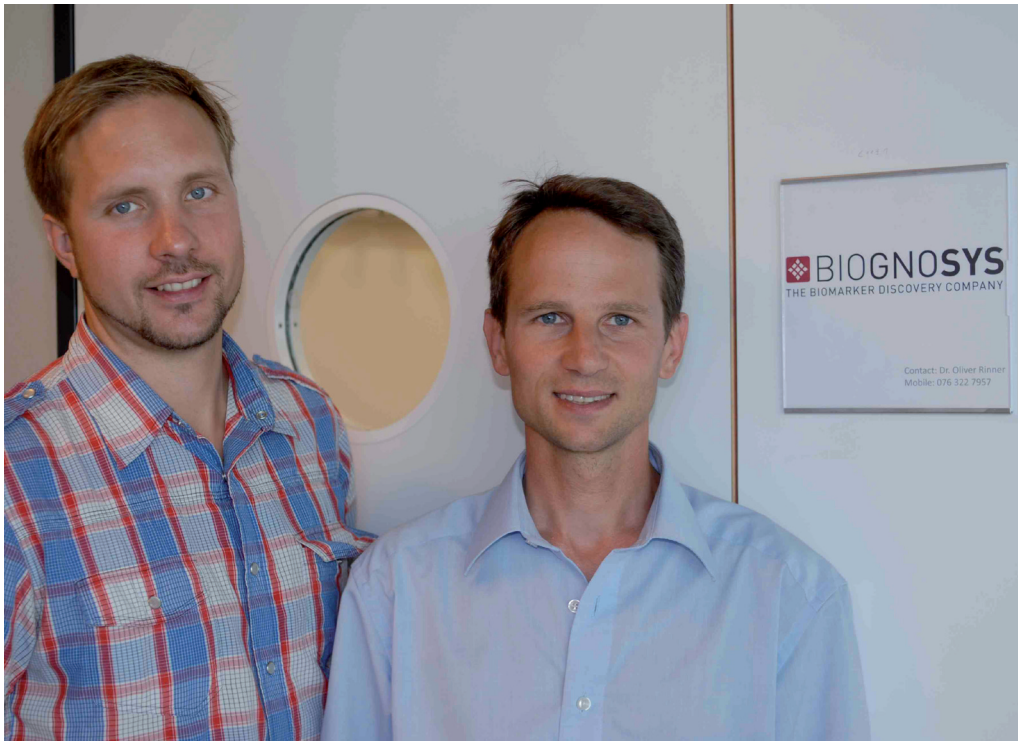
SystemsX.ch Newsletter #19
October 2009

X-Letter 19



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 sidewing of IMSB on ETH Campus Hönggerberg, 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?

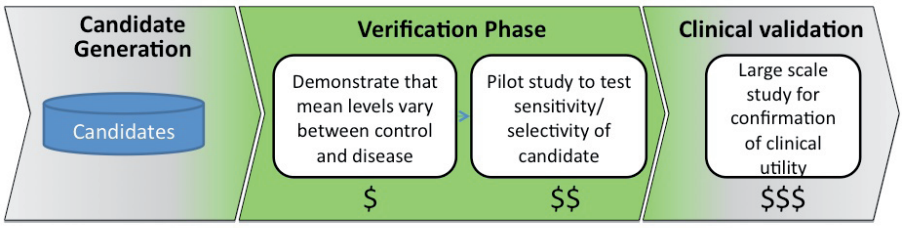
Dr. René Imhof, Head of Research Roche Pharma, Basel

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



Current candidate flux	10-100	10's	1-2
Biognosys candidate flux	**500-100**	**100-1000**	**10-100**
Potential benefit	**$**	**$$**	**$$$**

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 start-up experience as a manager, as well as the head of PhosphoNetX, Ruedi Aebersold, who also acts as scientific adviser.

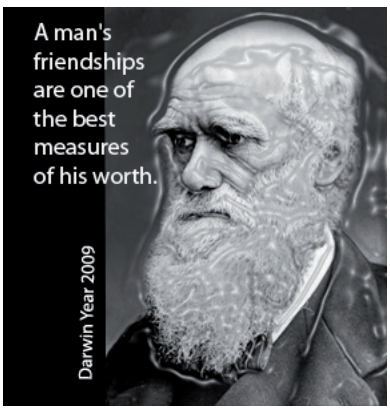
From net to bait

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 Rinner, Picotti owns the patent, which ETH Zurich has registered in Europe and the USA. As is usual is 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 a fax machine is a further goal of Biognosys.

BIOGNOSYS
THE BIOMARKER DISCOVERY COMPANY

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. **«PhoshpoNetX» 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**

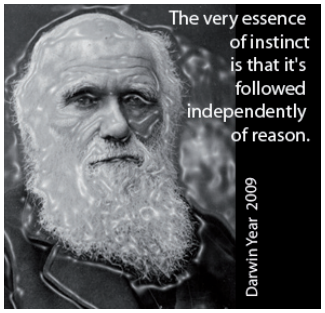
continuation from page 3

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

This is why PhoshpoNetX 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 Mühll

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 Mühll) or «venture lab» (B. Schillig) would be happy to answer any questions.

Further info: www.venturekick.ch. / 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 offers 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

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!