

# -Letter

# 19

## STEERING CELLS

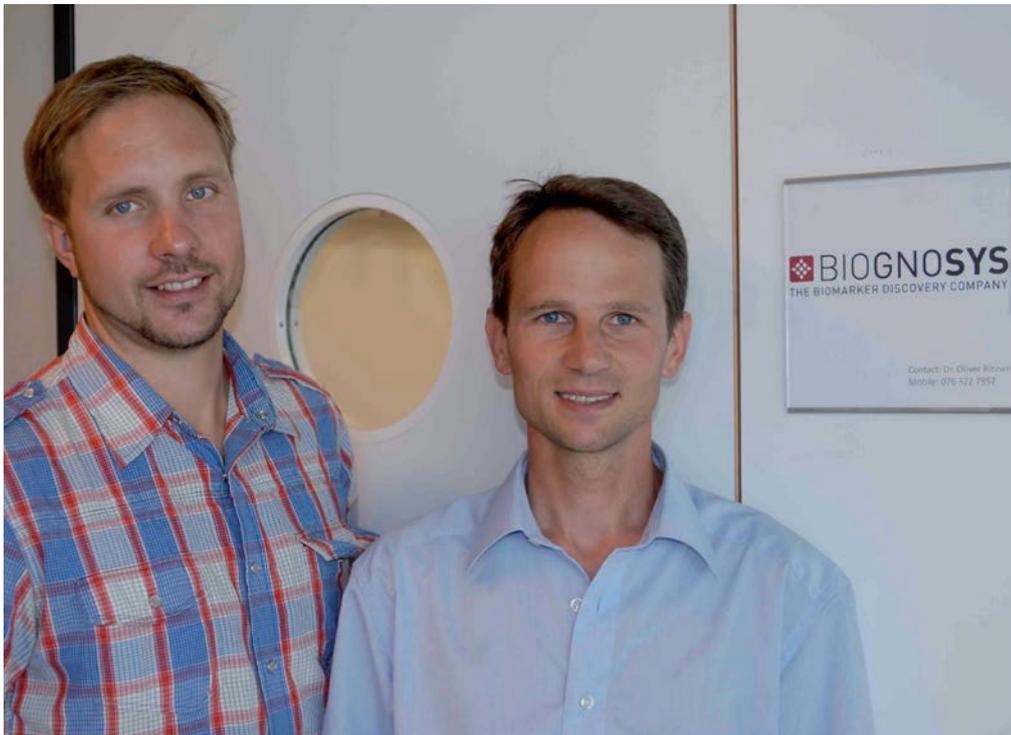
SystemsX.ch scientists crack the most important regulatory system of cells 3

## CREATING CONTACTS

Science and Rambling during the first student retreat in Weggis 5

## VARIETY DESPITE SAMENESS

Why genetically similar cells have different properties 6



Johan Malmström and Oliver Rinner, founders of Biognosys, heavily into biomarkers.

Photo: thm

## A spin-off from the SystemsX.ch project «PhosphoNetX» is seeking a seed investment from an investor

**Zurich.** As so often with scientific research, it all started in the coffee break. Johan Malmström (34) and Oliver Rinner (35), both researchers in Professor Ruedi Aebersold's laboratory at the Institute of Molecular Systems Biology at ETH Zurich, had independently arrived at the same idea; namely that the paradigm shift underway in proteomics must open up a great market potential for biomarkers. At the end of the coffee break, which lasted a bit longer than usual, the

start-up project «Biognosys» had been born.

That was in September 2007. A year later, start capital of CHF 100'000 had been secured and the company had been registered according to the laws of the land. Domicile: ETH Zurich, IMSB HPT C119. Here, in a side-wing of IMSB on ETH Campus Höggerberg, they both pushed ahead with the development of the company. Malmström acted as managing director, Rinner as head of re-

continued on page 2

## Magic?

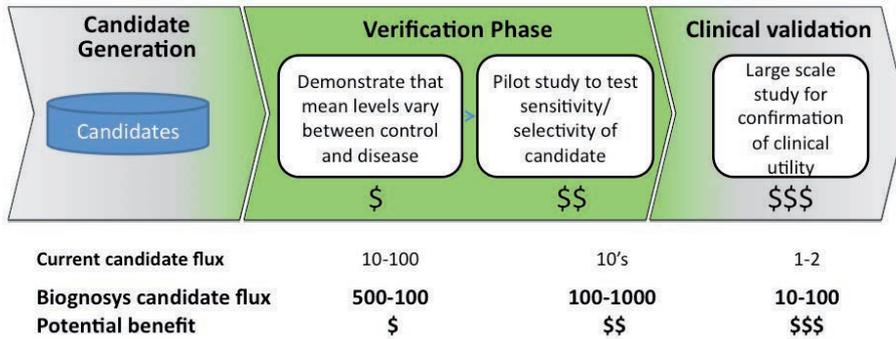
Dr. René Imhof, Head of Research Roche Pharma, Basel

