insertions and deletions were shown to contribute to phenotypic differences by modifying the expression levels of genes within the aneuploid segments. We have recently shown that not only the genes mapping within the microdeletion that causes Williams–Beuren Syndrome (WBS), but also that the 7q11.23 normal copy neighboring genes showed decreased relative levels of expression. Our results suggest that not only the aneuploid genes, but also the flanking genes that map several megabases away from a genomic rearrangement should be considered as possible contributors to the phenotypic variation in genomic disorders. Thus we can hypothesize that changes in genome structure will modify the phenotype not only by changing levels of expression of genes mapping within the rearranged region, but also of genes mapping nearby. We will test this hypothesis by measuring relative expression levels of these genes (i) in cell lines without or with a rearrangement, namely recurrent deletions, balanced translocations and inversions; and (ii) in mouse tissues with varying copy numbers of CNPs. This should allow better understanding on how large size variation are influencing the expression genes and possibly the phenotype.

Group

GROUP LEADER

Alexandre Reymond
alexandre.reymond@unil.ch

TECHNICIAN

Jacqueline Chrast

POSTDOCTORAL FELLOWS

Gérard Didelot
Louise Harewood

PhD STUDENTS

Charlotte Henrichsen
Evelyne Chaignat
Cédric Howald

ADMINISTRATIVE ASSISTANT

Annick Crevoisier

Publications

RESEARCH ARTICLES

Eyras E, Reymond A, Castelo R, Bye JM, Camara F, Flicek P, Elizabeth J, Huckle EJ, Parra G, Shteynberg DD, Wyss C, Rogers J, Antonarakis SE, Birney E, Guigo R, Brent MR (2005)
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Different mechanisms preclude mutant CLDN14 proteins to form tight junctions in vitro. Hum Mutat 25: 543–549

Castelo R, Reymond A, Wyss C, Camara F, Parra G, Antonarakis SE, Guigó R, Eyras E (2005)
Comparative gene finding in chicken indicates that we are closing in on the human gene set. Nucleic Acids Res 33: 1935–1939

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GENCODE: Producing a reference annotation for ENCODE. Genome Biol 7 Suppl 1: S4 1–9
**equal author contribution*

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Collaborations

S. E. Antonarakis,
University of Geneva, Switzerland

A. Ballabio,
Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy

E. Birney,
European Bioinformatics Institute, Hinxton, UK

E. Blennow,
Karolinska University Hospital Solna, Stockholm, Sweden

H. G. Brunner,
Stichting Katholieke Universiteit, Nijmegen, Netherlands S. Eliez, University of Geneva, Switzerland

D. FitzPatrick,
Medical Research Council (MRC), Edinburgh, UK

T. E. Gingeras,
Affymetrix Inc., Santa Clara, USA

R. Guigo,
Centre de Regulació Genomica, Barcelona, Spain

J. Harrow and T. Hubbard,
Wellcome Trust Sanger Institut, Hinxton, UK

Y. Herault,
CNRS, Orléans, France

M. del Mar Dierssen Soto and X. Estivill,
Centre de Regulació Genomica, Barcelona, Spain

G. Merla,
IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy

L. Pérez Jurado,
Universitat Pompeu Fabra, Barcelona, Spain

M. Ruedi,
Muséum d'Histoire Naturelle, Geneva, Switzerland

M.–L. Yaspo,
Max Planck Institute for Molecular Genetics Berlin, Germany

M.–T. Zabot,
Hôpital Debrousse, Lyon, France

Henrik Kaessmann

Assistant Professor

Henrik Kaessmann received his PhD in 2001 from the University of Leipzig, after working on the genetic diversity of humans and the great apes in the laboratory of Dr. Svante Pääbo at the University of Munich and subsequently at the Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany. He obtained his postdoctoral training with Dr. Wen–Hsiung Li in the Department of Ecology and Evolution at the University of Chicago, USA, where he worked on the origin of human genes and gene structures. He joined the Center for Integrative Genomics in 2003.

Evolutionary Genomics

The research of my group focuses on the origin and evolution of new genes (and gene structures) that emerged recently on the primate lineage leading to humans from duplicate gene copies. We have in particular focused on the origin of new genes by retroposition (or retroduplication), where the mRNA of a parental source gene is reverse–transcribed and integrated into a new genomic position (mediated by enzymes derived from L1 retrotransposable elements), generating intronless retrocopies of the parent. We showed that retroduplication has generated a significant number of functional retrogenes on the primate lineage leading to humans, about one new retrogene per million years during primate evolution. To understand the source of regulatory elements of retrogenes that allows for their functionality, we systematically studied retrocopy transcription. We found that retrocopies often profit from the transcription of nearby genes, either by directly utilizing the transcriptional machinery of host genes (e.g. by gene fusion), or by profiting from cis–acting regulatory elements and/or open chromatin of nearby genes.

In a systematic evolutionary survey of primate retrocopies, we pinpointed several functional human retrogenes that emerged between ~18 to ~35 million years ago. In addition to showing a more tissue–specific expression pattern, several of these young retrogenes displayed signatures of positive selection, indicative of new or modified protein functions. With respect to their spatial expression patterns, we found that, generally, these retrogenes revealed a testis expression bias, which is probably due to the generally promiscuous transcription of chromatin in late male meiosis. This initially mechanistically–driven transcription may have allowed retrocopies to often initially evolve into retrogenes with functions in testis. However, later in their evolution they may evolve functions in other tissues. Indeed, we have discovered and characterized several intriguing brain–expressed retrogenes (e.g. GLUD2 and CDC14Bretro) that originated recently in the hominoid ancestor, experienced intense positive selection, and may thus have contributed to the evolution of the more complex human brain.

We are currently expanding our work on duplicate genes to study the evolution and phenotypic impact of very recent (and hence polymorphic) human and chimpanzee genes contained within duplicated chromosomal segments (so called segmental duplications).

In addition to these major lines of research, we have been collaborating with several groups at the University of Lausanne and abroad to work on various projects pertaining to molecular evolution, such as the evolution of viral host defense genes (with A. Telenti, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne), or the evolutionary fate of egg yolk genes in mammals (with W. Wahli, CIG).

Group

GROUP LEADER
Henrik Kaessmann
henrik.kaessmann@unil.ch

TECHNICIAN
Manuela Weier

POSTDOCTORAL FELLOWS
Jean–Vincent Chamary
Isabelle Dupanloup*
Maxwell Ingman
Lia Rosso

PhD STUDENTS
David Brawand
Ana Machado Rebelo Marques
Lukasz Potrzebowski
Nicolas Vinckenbosch
Lionel Maquelin

MASTER STUDENT
Lionel Maquelin*

ADMINISTRATIVE ASSISTANT
Annick Crevoisier

*left the group

Publications

RESEARCH ARTICLES

Marques A*, Dupanloup I*, Vinckenbosch N, Reymond A, Kaessmann H (2005)
Emergence of young human genes after a burst of retroposition in primates. PLoS Biol 3 : e357
**equal author contribution*

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Collaborations

S. Bahn,
Centre for Neuropsychiatric Research, Cambridge, UK

L. Hurst,
University of Bath, UK

L. Keller and R. Hammond,
University of Lausanne, Switzerland

S. Pääbo,
Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

A. Telenti,
Centre Hospitalier Universitaire (CHUV) and University of Lausanne, Switzerland

W. Wahli,
University of Lausanne, Switzerland

Victor Jongeneel

Associate professor ad personam

Victor Jongeneel got his Lic. Sc. From the University of Lausanne in 1974 and his PhD from the University of North Carolina at Chapel Hill , USA (1980). He did his post doctoral training at the University of California, San Francisco, USA between 1980 and 1983 and at the Swiss Institute for Experimental Cancer Research (ISREC) between 1983 and 1985. He then became an Assistant Member and Associate Member of the Lausanne Branch of the Ludwig Institute for Cancer Research (LICR) (1986–1996), and later Director of the Office of Information Technology, LICR worldwide (1998–2006), He is a founding Member and the first Director of the Swiss Institute of Bioinformatics (SIB) (1998–2002), and is Associate Professor ad personam at the University of Lausanne since 2002. He is associated with CIG since 2005 and is directing the Vital-IT Center since 2003.

Cancer genomics

Recent evolution of genes coding for cancer–testis (CT) antigens: We are comparing the sequence, structure and chromosomal localization of CT antigens between the chimpanzee and human genomes. Our data show that as expected, the human and chimpanzee CT gene families are found in the same genomic neighborhoods. However, it is clear that CT genes, both on the X chromosome and on autosomes, are under strong diversifying selection, as witnessed by high non–synonymous substitution rates and hominid–specific gene duplications. In fact, CT genes account for much of the excess positive selection observed on the X chromosome relative to autosomes.

Establishing a comprehensive catalog of human X–linked CT genes: The literature on CT–X genes is rather fragmented, with inconsistent nomenclatures and often inconclusive data to support the classification and inventory of gene families. We are in the process of trying to establish a “definitive” catalog of CT–X genes, with the aim to publish an authoritative review on the subject.

Identification of novel tumor antigens in colon carcinomas: Using MPSS and EST data, we have identified several new genes that are differentially expressed in colon carcinomas relative to normal colon epithelium. Their differential expression has been verified by Q–PCR on multiple tumor biopsies. Their potential as targets for immunotherapy is currently being investigated.

Analysis of the mouse reference transcriptome: Several Institutes within the NIH have commissioned the production of an in–depth analysis of the mouse transcriptome using the MPSS technique. This project is not quite finished, as several of the selected tissue transcriptomes have proven not be tractable to analysis by this technique. We have already produced some interesting results from the dataset in its current state. The data have also raised some important questions regarding the relative information content and reliability of SAGE and MPSS data. We are currently modeling the properties of the data generated by the two types of experimental approaches using statistical methods, and verifying the models against experimental data, the aim being to establish reasonable criteria for the biological interpretation of such data.

Software development for genomics: C. Iseli has written a series of software packages to perform sequence analysis tasks: high–throughput alignment of cDNA to genome sequences (SIBsim4), fast mapping of large tag sequence collections to a reference genome or transcriptome (tagger and fetchGW), and derivation of detailed gene models with alternative splicing from a collection of cDNA to genome alignments (tromer). We are in the process of benchmarking these programs against other publicly available software and of documenting them in detail.

Group

GROUP LEADER
Victor Jongeneel
cornelisvictor.jongeneel@unil.ch

ASSISTANT INVESTIGATORS
Christian Iseli
Brian Stevenson

BIOINFORMATICS SPECIALIST
Dimitry Kuznetsov

EDITORIAL ASSISTANT, DATABASE CURATOR
Monique Zahn–Zabal

MASTER STUDENT
Ludivine Rielle

ADMINISTRATIVE ASSISTANT
Jocelyne Muller

Publications

RESEARCH ARTICLES

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Collaborations

C. Austin,
National Institutes of Health (NIH), Bethesda, USA

Y. Chen,
Cornell University Medical Center, New York, USA

M. Delorenzi,
NCCR Molecular Oncology and Swiss Institute of Bioinformatics (SIB), Lausanne, Switzerland

W. Hide,
University of the Western Cape, Bellville, South Africa

F. Levy,
Ludwig Institute for Cancer Research (LICR), Lausanne, Switzerland

F. Naef,
EPFL (Ecole Polytechnique fédérale de Lausanne), Switzerland

C. Notredame,
CNRS, Marseille, France

A. Simpson,
Ludwig Institute for Cancer Research (LICR), New York, USA

A. Telenti,
Centre Hospitalier Universitaire (CHUV) and University of Lausanne, Switzerland

Numerous collaborations through Vital-IT projects

Nouria Hernandez

Professor

Nouria Hernandez performed her thesis research on mRNA splicing with Dr. Walter Keller at the University of Heidelberg in Germany and received her PhD in 1983. She did her postdoctoral studies with Dr. Alan M. Weiner at Yale University in New Haven, Connecticut, USA, working on the 3' end formation of the U1 small nuclear RNA. She then joined Cold Spring Harbor Laboratory at Cold Spring Harbor, New York, USA, 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.

Mechanisms of transcription regulation

With the sequencing of entire genomes from several organisms, we are faced with the challenge of understanding how individual genes are specifically expressed, and how such expression is regulated. A large part of the regulation of gene expression occurs at the transcriptional level. We are interested in understanding fundamental mechanisms of transcription regulation. As a model system, we use the human small nuclear RNA (snRNA) genes. The U1 and U2 snRNA genes are transcribed by RNA polymerase (pol) II whereas the U6 snRNA gene is transcribed by pol III, yet all snRNA genes share very similar promoter structures and thus constitute a model system to study how RNA polymerase specificity is determined. Moreover, we can reconstitute basal U6 transcription in vitro with well–defined factors; since the basal transcription machinery is the ultimate target of signal transduction pathways, this gives us a unique opportunity to study mechanisms of regulation. Lately we have concentrated on the characterization of the TFIIB–related factor 2 (Brf2), a key factor in the determination of pol III specificity, as well as on the identification of new factors that regulate pol III transcription.