For bright scientists in academia, work is concerned with posing novel questions in a chosen field in order to understand the nature of nature and to find radical approaches for simplifying problems and finding solutions. For «drug creators» in the pharma industry, work is more about reaching explicit objectives by finding answers to medical problems. Here though, the complexity of the physiological systems involved should be retained as far as possible.

So, is there anything magic about collaboration between academe and industry? Yes and no! No, we don't need magic to understand the fundamental difference. But, yes, there is something magic when it comes to defining mutually rewarding collaborations and partnerships. We were well aware of this «magic» element when we launched a collaborative initiative with the Competence Center for Systems Physiology and Metabolic Diseases at ETH Zurich. We set up a conclave and invited representative scientists from academia and Roche to participate. The conclave was conceived as a way to foster the free flow of intuitive and inspiring thoughts and proposals. The outcome of this meeting was:

continued on page 4

## Biognosys has registered the patent



Biognosys enlargens the bottleneck of new biomarkers findings.

Graphic: Rinner

continuation from page 1

search. Both were also engaged in the SystemsX.ch project, PhosphoNetX (cf. article on page 3). Working alongside these two is a third chemistry scientist, Philipp Antoni, who also has startup experience as a manager, as well as the head of PhosphoNetX, Ruedi Aebersold, who also acts as scientific adviser.

### From net to bait

The basic idea of the company is already in the name: Biognosys. With the help of Systems Biology the aim is to find diagnostic tools that could detect diseases or contamination in foodstuffs – in other words, biomarkers. Rinner envisions how cancers, for instance, could be discovered at a very early stage, thus increasing healing chances compared to treatment after the actual localization of a tumor. Rinner is skeptical, however, regarding diagnostics that identify illnesses or diseases for which no treatment or cure is possible and which cannot be influenced by a change of lifestyle.

«Up until now the proteomics to discover biomarkers has been disappointing», says Rinner. Certainly, it was now

possible to simultaneously detect a great number of proteins in a bodily fluid. But the important proteins are easily overlooked with this unspecific approach, which is rather like fishing with a wide-meshed net

This is why Rinner and Malmström have decided to use a rod-and-bait approach. Using their new technology to fish in the obscure diversity of proteins and their fragments they only fish for those which they have reason to believe to be relevant for a given disease. This means that they have to know beforehand what they are looking for and they draw this knowledge either from the scientific literature or from preliminary experiments, so-called targeted proteomics.

This approach represents the paradigm shift in proteomics. Until now scientists have attempted with the help of mass spectrometers to catalogue all proteins that occur in the human body. So far they have succeeded in around 40 per cent by starting with the proteins postulated in gene sequences. Ruedi Aebersold was closely involved in the development of the technologies needed for this and, once again, he is also on the front line in targeted proteomics research.

### As simple as a fax machine

«Up to now the bottleneck has been caused by the verification, whether candidates are really worth their salt», is how Rinner characterizes the main problem of discovering biomarkers. With the new technologies they've developed, Malmström and Rinner hope to solve this problem. «It takes only a twentieth of the time to test whether it's worthwhile to subject a candidate to a clinical trial», says Rinner referring to their Innovation. Moreover, Biognosys

has already started to look for such candidates. Clearly, a three-man company is far too small for a clinical trial, especially when it comes to funding. They are therefore looking for partners. «In the long term we want to do the clinical trials ourselves», says Rinner, because the potential return on a marketable biomarker would naturally be much higher than for biomarker candidates that have not been clinically validated (cf. graphics). To begin with though they could see themselves carrying out commissioned research for a biotech or pharmaceutical company in order to obtain financial means.