TFIIB, Brf1, and Brf2 are part of a family of transcription factors that share very similar N–terminal zinc ribbon and core domains. Brf1 and Brf2 have in addition C–terminal extensions absent in TFIIB. TFIIB is essential for the recruitment of pol II to promoter sequences whereas Brf1 and Brf2 are essential for pol III transcription. We found that the C–terminal extension of Brf2, although at first sight unrelated to that of Brf1, has in fact a similar function, being essential for the assembly of a pol III preinitiaiton complex. This indicates that the C–terminal extensions in Brf1 and Brf2 are key to specific recruitment of pol III over pol II.

To identify new players in the regulation of snRNA gene transcription, we generated cell lines expressing a doubly tagged subunit of the snRNA activating protein complex (SNAP$_C$), a factor required for transcription of both pol II and pol III snRNA genes, and used this cell line to purify SNAP$_C$ and associated factors. This led to the identification of Yin Yang–1 (YY1) as a SNAP$_C$–associated factor involved in the assembly of the U6 transcription initiation complex. Moreover, we tested whether the human homolog of yeast Maf1 plays a role in pol III transcription. Yeast Maf1 was recently identified as a factor required for repression of pol III transcription after stress. Our results show that human Maf1 keeps pol III transcription in check in dividing cells and is required for repression of pol III transcription after stresses such as DNA damage. Thus, human Maf1 is a central regulator of pol III transcription in human cells. Since pol III transcription is upregulated in malignant cells, it is likely that either Maf1 itself or factors required for the activation of Maf1 are deregulated in cancer cells.

Group

GROUP LEADER
Nouria Hernandez
nouria.hernandez@unil.ch

TECHNICIAN
Pascal Cousin
Philippe L'Hôte

MAITRE–ASSISTANT
Erwann Vieu**

POSTDOCTORAL FELLOWS
Teldja Neige Azzouz
Michaël Boyer–Guittaut*
Annemieke Michels
Erwann Vieu**

PhD STUDENTS
Agnès Déglon–Fischer*
Jaime Humberto Reina

MASTER STUDENTS
Claire Bertelli*
Henrieta Hrobova Crausaz*

ADMINISTRATIVE ASSISTANT
Nathalie Clerc

*left the group
**changed function

Publications

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Collaborations

C. Carles,
Life Sciences Division, CEA, Saclay, France

I. Grummt,
German Cancer Research Center, Heidelberg, Germany

Winship Herr
Professor

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

Regulation of cell proliferation

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

To investigate these processes, we study a key regulator of the human cell–proliferation cycle that was originally discovered in studies of herpes simplex virus (HSV) transcription – the HSV host–cell factor HCF–1. Recent studies reveal that HCF–1 plays important roles in chromosome function at distinct stages of the cell cycle.

HCF–1 is unusual. It is an abundant, conserved, and chromatin–bound protein that undergoes proteolytic maturation resulting in stably associated amino– (HCF–1n) and carboxy– (HCF–1c) terminal subunits. Proteolytic maturation to form heterodimeric HCF complexes has been conserved between vertebrates and insects but the proteolytic mechanisms involved differ. We hypothesize that the mechanisms of HCF–protein maturation have evolved more than once.

In human cells, the HCF–1n and HCF–1c subunits play roles in two separate cell–cycle phases: the G1 and M phases, respectively. Consistent with pivotal roles in these processes, the HCF–1n subunit promotes G1–phase progression by associating with regulators of G1–phase transcription and recruiting trithorax–related histone H3 lysine 4 methyltransferases of the mixed–lineage leukemia family to promoters to effect histone modification and transcriptional activation. In contrast, during mitosis, the HCF–1c subunit controls chromosome dynamics, and histone phosphorylation and methylation, as well as associates with mitotic structures. We hypothesize that the two different subunits, via regulated association, influence each other's activity and help coordinate the M/G1 phase of the cell cycle.

Our current interests continue to focus on understanding how HCF–1 regulates cell proliferation – especially as it pertains to cancer – and cell differentiation.

Group

GROUP LEADER
Winship Herr
winship.herr@unil.ch

TECHNICIANS
Philippe L'Hôte
Fabienne Messerli

POSTDOCTORAL FELLOWS
Pei–Jiun Chen
Christina Hertel
Virginie Horn
Joëlle Michaud
Sara Rodriguez–Jato
Shweta Tyagi

PhD STUDENTS
Monica Albarca
Francesca Capotosti
Sophie Guernier

MASTER STUDENT
Coralie Carrascosa

ADMINISTRATIVE ASSISTANT
Nathalie Clerc

Publications

RESEARCH ARTICLES

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Collaborations

A. Busturia,
Universidad Autonoma de Madrid, Madrid, Spain

M. Hengartner,
University of Zurich, Zurich, Switzerland

J. Hsieh,
Washington University of California, St. Louis, USA

J. Tamkun,
University of California, Santa Cruz, USA

Christian Fankhauser
Associate professor

Christian Fankhauser carried out his thesis at the Swiss Institute for Experimental Cancer Research (ISREC) in the laboratory of Dr. Viesturs Simanis and received his PhD from the University of Lausanne in 1994. He did his postdoctoral training with Dr. Marty Yanofsky at University of California, San Diego, USA, and then with Dr. Joanne Chory at The Salk Institute for Biological Studies in San Diego. He then moved to the University of Geneva in 2000 as a Swiss National Science Foundation Assistant Professor at the Department of Molecular Biology. He joined the Center for Integrative Genomics in January 2005 as an associate Professor.

Light–regulated development in plants

Growth and development are influenced by both genetic and environmental factors. The effect of the environment is particularly apparent in the sessile plants. Being photoautotrophic, plants are exquisitely sensitive to changing light conditions. Molecular genetic studies in the model plant Arabidopsis thaliana have identified 3 photoreceptor families that are present in all higher plants: the blue light sensing cryptochromes and phototropins, and the phytochromes that maximally absorb red and far–red light (cry1–cry3, phot1, phot2, phyA–phyE in Arabidopsis). Photon capture by these photoreceptors induces a suite of developmental responses including seed germination, seedling de–etiolation, regulation of tropic growth, shade avoidance and the control of flowering time. Recent progress in deciphering phytochrome signaling has revealed: 1) in response to light the phytochromes enter the nucleus where they can directly interact with several bHLH class transcription factors (referred to as PIFs) suggesting that the phytochromes may directly modulate light–regulated gene expression, 2) the importance of light–regulated proteolysis involving the evolutionary conserved E3 ligase COP1 (COnstitutively Photomorphogenic 1); several phytochrome signaling components including phyA and members of the PIF family are subjected to this regulation, 3) cytoplasmic events in phytochrome signaling are still very poorly understood.

Our studies are mainly but not exclusively centered on phyA. At the physiological level we primarily analyze two responses: light regulation of tropic growth and the shade avoidance response. Recent studies have shown that these two modes of adaptation are particularly important to determine the success of plants grown in dense vegetation. At the molecular level we study phyA signaling in the cytoplasm and the nucleus. PKS1 (Phytochrome Kinase Substrate 1) is the starting point for our exploration of cytoplasmic events. PKS1 is a cytoplasmically–localized phy–signaling component member of a gene family in Arabidopsis (PKS1–PKS4). HFR1 (long Hypocotyl in FR light 1) is a nuclear phyA–signaling component related to the PIFs. The abundance of HFR1 is regulated by COP1 and phosphorylation. Studying the role of phosphorylation and light–regulated proteolysis is a central element of our research. Finally we are particularly interested in identifying the target genes of members of the PIF family of bHLH class transcription factors during light–controlled gene expression.

Group

GROUP LEADER
Christian Fankhauser
christian.fankhauser@unil.ch

TECHNICIANS
Laure Allenbach
Martine Trevisan

POSTDOCTORAL FELLOWS
Paula Duek Roggli*
Thierry Genoud
Chitose Kami
Séverine Lorrain
Isabelle Schepens

PhD STUDENTS
Matthieu De Carbonnel
Dimitry Debrieux
Vincent Fiechter
Patricia Hornitschek

MASTER STUDENT
Fabian Schweizer

ADMINISTRATIVE ASSISTANT
Nathalie Clerc

*left the group

Publications

RESEARCH ARTICLES

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Collaborations

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POPULARIZATION

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Y. Barral,
Swiss Federal Institute of Technology Zurich (ETHZ), Switzerland

J. Casal,
University of Buenos Aires, Argentina

M. Geisler and E Martinoia,
University of Zurich, Switzerland

U. Genick,
University of Brandeis, USA

R. Hedrich,
University of Würzburg, Germany

E. Liscum,
University of Missouri, Columbia, USA

J. Maloof,
University of California, Davis, USA

A. Murphy,
University of Purdue, USA

E. Schaefer,
University of Freiburg, Germany

C. de Virgilio,
University of Geneva, Switzerland

G. Whitelam,
University of Leicester, UK

Mehdi Tafti

Associate professor

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

Genetics of sleep and the sleep EEG

Based on available literature there is no doubt that many aspects of sleep are under a genetic control in both humans and animal models. These include not only the amount and the distribution of sleep but also very specific electroencephalographic (EEG) features of sleep and wakefulness. By using the inbred mouse as a genetic tool, we have been able to demonstrate that sleep as a quantitative trait is amenable to quantitative trait loci analysis (QTL). Although many genes with small effects might affect the amount and the distribution of sleep, some aspects such as the daily amount of paradoxical sleep may be under a major gene control. We have localized such a gene on the mouse chromosome 1 and are currently fine mapping the region to ultimately identify the responsible gene. We have been the first to report that a single gene may dramatically affect the quantitative sleep EEG. An EEG variant specific to paradoxical sleep (slow theta frequency) has been identified as the most heritable phenotype in inbred mice and subsequent mapping and functional studies identified Acads (acyl Coenzyme A dehydrogenase for short chain fatty acids) as the underlying gene. More recently, we have shown that the slow wave activity during sleep is also affected by a single gene (Rarb) involved in the vitamin A signaling pathway. We are now concentrating our research efforts on the genetic dissection of sleep need. Sleep need is homeostatically regulated (loss of sleep leads to compensatory processes, which are responsible for deeper recovery sleep). A gene for sleep need has been mapped on the mouse chromosome 13. Fine mapping studies in the identified region are ongoing. We use also gene expression profiling after sleep deprivation to investigate the molecular correlates of prolonged wakefulness. Finally, we are interested in sleep and circadian rhythms and their molecular basis in social species such as ants.

GENETICS OF SLEEP DISORDERS

Many sleep disorders run in families but their genetic bases are poorly understood. Our laboratory is specialized in the genetics of narcolepsy and sleepwalking. We perform family– and population–based studies using linkage, candidate gene, and genome–wide associations. We have also initiated a new Center for Investigation and Research on Sleep (CIRS) in collaboration with the Medical Department of the CHUV (Centre Hospitalier Universitaire Vaudois), where we plan to conduct sleep research in normal subjects and patients with sleep disorders. We have localized the first familial susceptibility gene for narcolepsy and have reported the first genetic evidence in sleepwalking. Future plans include genetics of normal sleep in twins and families.

Group

GROUP LEADER
Mehdi Tafti
mehdi.tafti@unil.ch

TECHNICIANS
Brice Petit
Corinne Pfister

POSTDOCTORAL FELLOWS
Laure Gurcel**
Anne Vassali

PhD STUDENTS
Stéphane Dorsaz
Laure Gurcel**
Subah Hasan
Stéphanie Maret
Danielle Mersch
Julie Vienne

MASTER STUDENTS
Valérie Calpini*
Sébastien Del Rizzo
Anne–Catherine Robyr*
Salma Tawffik*

ADMINISTRATIVE ASSISTANT
Annick Crevoisier

*left the group
**changed function

Publications

RESEARCH ARTICLES

Maret S, Franken P, Dauvilliers Y, Ghyselinck NB, Chambon P, Tafti M (2005)
Retinoic acid signaling affects cortical synchrony during sleep. Science 310: 111–113

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Collaborations

REVIEW ARTICLES

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Dauvilliers Y, Tafti M (2006)
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B. Bettler,
University of Basel, Switzerland

Y. Dauvilliers,
Centre Hospitalier Universitaire (CHU), Montpellier, France

L. Keller,
University of Lausanne, Switzerland

M. Mühlethaler,
University of Geneva, Switzerland

U. Schibler,
University of Geneva, Switzerland

Paul Franken

Maître d'enseignement et de recherche

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

Genetics and Energetics of sleep homeostasis and circadian rythms

In the study of sleep two main regulatory processes have to be considered: a homeostatic process that is activated by and counters the effects of sleep loss and a circadian process that determines the time–of–day sleep preferably occurs. The fine–tuned interaction between the two permits us to stay awake and alert throughout the day and to remain asleep at night. To gain inside into the molecular correlates of the homeostatic process and its interaction with the circadian process we apply both forward and reverse genetic approaches in the mouse.

Using Quantitative Trait Loci (QTL) analysis as a forward genetics tool we found several genomic regions affecting sleep and EEG traits indicating the presence of major genes. Especially EEG traits were found to be under strong genetic control. Thus far, we were successful in identifying the genes modifying two such traits thereby implicating novel signaling pathways involved in rhythmic brain activity. Currently, we focus on fine mapping the dps1 QTL that alters the highly predictive relationship between time–spent–awake and EEG delta power hoping to identify the molecular mechanisms of sleep homeostasis.

Although the circadian and homeostatic processes are thought to operate independently, we found that the genes known to set circadian time are also involved in the homeostatic regulation of sleep. Thus, in mice that lack one or more of the core clock components (e.g. clock, bmal1, npas2, cry1 and cry2) sleep homeostasis is altered. We also showed that the expression of the clock genes per1 and per2 in the forebrain is tightly linked to the prior sleep–wake history. Thus at a cellular level the same molecular circuitry seems to be implicated in both circadian rhythms and sleep homeostasis. We investigate the mechanisms that link clock gene expression to the time–spent–awake. The observation that the transcriptional activity of CLOCK and NPAS2 depends on and affects intracellular energy charge is an exciting first clue we are currently pursuing by using redox–sensitive GFP probes and developing in vivo imaging techniques.

Group

GROUP LEADER
Paul Franken
paul.franken@unil.ch

TECHNICIAN
Yann Emmenegger

POSTDOCTORAL FELLOW
Thomas Curie

Publications

RESEARCH ARTICLES

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R. Chrast,
University of Lausanne, Switzerland

C. Grundschober and C. Lopez,
Roche, Basel, Switzerland

H. Craig Heller and P. Bourgin,
Stanford University, USA

S. McKnight,
UT Southwestern Medical Center, Dallas, USA

B. O'Hara,
University of Kentucky, Lexington, USA

M. Tafti,
University of Lausanne, Switzerland

Walter Wahli
Professor

After receiving his PhD in Bern, Walter Wahli carried out his postdoctoral education with Dr. Igor Dawid at the Department of Embryology, Carnegie Institution of Washington in Baltimore, USA. He then was at the Department of Biochemistry of the National Cancer Institute, NIH, in Bethesda, USA, as visiting fellow and visiting associate. He moved to Lausanne 1980, and is the Founding Director of the Center for Integrative Genomics (2002–2005).

Peroxisome Proliferator-Activated Receptors (PPARs) as regulators of metabolic and tissue repair processes

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

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

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

Group

GROUP LEADER
Walter Wahli
walter.wahli@unil.ch

MAITRE D'ENSEIGNEMENT ET DE RECHERCHE
Liliane Michalik

ANIMAL KEEPER
Marianne Wertenberg

TECHNICIANS
Berendina Bordier
Christiane Freymond
Sylvia Moreno
Norman Moullan
Corinne Tallichet Blanc

MAITRES–ASSISTANTS
Laurent Gelman*
Nicolas Rotman**

POSTDOCTORAL FELLOWS
Anen Delgado*
Radina Kostadinova
Alexandra Krauskopf
Alexandra Montagner
Nicolas Rotman**
Zofia Terreau–Haftek

PhD STUDENTS
Silvia Anghel
David Brawand*
Nathalie Constantin
Ilhem El Kochairi
Guillaume Icre*
José Iglesias
Virginie Jeronimo
Caroline Lathion*
Nicolas Leuenberger

MASTER STUDENTS
David Barras*
David Brawand*
Henrieta Hrobova Crausaz*
Matteo Ricci

APPRENTICES
Vanessa Hassler
Nataskha Pernet
Angélique Vaucher

ADMINISTRATIVE ASSISTANT
Marlène Petit
Joanna Schwab*

*left the group

**changed function

Publications

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K. Buttler,
Universitätsklinik Göttingen, Germany

D. Dombrowicz,
Institut Pasteur, Lille, France

D. Duboule,
University of Geneva, Switzerland

E. Hafen,
University of Zurich, Switzerland

P. Herrera,
University of Geneva, Switzerland

S. Nef,
University of Geneva, Switzerland

U. Schibler,
University of Geneva, Switzerland

M. Swartz,
EPFL (Ecole Polytechnique Fédérale de Lausanne), Switzerland

B. Thorens,
University of Lausanne, Switzerland

S. Werner,
Swiss Federal Institute of Technology Zurich (ETHZ), Switzerland

Bioresearch and Partners,
Monthey, Switzerland

Institut de recherche Pierre Fabre Dermo–cosmétique,
Toulouse, France

Béatrice Desvergne
Associate professor

Béatrice Desvergne was trained as a MD. She initially specialized in anesthesiology and reanimation, practiced medicine for a few years, but decided to move for fundamental research. After a further training in biology, she carried out a post–doctoral stay from 1988 to 1992 at the National Institutes of Health in Bethesda, USA, first as visiting fellow and then visiting associate in the National Institute of Diabetes and Digestive and Kidney Diseases. In 1992, she was appointed as assistant professor at the Institute of Animal Biology of the University of Lausanne, where she was then nominated as extraordinary professor in 1996 and associate professor in 1999. She also holds a bachelor degree in Philosophy. She joined the Center for Integrative Genomics in 2003.

PPAR beta and fine tunig of cell fate decision

As they mediate intracellular hormone action, nuclear receptors play a crucial multi–faceted role in coordinating growth during development, and homeostasis at adult stage. Among them, the peroxisome–proliferator activated receptors (PPARs) act as fatty acids sensors, responding to dietary as well as to endogenous challenges. Accordingly, they have an integrative role in controlling the expression of genes regulating the storage, mobilisation, and / or utilisation of lipids. Using various molecular, cellular, and animal approaches, our studies are aimed at understanding how PPARs are integrated in the main pathways that shape the organism during development on the one hand and maintain systemic homeostasis on the other hand.

During development we first demonstrated the crucial role of PPARbeta in the placenta. Indeed, PPARbeta is required for a proper differentiation of the trophoblast giant cell, via i) activation of the PI3K pathway II) inhibition of Id2 (inhibitor of differentiation 2) gene expression III) activation of Imfa1 gene expression. In the intestine, PPARbeta also promotes Paneth cell differentiation. However, the exploration of the corresponding molecular signalling lead us to uncover the inhibitory role of Indian Hedgehog on Paneth cell terminal differentiation. Our works demonstrate that Ihh is expressed at high levels in the Paneth cells of the adult intestine and that moderation via PPARbeta ensures the final maturation of Paneth cell precursors.

Because of our observations concerning the crucial role of PPARbeta in tissue repair seen in the skin (in collaboration with W. Wahli and L. Michalik), we explored the possible role of PPARbeta in various tissue injuries, with a dual aim: identifying the molecular mechanism controlled by PPARbeta in these contexts, and identifying possible clinical applications of PPARbeta activators. The models we have been using reflect quite common clinical situations: gut epithelial damages provoked by gamma–irradiation, acute ischemic renal failure, and middle cerebral artery occlusion. The most advanced work concerns the protective role of PPARbeta upon aute ischemic renal failure. We indeed have shown that PPARbeta+/- and PPARbeta-/- mutant mice exhibit much greater kidney dysfunction than wild type counterparts. Conversely, treatment of wild–type C57BL/6 mice with a PPARbeta ligand L–165041 remarkably prevented the ischemia/reperfusion–dependent glomerular and tubular dysfunction. Further analyses performed on HK–2 cells in culture indicated that exposure to a PPARbeta ligand reshape the cells, with flattening and spreading that have been shown in vivo to prevent backleakage of the glomerular filtrate during ischemic acute renal failure. Based on these studies, PPARbeta ligands seem to exert their protection in ischemic acute renal failure by both activating the antiapoptotic Akt signaling pathway and increasing epithelial cell spreading. These results point to PPARbeta as a remarkable target for preconditioning strategies.

Group

GROUP LEADER
Béatrice Desvergne
beatrice.desvergne@unil.ch

TECHNICIANS
Elisabeth Joye
Geneviève Metthez

MAITRE–ASSISTANT
Laurent Gelman*

POSTDOCTORAL FELLOWS
Elodie Bedu
Jérôme Feige
Karim Nadra*
Frédéric Varnat

PhD STUDENTS
Imtiyaz Ahmad
Jean–Marc Brunner
Alan Gerber
He Fu
Matthew Hall
Sajit Thottathil Oommen

MASTER STUDENTS
Daniel Rossi*
Beatriz Tavera Tolmo*

ADMINISTRATIVE ASSISTANT
Marlène Petit
Joanna Schwab*

*left the group

Publications

RESEARCH ARTICLES

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Collaborations

L. Baud and E. Letavernier,
INSERM, Paris, France

M. Crestiani,
University of Milan, Italy

S. Dedhar,
British Columbia Research Center, Vancouver, Canada

P. Desreumaux,
Dubuquoy L and chamaillard E, Université de Lille, France

S. K. Dey and R. Dubois,
Vanderbilt University Medical Center and Vanderbilt–Ingram Cancer Center, Nashville, USA

Y. Enghelborgs,
Université de Leuven, Belgique

F. Gonzalez,
National Cancer Institute, Bethesda, USA

M. Janier and M. Wiart,
CNRS Plateforme Animage, Lyon, France

R. Métivier,
Université de Rennes, France

D. Metzger and P. Chambon,
Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch–Strasbourg, France

J. A. Mitchell,
Imperial College London, London, UK

L. Nagy,
University of Debrecen, Hungary

Liliane Michalik

Maître d'enseignement et de recherche

Liliane Michalik received her PhD from the University Louis Pasteur of Strasbourg, France, in 1993. She then was a postdoctoral fellow in the lab of Walter Wahli at the University of Lausanne, where she started a research project aimed at elucidating the roles of the nuclear hormone receptor PPARs in skin homeostasis and repair. Between 1996 and 2002, she was maître assistant at the Institute for Animal Biology and then joined the Center for Integrative Genomics in 2003 as maître d'enseignement et de recherche.

Roles of PPARs in skin biology and angiogenesis

The skin is a barrier that protects the organism from various insults. Due to its peripheral localization, it is prone to be damaged, for instance by mechanical injury or UV radiations. The repair process after an injury is a life–saving process that involves keratinocytes, immune cells, fibroblasts and blood vessels. The molecular mechanisms and cell functions implicated in repair share many common characteristics with the uncontrolled development of skin cancers. We are interested in understanding the roles of the nuclear receptors PPARs as transcriptional regulators of skin repair, UV induced carcinogenesis and angiogenesis. As a model system, we use various mouse lines in which the expression of PPARs is modified, as well as Xenopus laevis. We have observed that the wound healing process is delayed in the absence of PPARbeta, and that PPARbeta controls many properties of the keratinocytes that are essential for rapid wound closure. Our current interest is to understand the role of PPARs in the other cell types involved in skin repair and in the development of skin carcinomas, with a particular focus on angiogenesis.

Group

GROUP LEADER

Liliane Michalik
liliane.michalik@unil.ch

TECHNICIAN

Cécile Duléry

PhD STUDENTS

Raphaël Terrier
Marta Wawrzyniak

Publications

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Collaborations

S. Werner,
Swiss Federal Institute of Technology Zurich (ETHZ), Switzerland

D. Hohl,
Centre Hospitalier Universitaire (CHUV), Lausanne, Switzerland

O. Michielin and V. Zoete,
Swiss Institute for Bioinformatics, Lausanne, Switzerland

M. Swartz,
EPFL (Ecole Polytechnique Fédérale de Lausanne), Switzerland

D. Dombrowicz,
Institut Pasteur de Lille, France

Institut de recherche Pierre Fabre Dermo-cosmétique,
Toulouse, France

Bioresearch and Partners,
Monthey, Switzerland

Bernard Thorens
Professor

Bernard Thorens received his PhD in Geneva in 1984 for studies carried in the laboratory of Pierre Vassalli. He then did a postdoctoral fellowship at the Whitehead Institute for Biomedical Research in Cambridge, UK, with Harvey Lodish. In 1991 he received a Career Development Award from the Swiss National Science Foundation to establish his research group at the Department of Pharmacology and Toxicology of the University of Lausanne. Since 2002 he is Professor of Physiology at the University and since November 2005, he is working at the CIG.

Molecular and physiological analysis of energy homeostasis in health and disease

Glucose homeostasis and development of type 2 diabetes are critically regulated by the capacity of the insulin secreting beta–cells of the pancreas to secrete insulin according to the metabolic need of the organism. This secretory capacity depends on both the mass and function of the differentiated beta–cells.