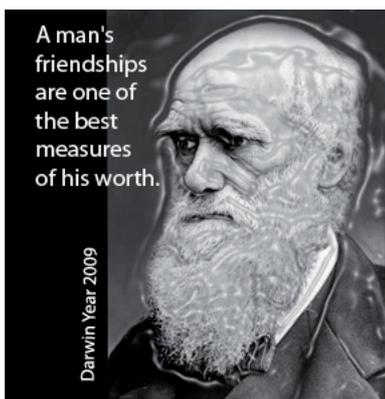
The technology employed for the verification of candidates was mainly developed by Paola Picotti, a postdoctoral researcher working in Ruedi Aebersold's laboratory. Along with Malmström and

 **BIOGNOSYS**  
THE BIOMARKER DISCOVERY COMPANY

Rinner, Picotti owns the patent, which ETH Zurich has registered in Europe and the USA. As is usual in such cases, ETHZ has handed the license back to the inventor, exclusively of course. The technology, which can measure 50 biomarker candidates simultaneously, is to be further developed. The development of a customized mass spectrometer to discover biomarkers that is as easy to use as a fax machine is a further goal of Biognosys.

### Due diligence underway

This will not be possible, however, without fresh money. A venture capitalist company is performing a due diligence evaluation of Biognosys to decide if the company should get a seed investment to lift off. «For us this would be the breakthrough, and we would be ready when the economy starts to recover», hopes Rinner. The firm has already reaped some of the scant venture capital available in Switzerland in competitions. It was awarded two venture kick prizes (cf. article on page 4) and Philipp Antoni won the title of «venture Leader» 2009, awarded by the Federal Commission for Technology and Innovation and the accountancy company Ernst & Young.



## Very little is known about the regulatory system of cells. «PhosphoNetX» aims to understand the phosphorylation process.



«PhosphoNetX will fundamentally change systems biology and, consequently, also biology», says head of project Ruedi Aebersold. Photo: Christian Flierl

Thomas Müller Zurich. Taking a car apart and laying out all its component parts would be no help in explaining how the car is able to drive, turn corners, brake, accelerate, indicate, sound its horn or carry out lots of other operations. Nonetheless, at times, biology conjures up the impression that if only all single components of a cell were known, then their functioning would explain themselves. It was supposed that biologists who worked on the sequencing of the human genome, for example, would «automatically» be led

to new knowledge concerning illness and health.

Unfortunately, this is not entirely true. Rather it transpired that the expression of genes, that is to say when which gene is activated or deactivated, turns out to be more complex than expected. But genes are only part of the story. Overlying the static genome – we have the same one all our lives – is the dynamic universe of the proteins. In the end it is these that determine life, and they too interact among themselves in a complicated way.

### Keeper of the genome

Thousands of proteins are simultaneously busy in our cells; some occur in great numbers, others in trifling quantities – which does not necessarily make them any less important. «We know very little about the most important regulatory system in our cells», says Ruedi Aebersold, Professor at the Institute of Molecular Systems Biology at ETH Zurich. Aebersold is head of the SystemsX.ch project «PhosphoNetX», which has the aim of eliminating this deficit.

It deals with the phosphorylation of proteins. So-called kinases hang a phosphate

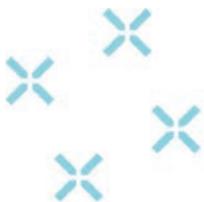
group on to proteins and cause a change in function. Conversely, the phosphatases turn the change in function off again.

One known example is the tumor suppressor protein, p53, and in certain ways this protein can be seen as the keeper of the genome. If a cell starts to divide uncontrollably and develops cancer-like characteristics, a phosphorylation of p53 causes the cell in question to «commit suicide», thus banning the cancer risk. This protein exhibits no fewer than 18 phosphorylation points, a sure indication that a lot of switching possibilities exist.

If one now considers that between a tenth and half of the proteins in a cell are controlled by this mechanism and that over 500 different kinases and about 150 phosphatases are active, we arrive at a colossal number of possible «switches». Aebersold estimates that to date only about ten per cent of the human kinome has been studied in vivo, i.e. examined to determine which stimuli kinases and phosphatases react to and which cellular processes they then release. «Most of our mathematical