One of our research project is to search for genes that are under the control of GLP–1 and GIP, two hormones that control the differentiation of pancreatic beta–cells from precursor cells, the proliferation of mature beta–cells and their protection against apoptosis. This search is based on transcriptomic analysis of genes expressed in islet cells in which the action of these two hormones has either been suppressed by gene knockout or, in contrast, activated by exposure of the cells to these hormones. The function of these genes is investigated by overexpression or down–expression (siRNA) studies in beta–cell lines, primary beta cells and in transgenic mice, followed by functional analysis of proliferation, apoptosis, and insulin secretion.

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

In this second line of investigation we aim at identifying, at the cellular and molecular levels, the mechanisms by which glucose is sensed by neurons, and how these sensing neurons regulate the function of the hypothalamic neuronal circuits controlling glucose and energy homeostasis. These studies are based on the analysis of gene knockout mice, which show loss of central glucose sensing and, as a consequence, deregulated control of feeding and energy expenditure. These studies are being pursued by genetically marking the glucose sensing cells to identify them and characterize the neuronal circuits they form. Transcriptomic analysis have also been performed to identify the set of genes that are regulated by these glucose sensing cells to identify novel molecular mechanisms of controlling feeding and energy expenditure. These investigations involve the use of molecular biology techniques, immunohistochemistry, in situ hybridization, and integrated physiological analysis of control or genetically modified mice.

In a third line of investigation, we analyze the changes in gene expression in liver and adipose tissues of mice with different genetic background and fed high fat diets to identify the changes in metabolic activity that underlie sensitivity or resistance to obesity development. These studies make extensive use of the microarray technologies provided by the DNA Array and Metabolic facilities of the CIG.

Group

GROUP LEADER
Bernard Thorens
bernard.thorens@unil.ch

BIOINFORMATICIAN
Carine Poussin

TECHNICIANS
Wanda Dolci
Martine Emery
Joël Gyger
David Tarussio

POSTDOCTORAL FELLOWS
Isabelle Bady*
Marie–Bernard Debril
Diana Hall
Maria Jimenez
Fabrice Marcillac
Matthieu Membrez*
Lourdes Mounien
Pascal Seyer

PhD STUDENTS
Marion Cornu
Sonia Klinger
Nell Annette Marty
Yann Ravussin*
Audrey Sambeat

MASTER STUDENT
Gilles Willemin*
Salima Metref

ADMINISTRATIVE ASSISTANTS
Claudia Hoffmann–Denarié
Christine Winkler*
Monique Laverrière–Schultz*

*left the group

Publications

RESEARCH ARTICLES

since B. Thorens arrival at the CIG (November 2005)

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Thorens B (2006)
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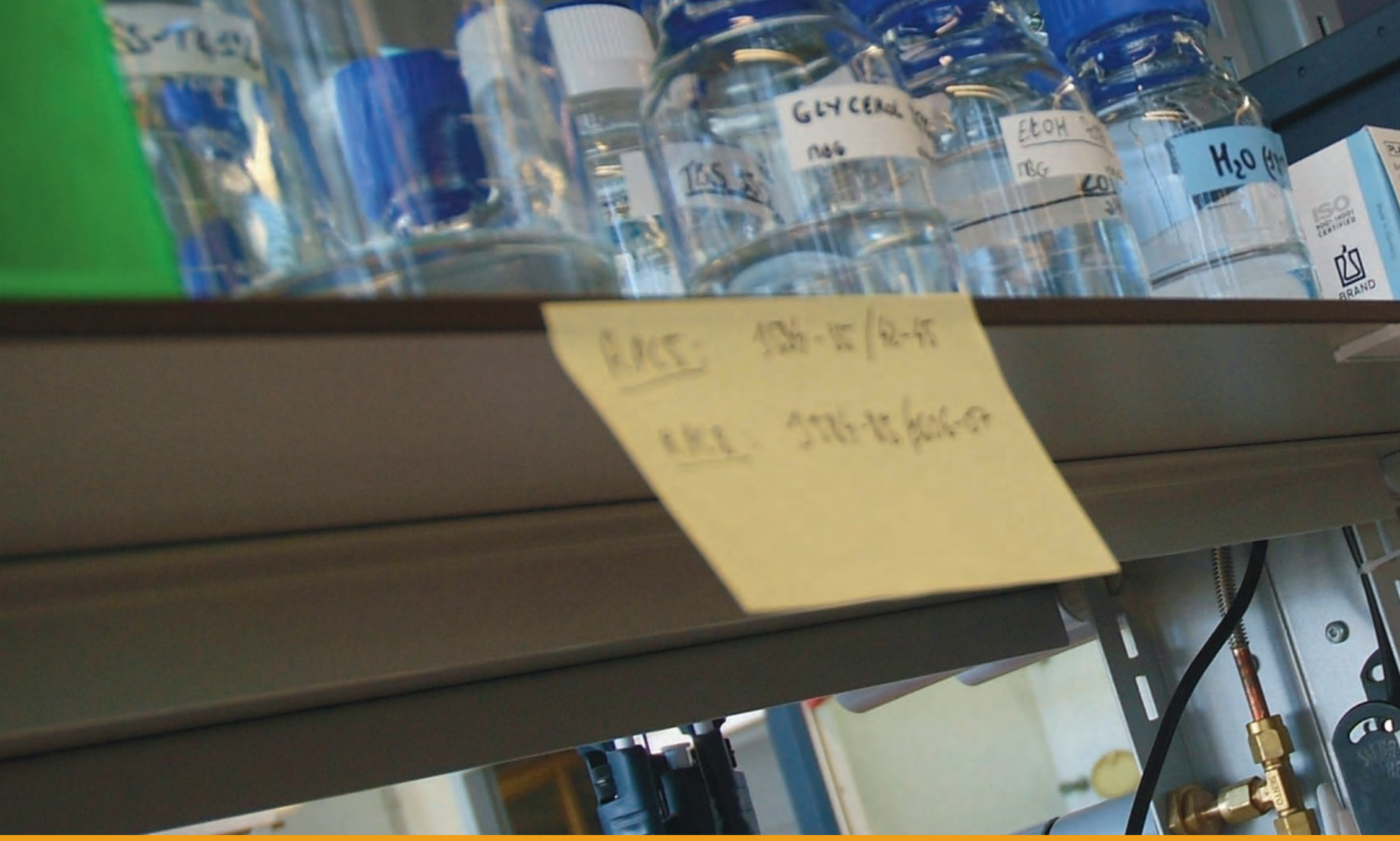
Collaborations

M. Donath,
University Hospital Zurich, Switzerland

C. Wollheim and P. Halban,
University of Geneva, Switzerland

All labs involved in the European projects HEPADIP & EURODIA


GLYCEROL
EtOH
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BRAND

core facilities

Keith Harshman

Coordinator of the facility
Maître d'enseignement et de recherche

Keith Harshman received his PhD in Biochemistry from the California Institute of Technology, USA, in 1990. Following post doctoral fellowships at the University of Zurich and the Sloan–Kettering Cancer Center, in 1993 he joined Myriad Genetics Inc. where he worked first as a Senior Scientist and later as the Director of Central Nervous System Disease Research. In 1997 he moved to the Department of Immunology & Oncology of the National Biotechnology Center in Madrid, Spain, as the Head of the Functional Genomics Unit. He has been the Coordinator of the Lausanne DNA Array Facility since November of 2002.

DNA Array Facility (DAF)

The primary goal of the Lausanne DNA Array Facility (DAFL) is to provide the user community with access to the state–of–the–art technologies as well as bioinformatic protocols used to detect, measure and analyze quantitative and qualitative variations in nucleic acids. The principal technology platforms supported by the DAFL to achieve this goal are the Affymetrix GeneChip oligonucleotide array platform, in–house spotted cDNA and oligonucleotide arrays as well as quantitative real–time PCR. The DAFL provides users with training and supervision in all aspects of the molecular biology and instrument manipulations associated with DNA microarray experiments. In many cases, the DAFL will perform all of the steps of the array experiment, beginning with RNA provided by the user. The facility provides access to and training in the use of the instrumentation and the consumables that are required to perform quantitative real–time PCR analyses using the Applied Biosystems 7900HT Sequence Detection System. The DAFL provides bioinformatics support and consultation services at the stages of experimental design, data collection and storage, image analysis and, when appropriate, higher level data analysis. To support these bioinformatic activities, the DAFL has a close collaboration with the Bioinformatic Core Facility of the NCCR Molecular Oncology Program. The DAFL also supports users in the production and use of protein microarrays and in the use of commercial array platforms designed for analyzing microRNA gene expression. The facility allows users to carry out their experiments in its laboratories by providing equipment and bench space. Furthermore, the DAFL maintains computer workstations and software with which users can analyze their data.

Group

GROUP LEADER
Keith Harshman
keith.harshman@unil.ch

COORDINATOR AFFYMETRIX PLATFORM
Otto Hagenbüchle

COORDINATOR MICROARRAYS AND qPCR PLATFORMS
Johann Weber

BIOINFORMATICIANS
Sylvain Pradervand
Darlene Goldstein
Beate Sick*
Gnanasekaran Thoppae*

TECHNICIANS
Manuel Bueno
Alexandra Paillusson
Jérôme Thomas
Sophie Wicker

ADMINISTRATIVE ASSISTANT
Fabienne Sauvain

*left the group

Collaborations

In 2005 and 2006, the DAF provided support for numerous projects from departments of the Faculty of Biology and Medicine of the UNIL and from the Centre Hopsitalier Universitaire Vaudois (CHUV), the Swiss Institute for Experimental Cancer Research (ISREC) and the EPFL (Ecole Polytechnique Fédérale de Lausanne) in Lausanne. Also, several projects came from other swiss universities (Geneva, Neuchâtel, Zurich).

Manfredo Quadroni

Coordinator of the facility
Maître d'enseignement et de recherche

Manfredo Quadroni got his PhD in Biochemistry at the Swiss Federal Institute of Technology Zurich (ETHZ) in 1996. 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 signalling complexes in immunology, and his second postdoctoral training at Swiss Federal Institute of Technology Zurich (ETHZ) (1998–2000) focused on development of methods for proteome analysis. He was then Maître assistant at the Institute of Biochemistry of the University of Lausanne between 2000 and 2003. He joined the CIG in March 2003 as maître d'enseignement et de recherche (MER) to coordinate the PAF facility.

Protein Analysis Facility (PAF)

Proteomics is becoming a viable approach to study the organization of complex cellular pathways. By combining labeling and separation techniques with high–throughput mass spectrometry, it is now possible to analyze complex protein mixtures to determine their composition and detect changes associated with a given biological process. This approach is most promising to analyze fractions of proteins that are connected by a functional relationship, typically by direct interaction (formation of a supramolecular complex) or co–localization to a functionally defined cellular compartment.

1) Independent technology development projects: We are pursuing the development of a technique to specifically identify in complex mixtures such as whole cell extracts the proteins that were synthesized at high rates during a given time. This approach will be based on metabolic labeling of cell cultures with stable isotope derivatives of amino acids (SILAC) and a specific detection by mass spectrometry of fragments of these proteins that have incorporated the label. We have preliminary evidence showing the viability of the approach in a biological system (infection of cells with Herpes Simplex virus). In addition, we are developing a novel method for relative protein quantification based on the same labeling scheme.

On the software side, we have collaborated with the Swiss Institute of Bioinformatics (SIB) in Geneva (group of R. Appel) to create and test MSIGHT, a freeware software for the representation and comparison of liquid–chromatography–mass spectrometry data (www.expasy.org/msight).

2) Collaborative studies on functionally related sets of proteins: We have several research efforts based on collaborations. These project are mainly focusing on the analysis of complexes of interacting proteins. We have been able to map extensively the proteins binding to RelA (an important member of the NF–kappaB family) through its transcription activation domain (with M. Hottiger, Zurich). We are also studying both the post–translational processing and the molecules interacting with two novel death–domain–containing proteins named PIDD and ZUD, whose function was until recently unknown (with J. Tschopp, University of Lausanne). We have also an ongoing project on the characterization of the SCF–like ubiquitin ligase complexes formed around Cullin–3 and Cullin–4A in human cells (with M. Peter, Swiss Federal Institute of Technology Zurich (ETHZ)).

Alternatively, we also tackle the characterization of proteins which share a common targeting fate and as such are also functionally correlated. So we have performed differential analysis of proteins present in lipid rafts on the surface of several melanoma cell lines, with the goal to establish possible correlations with the varying invasive phenotype of these cells (with C. Ruegg, Swiss Institute for Experimental Cancer Research (ISREC)/Multidisciplinary Oncology Center (CePO), Lausanne). Also with the group of M. Monod, (Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne), we have undertaken the comprehensive identification of the proteins secreted (the "secretome") by the two skin infecting fungi Trychophyton rubrum and Trychophyton violaceum. This fraction is highly enriched in proteases, which play a role in the invasion of the skin layers.

Group

GROUP LEADER
Manfredo Quadroni
manfredo.quadroni@unil.ch

COORDINATOR AT THE CIG
Patrice Waridel

BIOINFORMATICIAN
Gnanasekaran Thoppae

TECHNICIANS
Jachen Barblan
Alexandra Potts

POSTDOCTORAL FELLOW
Willy Bienvenut*

PhD STUDENT
Mara Colzani

*left the group

Publications

RESEARCH ARTICLES

Palagi PM, Walther D, Quadroni M, Catherinet S, Burgess J, Zimmermann–Ivol CG, Sanchez JC, Binz PA, Hochstrasser DF, Appel RD (2005)
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** equal contribution*

Collaborations

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

M. Hottiger,
University of Zurich, Switzerland

J. Tschopp,
University of Lausanne, Switzerland

M. Peter,
Swiss Federal Institute of Technology Zurich (ETHZ), Switzerland

C. Ruegg,
Centre Hospitalier Universitaire (CHUV) and University of Lausanne, Switzerland

M. Monod,
Centre Hospitalier Universitaire (CHUV) and University of Lausanne, Switzerland

Vital-IT

COORDINATOR:
V. Jongeneel
cornelisvictor.jongeneel@unil.ch

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

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

THE MAIN ACTIVITIES UNDERTAKEN BY VITAL-IT ARE:

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

WEBSITE:
http://www.vital-it.ch

The Cellular Imaging Facility (CIF)

COORDINATOR:
Jean–Yves Chatton
jean-yves.chatton@unil.ch

TECHNICAL MANAGER AT THE CIG:
Arnaud Paradis

The Cellular Imaging Facility (CIF) was created in 2003 initially as the result of a joint financial and structural effort of the Faculty of Biology and Medicine of the University of Lausanne and the University Hospital (Hospices/CHUV) and located in the Medical School building. Since Summer 2005, the CIF is also present on the Dorigny campus, at the CIG building and in the Biology building. The operations are overseen by a Steering Committee, with both strategic and scientific responsibilities, representing all involved institutions in addition to external partners. The mission of the CIF is to assist researchers with imaging needs ranging from wide–field fluorescence and transmission optical microscopy, confocal microscopy, time–lapse and ion imaging, to digital image processing and analysis. The CIF is organized around three complementary activities: (a) service activities: investigators are offered access to a panel of state–of–the–art imaging equipment and techniques; (b) teaching and Training: the CIF shares and diffuses the practical and theoretical know–how on these approaches through teaching and training to researchers, technicians, as well as pre– and post–graduate students; (c) research and technological development performed by investigators affiliated with the CIF who develop and implement most advanced optical and imaging technologies, eventually rendered accessible to more users of the CIF.

WEBSITE
http://www2.unil.ch/cif/

The Bioinformatics Core Facility (BCF)

COORDINATOR:
Mauro Delorenzi
mauro.delorenzi@isrec.unil.ch

The Bioinformatics Core Facility (BCF) is part of the Swiss National Fund funded NCCR Molecular Oncology program at Swiss Institute for Experimental Cancer Research (ISREC). Its mission falls into four general areas:

a) **Service:** provide basic bioinformatic and data analytic support at all stages of gene expression and other high throughput studies, from design to data acquisition, analysis, and interpretation, with a focus on clinical and cancer–related projects;

b) **Education:** train groups carrying out NCCR–supported projects in the application and interpretation of basic methods of data analysis through course and workshop offerings;

c) **Collaboration:** participate as collaborators for projects requiring advanced or individualized attention;

d) **Research:** have an active research program to advance methodological developments in the analysis of gene expression data and integration of these with other biological data, particularly to study the association of expression patterns with clinical and survival data;

The BCF "headquarter" is at the CIG with offices also at Swiss Institute for Experimental Cancer Research (ISREC) in Epalinges.

WEBSITE
http: //www.isrec.isb-sib.ch/BCF/

The Mouse Metabolic Evaluation Facility (MEF)

DIRECTOR:
Bernard Thorens
bernard.thorens@unil.ch

COORDINATOR:
Frédéric Preitner
frederic.preitner@unil.ch

The Mouse Metabolic Evaluation Facility (MEF) was created in 2006 as the result of a joint financial and structural effort of the Center for Integrative Genomics, the University Hospital in Lausanne (CHUV) and the NCCR Frontiers in Genetics. The MEF is located at CIG.

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

Given the high level of complexity of most techniques, the MEF provides services to the researchers. The MEF also provides teaching for those who want to introduce specific techniques into their own laboratories. In order to broaden the scope of phenotyping tests, the MEF aims also at developing new investigation techniques in partnership with laboratories at University of Lausanne, at the Centre Hospitalier Universitaire Vaudois (CHUV) and EPFL (Ecole Polytechnique Fédérale de Lausanne) The MEF is an integral part of the CHUV–UNIL CardioMet research center that gathers three coordinated investigative units, namely the MEF, the Rodent Cardiovascular Phenotyping Center (coordinated by Prof. Thierry Pedrazzini, at the UNIL) and the Clinical Investigation Center (coordinated by Prof. François Pralong at CHUV). CardioMet aims at fostering joint projects in clinical and basic research, in the cardiovascular and metabolic fields.

WEBSITE
http: //www.unil.ch/cig/page41381.html

Center for Investigation and Research on Sleep (CIRS)

CO-DIRECTOR:
Mehdi Tafti (CIG), with **Raphaël Heinzer** (Centre Hospitalier Universitaire Vaudois, CHUV)
mehdi.tafti@unil.ch

Sleep disorders are very prevalent, and represent an "emerging worldwide epidemic". However, despite an impressive progress during the last 3 decades, biological and molecular bases of most sleep disorders remain unknown. Consequently, almost all available treatments for sleep disorders are symptomatic and not evidence-based. Given their variety and impact on different biological systems (respiration, metabolism, motor control, cognition), a multidisciplinary approach is needed, not only for understanding the pathophysiology but also for diagnosis and treatment of sleep disorders. Thus, in collaboration with clinicians specialist in sleep disorders, we have established the Center for Investigation and Research on Sleep (CIRS). This joint venture between the CIG and the Centre Hospitalier Universitaire (CHUV), Lausanne, provides a state-of-the-art infrastructure to conduct high level basic and clinical research and to offer to the community the highest standard for diagnosis and treatment of sleep disorders.

The CIRS was officially inaugurated in January 2007.

education

The Student Program

EDUCATION IS CENTRAL TO THE MISSION OF THE CIG.

The CIG members give lectures, seminars and practical courses in the School of Biology of the Faculty of Biology and Medicine of the University of Lausanne, teach in other institutions, and organize workshops and courses. The group leaders mentor master and PhD students in their research, and also participate in an additional academic mentoring program.

Learning and interacting with other scientists is an essential component of a researcher's life all along her/his career. The CIG thus arranges regular presentations by external speakers: during the academic term, a weekly CIG/Génopode seminar–series is organized. Besides a scientific presentation by the speaker, this seminar–series is also the occasion for interactions at several levels: all participants meet after the presentation around a sandwich lunch, and special time is dedicated for a discussion between the speaker and students and postdocs, and for a dinner with the invited speaker and CIG/Génopode faculty members and others.

The CIG also co–organizes with other biology departments from the Faculty of Biology and Medicine monthly BIG seminars. Conferences and symposia are also organized, including the annual Lausanne Genomics Days and the CIG symposia of which the inaugural symposium was in October 2005.

"In House" interactions are also particularly precious. At the beginning of its existence, in spring 2005, the CIG organized an "Introducing the CIG" seminar series, which gave the occasion for all group leaders to present their work to their new colleagues. Now, seminars and presentations among groups working on similar fields are frequent, but it is also essential to promote interactions among CIG/Génopode members working on different fields. To this aim, a yearly retreat gathering all members is organized.

Last but not least, the CIG is very active in educational activities directed at people who are neither biology students nor directly involved in research, but who are interested and concerned by research and its outcomes. These activities take different forms and are addressed to adults or children as well as to biology teachers and schools.

THE MASTER

The CIG is principally involved in the UNIL Master of Science in Genomics and Experimental Biology (GBE). This program is designed for students who are curious, motivated, and enthusiastic about the exploration of life through the application of experimental biology methods and the new field of genomics. The master degree courses aim at providing key expertise required in this field. On the one hand, the training provides an in–depth knowledge of genetics and molecular biology, offering specialized courses on the interactions of molecules within networks that control the life of micro–organisms, plants and animals. On the other hand, considerable attention is dedicated to the learning and application of advanced techniques in genome annotation, gene expression analysis and bioinformatics.

The faculty member coordinating the Master of Science in Genomics and Experimental Biology (GBE) is Christian Fankhauser who succeeded Liliane Michalik in September 2005.

THE PhD PROGRAM

The CIG is committed to the success of its doctoral students. To promote a high level of student achievement, the faculty and administration take an active role in mentoring and supervising the students. With this goal in mind, the CIG has developed an academic mentoring program. Soon after commencement of his or her studies, each doctoral student selects, by mutual agreement of the mentor and mentee, a faculty member (Professor or Maître d'Enseignement et de Recherche (MER)) to be his or her academic mentor. The academic mentor follows the student's academic and research progress, and provides advice for the duration of the student's doctoral studies. The academic mentor complements and broadens the learning environment provided by the research mentor. Additionally, by getting to know their mentees well, academic mentors can promote students' careers and provide well–informed letters of recommendation. Thus, with dual research and academic mentoring, the CIG ensures a diversity of complementary support for better student development and future success.

Lectures And Courses Given By The CIG Members

BACHELOR COURSES

Henrik Kaessmann
Evolution moléculaire

Alexandre Reymond
Statistiques pour biologistes

Mehdi Tafti, Winship Herr, Alexandre Reymond
Du génome au phénome et du phénome au génome

Nouria Hernandez, Walter Wahli
Transcription et maturation de l'ARN

Béatrice Desvergne
Biologie animale et génétique
Génétique avancée
Biologie et Société

Liliane Michalik
Biologie cellulaire
Introduction à l'embryologie

Bernard Thorens
Cellule, organe, système
Digestion, métabolisme

MASTER COURSES

Alexandre Reymond, Henrik Kaessmann
Evolutionary and comparative genomics

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

Nouria Hernandez, Winship Herr, Christian Fankhauser, Victor Jongeneel
Cartographie, séquençage et structure des génomes

Mehdi Tafti
Neuroscience

Paul Franken, Keith Harshman, Manfredo Quadroni (with Johann Weber)
Genomics, proteomics and quantitative genetics

Walter Wahli
Chapitres choisis de Développement
Récepteurs nucléaires et régulation génétique

Béatrice Desvergne
Récepteurs nucléaires comme senseurs métaboliques
Les mécanismes régulateurs des voies métaboliques

Liliane Michalik
Développement précoce et voies de signalisation

Manfredo Quadroni
Introduction à la protéomique

Bernard Thorens
Métabolisme glucidique et homéostasie énergétique

PhD TUTORIALS

Winship Herr
Reasoning and logic in genetics and molecular and cell biology

Mehdi Tafti, Christian Fankhauser
Circadian clock

Walter Wahli, Liliane Michalik (co–instructor: Nicolas Rotman)
Nuclear Receptors (for the NCCR Frontiers in Genetics)

Bernard Thorens
Energy homeostasis (for the NCCR Frontiers in Genetics)

LABORATORY COURSES

Liliane Michalik and Nouria Hernandez, co–instructors: Erwann Vieu and Nicolas Rotman (maîtres assistants)
Biologie cellulaire et embryologie expérimentale

Walter Wahli, Nouria Hernandez, Winship Herr, co–instructors: Erwann Vieu and Nicolas Rotman (maîtres assistants)
Biologie moléculaire

Keith Harshman (with DAF members)
RNA expression profiling using DNA microarrays (for the SKMB)

MEDICAL STUDIES

Bernard Thorens
Introduction à l'endocrinologie
Métabolisme glucidique

COURSES IN OTHER ORGANIZATIONS

Alexandre Reymond
Human genetics
Bachelor level
University of Geneva

Functional genomics
PhD level
EPFL (Ecole Polytechnique Fédérale de Lausanne)

Victor Jongeneel
SIB–CIG workshops
PhD level
UNIL and EPFL (Ecole Polytechnique Fédérale de Lausanne)

Mehdi Tafti
Neurosciences
University of Geneva

PhD Theses

The following PhD theses have been successfully defended at the CIG:

GROUP BÉATRICE DESVERGNE

Karim Nadra (2005)
Role of PPARbeta and PPARgamma in mouse placental development

Alexandra Schumann (2006)
Early antibiotic administration affects the gut barrier function and the immune response to oral antigen in suckling rats

Jérôme Feige (2006)
Integrating receptor interactions and dynamics and interference with endocrine disruptors in the mechanisms of action of PPAR nuclear receptors

GROUP BERNARD THORENS

Nell Annette Marty (2005)
Rôle du transporteur de glucose GLUT2, dans les mécanismes centraux de glucodétection impliqués dans le contrôle de la sécrétion du glucagon et de la prise alimentaire