continued on page 4

### «PhosphoNetX – «Phosphorylation-Modulated Informational Networks of the Cell»



**PhosphoNetX**  
Phosphorylation-Modulated  
Networks of the Cell

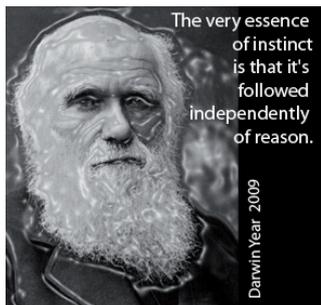
Principal investigator	Ruedi Aebersold, Institute of Molecular Systems Biology (IMSB), ETH Zurich
Involved research groups	Lucas Pelkmans, IMSB, ETHZ; Andreas Plückthun, Biochemical Institute, University of Zurich; Christian von Mering, Biology Department, ETHZ and Swiss Institute of Bioinformatics; Viola Vogel, Laboratory for Biologically Oriented Materials, ETHZ; Nelson Bradley, Institute of Robotics and Intelligent Systems, ETHZ
Number of research groups	6
Researchers : Administration	20 : 1
Biologists : Non-biologists	18 : 1
Overall budget (2008-2011)	8'585'400 CHF, thereof 4'200'000 CHF from SystemsX.ch

continuation from page 3  
models on the dynamics of biological systems are simply incomplete and probably wrong», concludes Aebersold.

This is why PhosphoNetX has set itself three goals. First of all, the network of 500 kinases and 150 phosphatases needs to be clearly understood. The second step concerns the actual flow of information through this network. The first step can be figuratively seen as the mapping out of Switzerland's railway network and the second as the train services that use it. Finally, the newly-won knowledge is to be applied to four areas: cell division, transport of information via the cell membrane, and the cell's response to mechanical stress, and cancer.

### Changing the biology

Because these aims cannot be achieved using today's methods, the development of new technology plays a big role. One example of such a method is SRM technology: «Selected Reaction Monitoring» makes it possible, in a short space of time, to determine all kinases and phosphatases involved in a given signalized route, qualitatively as well as quantitatively. The latter is central to the modeling of biological systems. Ruedi Aebersold is optimistic, «that the technologies and data generated by PhosphoNetX will fundamentally change Systems Biology, and, therewith, biology».



## «venture kick» plays midwife to promising companies



Winners of «venture kick» 2009: The founding team of InSphero, a company associated with the University of Zurich and ETH Zurich. Photo: IFJ

Daniel Vonder Mühl Bern. Without a doubt, the most effectual transfer of academic research into the private sector is the founding of a new company. «venture kick» also helps SystemsX.ch researchers to launch a spin-off and offers up to CHF 130,000 start-up capital.

The main prize this year of CHF 100,000 goes to «InSpehro», a company based in Zurich. «venture lab», the national program from CTI, a federal innovation promotion agency, offers a wide range of modules: from setting up a business plan to basic training in management to questions on the initial financing of a company.

«venture kick» wants to

double the number of companies founded from universities and thus boost the transformation into marketable products of as many research results as possible. Participants have only two conditions to meet: first, it must be a new company, not one that exists already, and, second, applications must come from a recognized institution of tertiary education (university, federal institute of technology, university of applied sciences). This means that all SystemsX.ch researchers are eligible.

### 60 Foundations

Applications can be sent in at any time. In the first round eight projects are given the

chance to be presented to a jury. The four chosen projects receive CHF 10,000 each and qualify for the next round. The two successful projects from the second round receive a further CHF 20,000 and the applicants the means to elaborate their projects. In the final round, there remains CHF 100,000 to be won.

The money – about three million Swiss francs in the last two years – is given with no strings attached. The last 100'000 francs do not go to the founders, but to the newly founded company. Of the 89 supported start-up projects so far, over 60 eventually evolved into the founding of a company.

The «venture lab» modules and, especially, «venture kick», have helped the first spin-off from SystemsX.ch, Biognosys (cf. front-page article) on its way. «venture lab» is looking forward to an abundance of participants among SystemsX.ch researchers. The Management Office (D. Vonder Mühl) or «venture lab» (B. Schillig) would be happy to answer any questions.

Further info: [www.venturekick.ch/](http://www.venturekick.ch/) [www.venturelab.ch](http://www.venturelab.ch)

## SystemsX.ch promotes Industry-Cooperation

Zurich. SystemsX.ch launches two new types of project: BIP aims to raise the gross national product, ISA (Industry Sabbatical@ Academia) invites scientists from the private sector a training in academia.