Mathieu Membrez (2005)
Etude de la fonction de GLUT8 sur un modèle de souris knock out

Mathieu Widmer (2006)
Characterization of GLUT8 and GLUT9, two novel glucose transporter isoforms

Sonia Klinger (2006)
Regulation of mass and function of pancreatic b–cells: identification of anti–apoptotic peptides and role of GLP–1

GROUP WALTER WAHLI

Raphaël Genolet (2005)
Peroxisome proleferator–activated receptor a: Involvement in Liver Metabolism and Inflammation

David Mutch (2005)
Exploring the mechanisms regulating nutrient bioavailability and lipid metabolism through a nutrigenomics approach

GROUP LILIANE MICHALIK

Guillaume Icre (2006)
Role of PPARbeta in keratinocyte adhesion and migration during skin wound healing

Prizes

The following prizes have been awarded to students at the CIG during the years 2005–2006

Prix d'excellence du jeune chercheur, Faculty of Biology and Medicine, University of Lausanne (2005)
Nicolas Di Poï
Group Walter Wahli

Prix de l'Association Vaudoise des Femmes Diplômées des Universités (2006)
Stéphanie Maret
Group Mehdi Tafti

Prix de la Société Suisse de Diabète (2006)
Nell Marty
Group Bernard Thorens

Seminars

CIG SEMINARS

Ueli Schibler
University of Geneva
Geneva, Switzerland
Circadian time keeping: the ups and downs of genes, cells and organs

Jacques Dubochet
University of Lausanne
Lausanne, Switzerland
CEMOVIS (cryo–electron microscopy of vitreous sections) and CET (computerized electron tomography): zowards sn stomic model of the cell

Melody Swartz
EPFL (Ecole Polytechnique Fédérale de Lausanne)
Lausanne, Switzerland
Lymphangiogenesis and tumor invasion: molecular vs. biophysical regulators

Pierre Magistretti
University of Lausanne and EPFL (Ecole Polytechnique Fédérale de Lausanne)
Lausanne, Switzerland
Neuron–gliaMetabolic coupling: relevance for functional brain imaging

Juerg Tschopp
University of Lausanne
Lausanne, Switzerland
The inflammasome: a caspase–activating complex controlling innate immunity

Guy Rousseau
Université Catholique de Louvain
Louvain, Belgium
One cut transcription factors control pancreas and liver development

Nicolas Mermod
University of Lausanne
Lausanne, Switzerland
Control of gene expression: from genomics to biotechnology

Ralph Greenspan
The Neurosciences Institute
San Diego, USA
From somnolence to alertness: dopamine as a modulator of arousal in Drosophila

Jerzy Paszkowski
University of Geneva
Geneva, Switzerland
Mapping the arabidopsis epigenome

Jonathan Flint
Wellcome Trust Centre for Human Genetics
Oxford, UK
The genetic basis of anxiety

Gisou Van Der Goot
University of Geneva
Geneva, Switzerland
Fundamental cellular processes revealed by bacterial toxins

Andrew Hattersley
Universities of Exeter & Plymouth
Exeter & Plymouth, UK
Dissecting the beta cell using monogenic diabetes

Joanna Wysocka
The Rockfeller University
New York, USA
Reading and writing an epigenetic mark associated with gene activation: coupling of the covalent and no–covalent chromatin modification mechanisms

Amanda Fisher
Imperial College London
London, UK
Chromatin profiling of stem cells

Eileen Furlong
European Molecular Biology Laboratory (EMBL)
Heidelberg, Germany
Transcriptional networks during mesoderm development: dissecting the logics

Michael Hengartner
University of Zurich
Zurich, Switzerland
Roads to ruin: apoptotic pathways in the nematode C. elegans

Vassily Hatzimanikatis
EPFL (Ecole Polytechnique Fédérale de Lausanne)
Lausanne, Switzerland
Mathematical modeling and analysis of complex biological systems

BIG SEMINARS INVITATIONS BY CIG MEMBERS)

Edith Heard
Curie Institute
Paris, France
The epigenetic dynamics of X–chromosome inactivation in the mouse

Joan Steitz
Yale University, Howard Hughes Medical Institute
New Heaven, USA
Regulatory RNAs: Altering outcomes in gene expression

Robert Tjian
University of California at Berkeley
Berkeley, USA
Mechanisms of transcriptional regulation: cross–talk between activators, co–activators and the PIC

AD HOC SEMINARS AT THE CIG

Philippe Cettour–Rose
Hôpitaux Universitaires de Genève
Geneva, Switzerland
Reciprocal interactions of thyroid hormones and leptin

Manuel Vazquez Carrera
University of Barcelona
Barcelona, Spain
New mechanisms involved in the development of insulin resistance and cardiac hypertrophy

Kateryna Makova
Penn State University
University Park, USA
Strong and weak male mutation bias at different sites in the primate genomes

Anton Nekrutenko
Penn State University
University Park, USA
XLs/ALEX: forced compensatory evolution of essential signalling proteins encoded by overlapping reading frames

Carley Benton
University of Waterloo
Waterloo, Canada
Fatty acid transporters and their regulation in muscle metabolism

Michael Duszenko
University of Tuebingen
Tuebingen, Germany
Prostaglandins and PPARgamma in the protozoan parasite Trypanosoma brucei, the causative agent of sleeping sickness

David Dombrowicz
Institut Pasteur de Lille
Lille, France
Skin and mucosal allergic diseases: immunomodulation and role of Fc receptors

Michel Simon
Université Paul Sabatier
Toulouse, France
Peptidylarginine deiminases are new targets for therapy. Their function in keratinocyte terminal differenciation

Wei Sha
Virginia Polytechnic Institute and State University
Blackburg, USA
Miccroarray data analysis for the genome–wide kinetics of Saccharomyces cerevisiae response to oxidative stress

Alea Mills
Cold Spring Harbor Laboratory
New York, USA
p63: a new link between cancer, senescence, and aging

Hans–Peter Landolt
University of Zurich
Zurich, Switzerland
Possible contributions of the adenosinergic system to trait–like individual differences in the human sleep EEG

Hilary Gates
University of London
London, UK
Complex cross–talk: mutational studies demonstrate how oestrogen receptors make the most of their differences

(continued on next page)

AD HOC SEMINARS AT THE CIG (CONTINUED)

Sophie Van Linthout
University of Medicine of Berlin
Berlin, Germany
Are HDL linked to the adiponectin system ?

Gerd Kullak–Ublick
University Hospital Zurich
Zurich, Switzerland
Genetic regulation of drug and bile acid transporters : role of nuclear receptors

Pierre Desreumaux
Hôpital Claude Huriez
Lille, France
PPARgamma, an unknown receptor involved in gut homeostasis

Pipat Nawathean
Brandeis University
Waltham, USA
Phosphorylation of PERIOD and TIMELESS, and Circadian Rhythm Regulation in Drosophila

Olivier Deloche
University of Geneva
Geneva, Switzerland
Translational control of gene expression : How cells survive a secretory stress ?

André Gerber
Swiss Federal Institute of Technology (ETHZ) Zurich, Switzerland
Coordination of Functionally Related mRNAs by RNA–binding proteins

Sophie Martin
Columbia University
New York, USA
Regulation of actin assembly by formins and microtubules in cell polarization

Jennifer Cobb
University of Geneva
Geneva, Switzerland
ATR kinase and RecQ helicase orthologs in yeast prevent replication fork collapse

David Kony
Swiss Federal Institute of Technology (ETHZ)
Zurich, Switzerland
Force field development and molecular dynamics simulations : applications to carbohydrates and proteins

Richard Benton
The Rockefeller University
New York, USA
How flies smell : the molecular biology of Drosophila olfaction

Olivier Pertz
The Scripps Research Institute
La Jolla, USA
Spatio–temporal control of RhoA activity during cell migration

Thibault Mayor
California Institute of Technology
Pasadena, USA
Profiling the ubiquitin proteome by quantitative mass spectrometry and identification of proteasomal receptor targets

Marc Fivaz
Clark Center
Stanford, USA
Spatio–temporal regulation of Ras signaling in neurons

Ariella Oppenheim
Hebrew University–Hadassah Medical School
Jerusalem, Israel
In vitro assembly of DNA in SV40 nanoparticles for gene delivery

Matt Webster
University of Dublin
Dublin, Ireland
Regional biases in nucleotide substitution patterns during vertebrate genome evolution

Adriana Pruzinska
University of Bern
Bern, Switzerland
Biochemical and molecular characterization of chlorophyll degradation in higher plants

Martin Kussmann
Nestlé Research Center
Lausanne, Switzerland
OMICS for food–gene, protein and metabolite profiling to find markers and explain benefits

Christophe Carles
Laboratory of Molecular Biochemistry and Genetics
Paris, France
The level of all ribosome components is subordinated to the control of RNA polymerase I activity

Jan Kopecky
Academy of Sciences of the Czech Republic
Prague, Czech Republic
Induction of metabolic switch by omega–3 polynsaturated fatty acids in white fat

Zoltan Peterfi
University of Szeged
Szeged, Hungary
Hormonal influences on the regulation of sleep

Eric R. Prossnitz
University of New Mexico
Albuquerque, USA
GPR30 : a novel intracellular transmembrane G protein–coupled estrogen receptor

Adriana Maggi
University of Milan
Milan, Italy
Novel mechanisms regulating estrogen receptor activity revealed by in vivo imaging

Cédric Notredame
CNRS
Marseille, France
T–Coffee tools : what's new in the grinder ?

Patrick Reilly
University of Toronto
Toronto, Canada
Studies of the ANP32 family in mice (because they have sex)

Marie–Agnès Doucey
Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne
Lausanne, Switzerland
Profiling signal transduction in human memory T cells using Protein Microarrays

Andrew Hanushevsky
Stanford University
Stanford, USA
Designing high performance data access systems

Ake Bergman
Stockholm University
Stockholm, Sweden
PCB metabolites of concern : bioaccumulative and toxic polychlorobiphenylols and methylsulfonyl–PCBs

Ruben Nogueiras
University of Santiago of Compostela.
Compostela, Spain
Distribution and biological actions of resistin and which is the role of visfatin in energy homeostasis ?

Jan H.J. Hoeijmakers
Erasmus Medical Center
Rotterdam, The Netherlands
DNA damage and the impact on cancer and aging, metabolism and the IGF, lifespan regulation

Jean Buteau
Columbia University
New York, USA
Identification and characterization of CCN3, A NOVel transcriptional target of Fox01 in the beta–cell

Jaya Krishnan
Swiss Federal Institute of Technology (ETHZ)
Zurich, Switzerland
HIF–1a in heart disease

Philippe Besnard
University de Bourgogne
Dijon, France
Do we taste fat ?

Paolo Di Nardo
University of Rome Tor Vergata
Rome, Italy
Phenotype determinants of hypertrophic cardiomyopathy

Andrzej Stasiak
University of Lausanne
Lausanne, Switzerland
Mechanisms of DNA recombination, as revealed by electron microscopy. Roe of helices and rings

Antje Gohla
Heinrich–Heine–Universität
Düsseldorf, Germany
Regulation of cytoskeletal dynamics by Chronophin, a novel HAD–type phosphatase

Ferenc Nagy
Biological Research Center
Szeged, Hungary
What is the function of phyB containing nuclear bodies in light induced signaling ?

Stacey Harmer
UC Davis
Davis, USA
Rhythms and Greens : The plant clock and its outputs

Toshihiko Yada
Jichi Medical University, School of Medicine
Minamikawachi–machi, Japan
Hypothalamic NPY neurons integrate metabolic signals to regulate feeding and energy homeostasis

Seth Davis
Max Planck Institute for Plant Breeding Research
Cologne, Germany
Molecular detection of the day–night cycle in Arabidopsis

Sacco De Vries
Wageningen University
Wageningen, The Netherlands
Brassinosteroid signalling in Arabidopsis : the role of co–receptors

Michael Rhodes
Applied Biosystems
Foster City, USA
Sequencing by oligonucleotide ligation and detection (SOLiD) : next generation technology for ultra–high throughput genetic and DNA analysis

Johan Auwerx
University of Strasbourg
Strasbourg, France
Turning on energy expenditure with bile acids or resveratrol

Claus Schwechheimer
University of Tuebingen
Tuebingen, Germany
Regulating plant development by regulated protein degradation

Jan Lohmann
Max–Planck–Gesellschaft
Tübingen, Germany
Regulatory Networks in Plant Stem Cell control

Oliver Mühlemann
University of Bern
Bern, Switzerland
Quality control to gene expression : mechanisms for recognition and elimination of nonsense mRNA

Roman Kurek
Ambion (Europe) Ltd/Applied Biosystems
Small Regulatory RNAs and the Growing RNA World

Monica Gotta
Swiss Federal Institute of Technology (ETHZ)
Zurich, Switzerland
Asymetric cell division and cell fate specification in C.elegans

Jiri Friml
University of Tübingen
Tübingen, Germany
Auxin–Cell Polarity and Tissue Patterning in Plants

Marc Foretz
University René Descartes Paris 5, France
Régulation de l'oxydation des acides gras par l'AMPK au cours du jeûne dans le foie

Andrej Hanzlowsky
Michigan State University
East Lansing, USA
Cloning, expression, purification and characterization of mSNAPc

Juergen Brosius
University of Muenster
Muenster, Germany
The pervasive role of RNA in genome evolution and cellular function

Bernhard Bettler
University of Basel
Basel, Switzerland
Genetic dissociation of GABA–B receptor functions

Richard Benton
The Rockefeller University
New York, USA
How flies smell : the molecular biology of Drosophila olfaction

Sophie Martin
Columbia University
New York, USA
Regulation of actin assembly by formins and microtubules in cell polarization

Halyna Shcherbata
University of Washington
Seattle, USA
Stem cell division regulated by microRNAs in Drosophila

Dorota Retelska
Copenhagen University
Copenhagen, Denmark
Detecting relevant transcription factor binding sites in promoters of coexpressed genes

Frank Buchholz
Max Planck Institute for Molecular Cell Biology and Genetics
Dresden, Germany
Phenotypic driven mammalian functional genomics : applications to cancer– and stem cell–biology

Kateryna Makova
The Pennsylvania State University
University Park, USA
Male mutation bias and X chromosome inactivation in the age of genomics

Laurence Macia
Institut Pasteur de Lille
Lille, France
Obésité et immunité : approche intégrée des interrelations entre les systèmes neuroendocrinien et immunitaire

Bernard Weiss
University of Rochester
Rochester, USA
Over the course of a lifetime, from foetal life to old age, brain function is threatened by environmental chemicals that disrupt hormone action

John Christie
University of Glasgow
Glasgow, UK
Structure and function of the phototropin light–receptor kinases

Ana M. Soto
Tufts University
Boston, USA
Fetal origins of adult disease : xenoestrogens and breast cancer

LAUSANNE GENOMICS DAYS

Organized within the "IIIe cycle Romand en Sciences Biologiques"

OCTOBER 6 AND 7, 2005

(organizers: J.Beckmann, K.Harshman, V.Jongeneel, O.Hagenbüchle, C.Fankhauser, P.Reymond, L.Keller)

Timothy Hughes
University of Toronto
Toronto, Canada
Functional and mechanistic analysis of the mouse transcriptome

Robert Strausberg
Venter Institute
Rockville, USA
Cancer genomics: Integrating basic and clinical research

Dietmar Schmucker
Harvard University
Boston, USA
Expansion of alternative splicing as an evolutionary strategy to generate Ig–receptor diversity

Uri Alon
Weizmann Institute
Rehovot, Israel
Design principles in biology

Mathias Uhlen
KTH Biotechnology
Stockholm, Sweden
Towards a human proteome atlas

Panos Deloukas
Sanger Institute
Cambridge, UK
Human DNA variation – The HapMap project

Susan Wessler
University of Georgia
Athens, USA
Transposable elements: Teaching old genomes new tricks

Marla Sokolowski
University of Toronto
Mississauga, Canada
The foraging gene: From nature to molecule and back again

Justin Borevitz
University of Chicago
Chicago, USA
Natural variation in light response using whole genome tiling arrays

Greg Gibson
North Carolina State University
Raleigh, USA
Quantitative transcriptomics: the nature of gene expression variation

Detlef Weigel
MPI
Tübingen, Germany
Flowering: mechanisms and natural variations

Laurent Duret
University Claude–Bernard
Lyon, France
Relationships between genome organization and gene expression in mammals: Selective constraints or neutral evolution ?

OCTOBER 5 AND 6, 2006

(organizers: J.Beckmann, K.Harshman, V.Jongeneel, O.Hagenbüchle, C.Fankhauser, P.Reymond, L.Keller, F.Naef, P.Franken)

Michael Lynch
Indiana University
Bloomington, USA
The origins of eukaryotic gene structure

Daniel Tawfik
Weizmann Institute
Rehovot, Israel
Protein evolution – a reconstructive approach

Trudy Mackay
North Carolina State University
Raleigh, USA
Quantitative genomics and genetic architecture of complex traits

Vincent Colot
CNRS
Evry, France
Epigenetic variation and its phenotypic impact in Arabidopsis: from (epi)genomics to quantitative genetics

Julin Maloof
University of California
Davis, USA
Light and clock regulation of plant growth

Gregory Wray
Duke University
Durham, USA
Gene expression in primates: evolutionary mechanisms and functional consequences

Robert Williams
University of Tennessee
Memphis, USA
Getting inside the brain's black box: a new genomic paradigm in behavior genetics

Frank Holstege
University Medical Center
Utrecht, Netherlands
Understanding mechanisms of eukariotic transcription regulation across the genome

David Cox
Perlegen InC.
Mountain View, USA
Human DNA variation, genetic association, and complex traits

Matthieu Blanchette
McGill Center for Bioinformatics
Montreal, Canada
In silico reconstruction of an ancestral mammalian genome

John Quackenbush
Dana–Farber Cancer Institute
Boston, USA
Extracting biological meaning from high–dimensional "omic" data

Bing Ren
Ludwig Institute for Cancer research (LICR)
San Diego, USA
Mapping the genome's second code

INAURGURAL CIG SYMPOSIUM, OCTOBER 28, 2005

(organizers: W. Herr, H. Kaessmann, M. Tafti, B. Thorens)

Denis Duboule
University of Geneva
Geneva, Switzerland
Chromosome engineering to study mammalian development

Nancy Andrews
Harvard Medical School & Howard Hughes Medical Institute
Boston, USA
The iron balancing act

Ueli Grossniklaus
University of Zurich
Zurich, Switzerland
Sex, parental conflict, and infanticide

Gary Ruvkun
Harvard Medical School & Massachusetts General Hospital
Boston, USA
Dangerously dancing with circular logic: Using RNAi to study RNAi

Susan Gasser
Friedrich Miescher Institute for Biomedical Research (FMI)
Basel, Switzerland
3D "genomics"

Ernst Hafen
University of Zurich
Zurich, Switzerland
Genetics of growth control in Drosophila

CIG Retreat

To promote interactions among its members, the CIG migrates to the Swiss mountains for two to three days at the end of each year. The groups and facilities present their work in talks and posters. These retreats give opportunities for scientific discussions that can form the basis for interactive projects between groups. Perhaps more importantly, they are an occasion for CIG members to interact socially and have fun together, simply getting to know each other, and thus contribute to the development of a creative and supportive atmosphere at the CIG.

The 2005 and 2006 retreats were in Saas Fee November 23–25, 2005 and December 6–8, 2006.

The CIG and the public

A very important aspect of the education activity of the CIG is teaching directed at non–biologists. For these activities, we have been very fortunate to be able to collaborate with the Sciences–Society Interface (Interface Sciences–Société) and the Center for Continuing Education (Centre de formation continue) of the University of Lausanne. Our first initiative, spearheaded by maître assistant Laurent Gelman, was a collaboration with the artist Pierre–Philippe Freymond, who installed in the hall of the Génopode his work titled "HeLa". This installation, which had been presented first from March to June 2005 in Geneva during the festival "Science et Cité", is dedicated to Henrietta Lacks, a woman who died more than 55 years ago of cancer and whose cancer cells are still presently multiplied and used in laboratories worldwide for modern biology research. The display, a sober little white room with a picture of Henrietta Lacks, a catalogue of scientific publications reporting experiments with HeLa cells, and a dish of growing HeLa cells under a microscope, was inaugurated in the presence of the artist on February 16th 2006. It was a huge success and the work remained in the hallway of the Génopode until November 2006, time during which it was seen by many visitors in the context of several events, as for example during a visit by Connaissance 3 (a continuing education program for seniors) participants, during the "Journées de la Recherche en génétique", or during the University Open House days.

Another venture was the launching in the Summer 2006 of a first participation in the program "Passeport Vacances." This program is organized by the "Service de la jeunesse et des loisirs" of the Commune de Lausanne and gives children the opportunity to participate to all kinds of different activities, from a visit of a bakery to a try at golf, during school vacations. Starting with a suggestion from Nathalie Clerc, our 4th floor administrative assistant, we added a new possibility to the list of activities, that of spending a morning with DNA experts (Une matinée avec les experts de l'ADN). Children of two different age groups, from 10 to 12 and from 12 to 15, came to the Dorigny Campus and spent the first hour and a half with the Sciences–Society Interface, isolating some DNA in the Eprouvette, their public laboratory! They then came to the CIG for a snack and a visit with a scientist. CIG professors, graduate students, post–docs, and technicians gave some of their time to share with these kids their day–to–day experience in the laboratory. For example, some children looked at a small worm, C.elegans, while some others could get acquainted with the latest microscopy techniques. The kids were fascinated, and the scientists were amazed at the pertinence of some of the questions, especially from the younger children! We expect the Passeport Vacances to become one of our regular activities.

For adults, we launched with the Center for Continuing Education and the Sciences–Society Interface a series of lectures intended for a public with little or no knowledge in molecular biology and genetics. The lectures addressed basic subjects such as cell division, the genetic code, human development, and genetic diseases, and were followed by a practical course in the Eprouvette, during which the participants isolated DNA. When launching this series, we wondered, would anyone come? Was anyone ready to spend time and money to learn about how dividing cells deal with their genetic information, how DNA codes for proteins, how a cell can give rise to all the cell types in an organism, and how minuscule mistakes in the genetic code can have an immense influence on an organism? Well, an average of 40 people attended each lecture, with an overwhelmingly positive response. Given the success of this first "experiment," we will repeat it, with improvements induced by comments of the participants, in particular a greater emphasis on connections to disease causes.

Our ability to organize events for the general public, be it the "Portes ouvertes" or the "Passeports vacances" depends on the good will and voluntary help of the people working in the CIG and the Génopode: we thus address many thanks to the participants for imagining activities that they could share with the others, and for communicating their enthusiasm to them.

The CIG participated in the following events for the public:

HeLa, installation by Pierre–Philippe Freymond
CIG/Génopode participant:
L. Gelman
in collaboration with:
A. Kaufman, Interface Sciences–Société, University of Lausanne
February to November 2006

Journées de la Recherche en Génétique
in collaboration with:
L'Eprouvette, Interface Sciences–Société, University of Lausanne
May 2006

UNIL open house days
CIG participants:
M. De Carbonnel, B. Desvergne, M. Hall, N. Hernandez, V. Horn, A. Marques, A. Michels, S. Rodriguez–Jato, L. Rosso, J. Thomas, J. Weber, A. Paradis
June 2006

Passeport vacances
CIG participants:
G. Boss, N. Clerc, W. Herr, V. Horn, A. Marques, S. Rodriquez–Jato, L. Rosso, N. Vouilloz
in collaboration with:
L'Eprouvette, Interface Sciences–Société, University of Lausanne
July–August 2006

Lectures "continuing education"
CIG participants:
N. Hernandez, W. Herr, L. Michalik, A. Reymond
in collaboration with: Service de formation continue, University of Lausanne; L'Eprouvette, Interface Sciences–Société, University of Lausanne
November 2006

Lecture "continuing education for biology teachers"
CIG participant:
A. Reymond
in collaboration with:
L'Eprouvette, Interface Sciences–Société, University of Lausanne; Centre suisse de formation continue des professeurs de l'enseignement secondaire (CPS)
December 2006

OTHER VISITS TO THE CIG:

Connaissance 3 (Université du troisième âge du canton de Vaud)

Day "osez tous les métiers", and other visits for groups and schools

Acknowledgements

Today's scientific research, particularly in genomics, is a costly enterprise that cannot succeed without significant financial support. The CIG is a department of the Faculty of Biology and Medicine (FBM) of the University of Lausanne. As such, the Center is funded by the FBM and the University. In addition, the following organizations have awarded research grants to group leaders and personal fellowships to students and postdoctoral fellows during 2005–2006:

RESEARCH GRANTS TO GROUP LEADERS

Swiss National Science Foundation (FNS) Investigator–driven research grants

B. Desvergne
C. Fankhauser
P. Franken
N. Hernandez
W. Herr
H. Kaessmann
L. Michalik
M. Quadroni
A. Reymond
M. Tafti
B. Thorens
W. Wahli

Swiss National Science Foundation (FNS) targeted research grants

NCCR (National Center of Competence in Research) Frontiers in Genetics
W. Wahli
B. Desvergne
B. Thorens

NRP 50 (National Research Program 50) Endocrine Disruptors: Relevance to Humans, Animals and Ecosystems
W. Wahli
B. Desvergne

European projects

SOUTH
B. Desvergne

EMBRACE
ICGRSIB
V. Jongeneel

EuroDia
V. Jongeneel
B. Thorens

EU–STREP grant Molecular Evolution of Human Cognition
H. Kaessmann

anEUPloidy
A. Reymond

HEPADIP
B. Thorens

EUMORPHIA
W. Wahli
B. Desvergne

Other international projects

ENCODE, project of the National Human Genome Research Institute (NHGRI), USA
A. Reymond