In the «Bridge 2 Industry Projects» (BIP) academic and industrial researchers work together on a Systems Biology theme. The project runs for one year and will be supported by SystemsX.ch with

CHF 120,000. SEB will evaluate applications for projects four times a year. ISA (Industry Sabbatical@ Academia) invites scientists working in the private sector to a higher training program with an academic research group at a university. In economically difficult times this is an interesting opportunity to better get to know SystemsX.ch. VDM

[www.systemsX.ch/BIP-ISA](http://www.systemsX.ch/BIP-ISA)

## Magic?

continuation from page 1

the «life and fate of pancreatic beta-cells in the evolution of Diabetes Type 2». After three years of intense collaboration, we appreciate the mutually rewarding outcome: Novel biomarkers, drug targets imaging methods and predictive tools in bioinformatics – all of which are now up for evaluation as potentially novel tools in the diagnostics and therapeutics of Diabetes Type 2. Magic!

## The first **Student Retreat of SystemsX.ch** was a **success**. 25 PhD students and three guest speakers got to know one another and exchanged experiences.



Doctoral students get to know one another's projects in a poster session.

Photo VDM

Andrej Bicanski\* **Weggis**. The first SystemsX.ch meeting for graduate students that took place on the 11th/12th of September 2009 was the first of its kind. All participants were correspondingly timid to start with. Who are these people that have made their way to this more or less remote, but idyllic, Weggis, was what many participants were probably asking themselves. But the welcome from the conference manager (chair) Franziska Biellmann and a presentation that was both interesting and educative from Greg Stephanopolous (Massachusetts Institute of Technology) quickly broke the ice.

### Funny situation fosters exchange

The concluding boat trip on Lake Lucerne and a ramble through the geologically interesting Rigi region surrounded by a breathtakingly beautiful landscape, raised the spirits to even higher levels. Unfortunately, tenacious fog made it impossible to admire the spectacular views, but it provided the excursion with an element of situation

comedy that fostered social exchanges between the participants. It was also an occasion where it was possible to enter into conversation with guest speakers.

### Numerous guest speakers

During an aperitif and snacks followed by a poster session, more information was gained about the scientific background of participants and their work within the framework of the SystemsX.ch initiative. At the dinner in the evening in Hotel Alpenblick is was surprising to find that in a single day this colorful and diverse group of young scientists had developed a degree of intimacy among themselves. The three invited guest speakers also enriched their dinner conversations with personal experiences and scientific expertise. The eventful day ended with a glass of good wine.

The following day, Saturday, was entirely devoted to science. The two plenary speakers, David Fell (Oxford Brookes University) and Erik van Nimwegen (University of Basel) opened the morning and afternoon sessions with highly

interesting lectures in which the stage was handed over to the graduate students.

### Foundations are laid

Even though, on reflection, there were clear thematic emphases in the meeting, participants were able to look back on a wide range of interesting presentations. Despite the variety it was possible to gain an overview of the different approaches used in the SystemsX.ch initiative. And, perhaps more importantly, those working on the projects gained a first, rudimentary feeling of belonging. Although the timetable was somewhat fast-forwarded this first SystemsX.ch doctoral students day successfully laid the foundations for future friendships and fruitful professional contacts.

\*Andrej Bicanski is studying for an interdisciplinary doctoral thesis under the guidance of Auke Ijspeert (EPFL) and Thierry Wannier (University of Freiburg) entitled «Decoding the mechanisms of gait generation and gait transition in salamander: a Systems Biology approach».



A boat trip from Weggis to the valley station of the Rigi train in Vitznau.

Photo VDM

## NEWS

**Workshop for SMEs in October**

**Zürich.** The Swiss Biotech Association, Toolpoint for Life Sciences, and SystemsX.ch are organizing a half-day SME-workshop at ETH Zurich (Center). On 19th October 2009 SystemsX.ch groups and three SMEs (Quiagen, Tecan, Xavo) will be presenting their research. The discussion followed by lunch aim to facilitate networking to establish as diverse contact points as possible for collaborative work between SMEs and SystemsX.ch groups. VDM Registration at [www.SystemsX.ch/SME](http://www.SystemsX.ch/SME)

**How addiction begins**

**Geneva.** SystemsX.ch Scientists working with Christian Lüscher (University of Geneva) have discovered a mechanism that reduces the addictive potential of cocaine in mice. The mechanism could help to explain drug addiction in human beings. thm

See [www.SystemsX.ch/News](http://www.SystemsX.ch/News)

**«It's the context, stupid!»**

**Zürich.** «It's the economy, stupid!» was the battle cry of Bill Clinton's campaign chief, James Carville, in 1992 when it was a question of getting the then President George Bush out of office. «It's the context, stupid!» is how Lucas Pelkman from the Institute for Molecular Systems Biology at ETH Zurich paraphrases his recent work.

An article, recently published in «Nature», explains for the first time why genetically similar cells in a population do not behave in the same way. Factors, such as the density of a population or the geographical location of the individual cells, also play a role in determining the phenotype of a cell.

This result might not seem very surprising, but it is of fundamental importance and has practical relevance. This is because, in a typical experiment, cell populations are compared to one another,

whereby both the control population and the population being experimented on are taken to be a pool of a cell type with «average characteristics».

**Better experiments**

«This unquestioned assumption has led to many wrong interpretations of experiments in the past», is how Pelkman depicts the meaning of his work. Scientists now have the means to correct or avoid such mistakes.

With the help of SystemsX.ch funding mathematical models have been developed that can predict the expected cell-to-cell variability with great precision. Conversely, it is also possible to come to grips with the influence exercised by the context in comparative cell cultures. In other words: in future, the interpretation of cell biology experiments will be more precise. thm

see also [www.ethlife.ch](http://www.ethlife.ch)

**The Glossary of SystemsX.ch**

**Research, Technology and Development Project (RTD project):**  
SystemsX.ch's flagship project, multi-year duration.

**Interdisciplinary Pilot Project (IPP):**  
Research involving risks. One-year duration.

**Interdisciplinary Doctorate (IPhD):**  
Duration of 3 to 4 years.

**Board of Directors (BoD):**  
SystemsX.ch's highest steering body composed of the presidents, rectors and directors of all participating institutions.

**Scientific Executive Board (SEB):**  
Operative committee composed of scientists from the participating institutions.



**SystemsX.ch**  
The Swiss Initiative in Systems Biology

**IMPRESSUM**

**Thomas Müller (thm)**  
**Head Communications**  
**Tel: +41 61 683 76 77**  
**Mobile: +41 79 614 06 77**  
**[Thomas.Mueller@SystemsX.ch](mailto:Thomas.Mueller@SystemsX.ch)**

**Natalia Emery Trindade (NET)**  
**Assistant Communications**  
**Tel: +41 44 632 02 50**  
**Fax: +41 44 632 15 64**  
**[Natalia.Emery@SystemsX.ch](mailto:Natalia.Emery@SystemsX.ch)**

**Dr. Daniel Vonder Mühl (VDM)**  
**Managing Director**  
**SystemsX.ch**  
**Tel: +41 44 632 78 88**  
**[Daniel.Vondermuehl@SystemsX.ch](mailto:Daniel.Vondermuehl@SystemsX.ch)**

**Postal Address:**  
**SystemsX.ch**  
**Clausiusstr. 45 - CLP D 7**  
**CH-8092 Zurich**  
**Web: [www.SystemsX.ch](http://www.SystemsX.ch)**

**To subscribe or unsubscribe to this newsletter, please contact:**  
**[Natalia.Emery@SystemsX.ch](mailto:Natalia.Emery@SystemsX.ch)**

**Ela Hunt joins SyBIT**

**Zürich:** Starting October 1st Dr Ela Hunt is joining Peter Kunszt as deputy manager for «SystemsX.ch Biology IT». She is a bioinformatics and database research leader and software engineer,

with expertise in large-scale biological data analysis and visualisation, and has done extensive research in data standards for proteomics, and database-supported DNA and protein analysis. She has authored over 30 papers, edited several volumes, and is active in peer review internationally.

Ela Hunt previously worked

for British Petroleum, the University of Glasgow, and the University of Strathclyde in the UK, for the Max Planck Institute for Molecular Genetics in Berlin, and in Switzerland for the University of Zurich and the ETH in Zurich. She holds masters degrees in English and in Scottish literature, and a BA and a PhD in computing.

**Conferences and Events**

Oct 12-15, 2009	Miptec - The leading European Event for Drug Discovery	Basel
Oct 19, 2009	Small and Medium Enterprises (SME) Workshop	Zurich
Nov 05-06, 2009	Mass Spec Europe	Barcelona
Nov 18, 2009	All-SystemsX.ch-Day 2009	Bern
March 3, 2010	EMBL Workshop on Visualizing Biological Data (VizBi)	Heidelberg
March 17-18, 2010	RNAi2010: Gene regulation by small RNAs	Oxford (UK)