Other contributors

Cancer Research Institute
V. Jongeneel

European Molecular Biology Organization (EMBO) Young Investigator Programme
H. Kaessmann

Faculty of Biology and Medicine, University of Lausanne, Grant for Interdisciplinary research
H. Kaessmann

Fondation Désirée et Niels Yde
A. Reymond

Fondation Jérôme LeJeune
A. Reymond

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A. Reymond

Germaine de Staëls program
B. Desvergne

Human Frontiers Science Program
C. Fankhauser

Juvenile Diabetes Research Foundation International
B. Thorens

Ludwig Institute for Cancer Research (LICR)
V. Jongeneel

National Institutes of Health (NIH), USA
P. Franken
N. Hernandez
W. Herr

Swiss Institute of Bioinformatics
V. Jongeneel

Telethon
A. Reymond

Vital-IT Consortium (University of Lausanne, University of Geneva, SIB, Intel Corp., Hewlett Packard)
V. Jongeneel

Corporate contributors

Basilea Pharmaceutica Ltd.
W. Wahli

Bioresearch
W. Wahli

GlaxoSmithKline
B. Desvergne

Johnson & Johnson Pharmaceuticals
M. Tafti

Pentapharm
W. Wahli

Sanofi Aventis
B. Thorens

Serono
W. Wahli

PERSONAL FELLOWSHIPS TO STUDENTS AND POSTDOCS

European Molecular Biology Organization (EMBO)
Jean–Vincent Chamary (Group Kaessmann)
Shweta Tyagi (Group Herr)

Federation of European Biochemical Societies (FEBS)
Christina Hertel (Group Herr)

Marie Heim–Vögtlin Fund
Anne Vassalli (Group Tafti)

NCCR plant survival
Matthieu De Carbonnel (Group Fankhauser)

Roche Research Foundation
Teldja Neige Azzouz (Groupe Hernandez)
Francesca Capostoti (Group Herr)
Séverine Lorrain (Group Fankhauser)

Toyobo Biotechnology Foundation
Chitose Kami (Group Fankhauser)

University of Lausanne
Matthieu De Carbonnel (Group Fankhauser)

The CIG community

The CIG community is composed of more than 170 people representing more than 20 nationalities from 5 continents; during the years 2005 and 2006 there were 14 group leaders or heads of facilities, 3 "maîtres assistants", 44 postdoctoral fellows, 44 PhD students and 17 master students. The good functioning of the CIG is also critically dependent on the administrative and technical staff working for the different research groups, facilities, central services and administration. Below are listed those individuals who worked at the CIG during 2005-2006:

Agoston Ildiko Stocks and ordering office; **Ahmad Imtiyaz** Group Desvergne; **Albarca Monica** Group Herr; **Allenbach Laure** Group Fankhauser; **Anghel Silvia** Group Wahli; **Azzouz Teldja Neige** Group Hernandez; **Bady Isabelle*** Group Thorens; **Barblan Jachen** Protein analysis facility – PAF; **Barras David*** Group Wahli; **Bauduret Armelle** Genotyping; **Bedu Elodie** Group Desvergne; **Ben Mabkhout Elisabeth** Washing facility; **Berger Marlyne** Stocks and ordering office; **Bertelli Claire*** Group Hernandez; **Bienvenut Willy*** Protein analysis facility – PAF; **Bolomey Stéfanie*** Animal facility; **Bordier Béatrice** Group Wahli; **Boss Gilles** Workshop / Common equipment laboratory; **Boyer-Guittaut Michaël*** Group Hernandez; **Brawand David** Group Kaessmann and Group Wahli; **Brunner Jean-Marc** Group Desvergne; **Bueno Manuel** DNA array facility – DAF; **Calpini Valérie*** Group Tafti; **Capotosti Francesca** Group Herr; **Carrard Marianne** Genotyping; **Carrascosa Coralie** Group Herr; **Cartier Delestre Muriel** Group Herr; **Cerutti Lorenzo** Vital-IT; **Chaignat Evelyne** Group Reymond; **Chamary Jean-Vincent*** Group Kaessmann; **Charrotton Joëlle** Animal facility; **Chen Pei-Jiun** Group Herr; **Chrast Jacqueline** Group Reymond; **Clerc Nathalie** Group Fankhauser, Group Hernandez and Group Herr; **Colzani Mara** Protein analysis facility – PAF; **Constantin Nathalie** Group Wahli; **Cornu Marion** Group Thorens; **Cousin Pascal** Group Hernandez; **Crevoisier Annick** Group Kaessmann, Group Reymond and Group Tafti; **Curie Thomas** Group Franken; **Dayer Geneviève*** Washing facility; **De Carbonnel Matthieu** Group Fankhauser; **Debrieux Dimitry** Group Fankhauser; **Debril Marie-Bernard** Group Thorens; **Déglon Agnès*** Group Hernandez; **Del Rizzo Sébastien*** Group Tafti; **Delgado Anen*** Group Wahli; **Dentan Corinne** Central administration; **Desvergne Béatrice** Group Desvergne; **Didelot Gérard** Group Reymond; **Dolci Wanda** Group Thorens; **Dorsaz Stéphane** Group Tafti; **Duek Roggli Paula*** Group Fankhauser; **Duléry Cécile** Group Michalik; **Dupanloup Isabelle*** Group Kaessmann; **Ebring Clotaire*** Animal facility; **El Kochairi Ilhem** Group Wahli; **Emery Martine** Group Thorens; **Emmenegger Yann** Group Franken; **Fabbretti Roberto** Vital-IT; **Falquet Laurent** Vital-IT; **Fankhauser Christian** Group Fankhauser; **Feige Jérôme** Group Desvergne; **Fiechter Vincent** Group Fankhauser; **Flegel Volker** Vital-IT; **Flückiger Laurence** Group Herr; **Franken Paul** Group Franken; **Freymond Christiane** Group Wahli; **Fu He** Group Desvergne; **Galaud Delphine*** Phenotyping; **Gelman Laurent*** Group Wahli and Group Desvergne; **Genoud Thierry** Group Fankhauser; **Gerber Alan** Group Desvergne; **Gnecchi Alain*** Animal facility; **Goldstein Darlene** DNA array facility – DAF; **Gouait Patrick** Animal facility; **Guernier Sophie** Group Herr; **Gurcel Laure** Group Tafti; **Gyger Joël** Group Thorens; **Hagenbüchle Otto** DNA array facility – DAF; **Hall Diana** Group Thorens; **Hall Matthew** Group Desvergne; **Hänggeli Corinne** Informatic support; **Harewood Louise** Group Reymond; **Harshman Keith** DNA array facility – DAF; **Hasan Subah** Group Tafti; **Hassler Vanessa** Group Wahli; **Hausherr Katharina** Genotyping; **Henrichsen Charlotte** Group Reymond; **Hernandez Nouria** Group Hernandez; **Herr Winship** Group Herr; **Hertel Christina** Group Herr; **Hoffmann-Denarié Claudia** Group Thorens; **Horn Virginie** Group Herr; **Hornitschek Patricia** Group Fankhauser; **Howald Cédric** Group Reymond; **Hrobova Crausaz Henrieta*** Group Wahli and Group Hernandez; **Icre Guillaume*** Group Wahli; **Iglésias José** Group Wahli; **Ingman Maxwell** Group Kaessmann; **Ioannidis Vassilios** Vital-IT; **Iseli Christian** Group Jongeneel; **Jeronimo Virginie** Group Wahli; **Jimenez Maria** Group Thorens; **Jongeneel Victor** Group Jongeneel and Vital-IT; **Joye Elisabeth** Phenotyping and Group Desvergne; **Junod Fabienne** Animal facility; **Kaessmann Henrik** Group Kaessmann; **Kami Chitose** Group Fankhauser; **Klinger Sonia** Group Thorens; **Kostadinova Radina** Group Wahli; **Krauskopf Alexandra** Group Wahli; **Kuznetsov Dimitry** Group Jongeneel; **Lathion Caroline*** Group Wahli; **Laverrière–Schultz Monique*** Group Thorens; **Leuenberger Nicolas** Group Wahli; **L'Hôte Philippe** Group Hernandez and Group Herr; **Liechti Robin** Vital-IT; **Long Li** Vital-IT; **Lorrain Séverine** Group Fankhauser; **Machado Rebelo Marques Ana** Group Kaessmann; **Maquelin Lionel*** Group Kaessmann; **Marcillac Fabrice** Group Thorens; **Maret Stéphanie** Group Tafti; **Margot Delphine** Library; **Marty Nell Annette** Group Thorens; **Membrez Mathieu*** Group Thorens; **Menétrey Bozena*** Library; **Mersch Danielle** Group Tafti; **Messerli Fabienne** Group Herr; **Metthez Geneviève** Group Desvergne; **Metref Salima** Group Thorens; **Michalik Liliane** Group Wahli; **Michaud Joëlle** Group Herr; **Michels Annemieke** Group Hernandez; **Montagner Alexandra** Group Wahli; **Morel Marc** Workshop; **Moreno Silvia** Group Wahli; **Moullan Norman** Group Wahli; **Mounien Lourdes** Group Thorens; **Muller Jocelyne** Group Jongeneel and Vital-IT; **Nadra Karim*** Group Desvergne; **Nagy Gergely** Informatic support; **Notari Brigitte** Animal facility; **Nyffeler Bruno** Vital-IT; **Pagni Marco** Vital-IT; **Paillusson Alexandra** DNA array facility – DAF; **Paradis Arnaud** Cellular imaging facility CIF; **Pernet Nataskha** Group Wahli; **Peter Corinne** Sequencing; **Petit Brice** Group Tafti; **Petit Marlène** Group Wahli and Group Desvergne; **Pfister Corinne** Group Tafti; **Potrzebowski Lukasz** Group Kaessmann; **Potts Alexandra** Protein analysis facility – PAF; **Poussin Carine** Group Thorens; **Pradervand Sylvain** DNA array facility – DAF; **Quadroni Manfredo** Protein analysis facility – PAF; **Ravussin Yann*** Group Thorens; **Ravy Caroline** Animal facility; **Reina Copete Jaime Humberto** Group Hernandez; **Reymond Alexandre** Group Reymond; **Ricci Matteo** Group Wahli; **Rielle Ludivine** Group Jongeneel; **Robyr Anne-Catherine*** Group Tafti; **Rodriguez-Jato Sara** Group Herr; **Rossi Daniel*** Group Desvergne; **Rosso Lia** Group Kaessmann; **Rotman Nicolas** Group Wahli; **Rougemont Jacques** Vital-IT; **Rufener Jézaëlle** Animal facility; **Sambeat Audrey** Group Thorens; **Sauvain Fabienne** DNA array facility – DAF; **Schepens Isabelle** Group Fankhauser; **Schüpbach Thierry** Vital-IT; **Schwab Joanna*** Group Wahli and Group Desvergne; **Schweizer Fabian** Group Fankhauser; **Seyer Pascal** Group Thorens; **Sick Beate*** DNA array facility – DAF; **Soyer Jérôme** Animal facility; **Stevenson Brian** Group Jongeneel; **Stockinger Heinz** Vital-IT; **Tafti Mehdi** Group Tafti; **Tallichet Blanc Corinne** Group Wahli; **Tarussio David** Group Thorens; **Tavera Tolmo Beatriz*** Group Desvergne; **Tawffik Salma*** Group Tafti; **Terreau-Haftek Zofia** Group Wahli; **Terrier Raphael** Group Michalik; **Thomas Jérôme** DNA array facility – DAF; **Thoppae Gnanasekaran** DNA array facility – DAF and Protein analysis facility – PAF; **Thorens Bernard** Group Thorens; **Thottathil Oommen Sajit** Group Desvergne; **Trevisan Martine** Group Fankhauser; **Tyagi Shweta** Group Herr; **Varnat Frédéric** Group Desvergne; **Vassalli Anne** Group Tafti; **Vaucher Angélique** Group Wahli; **Vienne Julie** Group Tafti; **Vieu Erwann** Group Hernandez; **Vinckenbosch Nicolas** Group Kaessmann; **Vouilloz Nicole** Central administration; **Wahli Walter** Group Wahli; **Waridel Patrice** Protein analysis facility – PAF; **Wawrzyniak Marta** Group Michalik; **Weber Johann** DNA array facility – DAF; **Weier Manuela** Group Kaessmann; **Wertenberg Marianne** Group Wahli; **Wicker Sophie** DNA array facility – DAF; **Wierzbicki Bartosz** Apprentice; **Willemin Gilles*** Group Thorens; **Winkler Christine*** Group Thorens; **Wyser Céline** Apprentice; **Zahn-Zabal Monique** Group Jongeneel; **Zimmermann Cynthia** Washing facility

*left the CIG