Luxembourg: A conversation with systems biologist Rudi Balling

"From A Network Point of View"

Rudi Balling, scientific director of the Helmholtz Centre for Infection Research in Braunschweig, Germany, has found himself a new challenge for 2010 - setting up the all-new Luxembourg Centre of Systems Biomedicine. In *Lab Times* he reveals his motives and his strategies for making this venture a success.

LT: You named your new institute Centre for Systems Biomedicine. What's the idea behind that name?

Rudi Balling: We thought quite a while about a name that really describes the work we're going to do. Basically, we want to do biomedical research at the level of systems. Therefore, logically, the institute's name is not Centre for Systems Biology but Centre for Systems Biomedicine. That means we try to get insights into disease pathogenesis from a network point of view. We not only want to look at small aspects and tiny details but we intend to look at the entire system, genome-, proteome-, metabolome-wide. We try to construct networks by looking at architecture, structure and dynamics of cells under different environmental conditions, perturbations, genetical influences. In order to do this one has to have a very close interplay between experiment and computation. We want to end up with a mathematical description of a biological process.

Which diseases will you focus on?

Balling: I have a completely free choice. I really like that. This freedom was one of the main reasons that attracted me to Luxembourg.

We suspect you have some favourites.

Balling: Right. I'd like to analyse inflammation processes. Inflammation is a major driver of many different diseases. There's also a clear connection between inflammation and cancer. When a cancer cell undergoes metastasis it shows many characteristics of inflammatory processes. Also interesting is neuroinflammation. The macrophages of the brain are the microglia. I'm very interested in making a comparative analysis between the brain macrophages and other macrophages like those in the liver. I'm also extremely interested in evolutionary aspects: how do microglia, neurons, macrophages or whole systems work in different animals such as fish, fly, mouse, human?

Will a systems- or network-based approach accelerate the medical progress?

Balling: Currently, there's a huge rush towards identifying and validating biomarkers in human and in mouse. Those biomarkers need to be validated on a scientific basis. If we can come up with really understanding a network, for example, the immune system, a macrophage or inflammation and if we compare the networks of mouse and human, I think we can make a huge step towards increasing the predictability of biomarkers, of the development of a disease and of potential therapies. Study the system, understand how the system reacts to inflammation in terms of plasticity and outcome - that's what we're going to do. Mathematically speaking, we are looking at the transform function.

Considering mathematics... we heard you recently poked your nose into dozens of mathematics books.

Balling: That's right. I spent some months at the Broad Institute in Cambridge, Boston and I really was a student in mathematics. I took courses in analysis and linear algebra. I'm of course not a mathematician but now I understand the language of mathematicians and I can talk to them, and to physicists and computer scientists. That's a huge step for me. It's all about language.... You know, the University of Luxembourg has two major pillars that this university stands for.

> ***"Mathematicians or physicists are equally afraid of biology as biologists of mathematics."***

Which ones?

Balling: One is multilingualism. Everybody speaks English, French, German and Luxembourgian. The second pillar is interdisciplinarity. Working interdisciplinary is also a question of multilingualism, in the sense that if you look into problems between disciplines you see how they do not relate and how scientists stay in their own corner. That is usually a question of language. For example, the word transformation means very different things in genetics and in mathematics. A mathematician thinks of something completely different to a geneticist or a cancer specialist. By the way, mathematicians or physicists are equally afraid of biology as biologists are of mathematics. They think biology is not confounding, not ordered, it is full of associations.

A cooperation with the Institute of Systems Biology (ISB) in Seattle was set up. What is that about?

Balling: We have two major projects running with the ISB, one sequencing and one proteomics project.

What's the background of that sequencing effort?

Balling: We want to sequence entire families with specific diseases. In contrast to normal genome-wide association studies involving only patients that are not related to each other, we plan to study the genomes of families, in order to follow the inheritance and the segregation of certain alleles. The statistical power of the conclusions you can draw from this kind of study is much higher than population studies without looking at familiar segregation. Most of that work will be done in Seattle. Right now, we're looking at craniofacial diseases as a proof of principle but we are also discussing going into neurodegeneration.

What about the proteomics project?

Balling: We want to develop a proteome atlas of humans and mice. Our approach is to have a systematically-based look into the protein profile of different organs. We want to study the protein setup in parts of the heart, liver, etc. and then compare that to the proteome in plasma or serum from humans as well as from mice.

Aren't you afraid of a similar fate as GeneProt, the Swiss proteomics company that spectacularly announced the analysis of the human plasma proteome but who completely failed?

Balling: No, I'm not afraid at all. We're an academic setting, so for us things are different than in industry. Apart from that, the excitement about what proteomics can really do is not over. I am convinced that commercial applications will also come, although with a delay - not immediately.

In Lab Times *4/2009 we talked to proteomics specialist Thierry Rabilloud. He told us that "people in proteomics claimed a lot and delivered little". Are you going to deliver something?*

Balling: Certainly, proteomics is becoming really interesting when you combine it with genetic data. However, you have to validate the data and that is a big problem for biotech companies. They simply do not have the money, the time and the patients to test biomarkers in large-scale population cohort studies. But unless that is done, biomarkers are useless in terms of moving them into industry. I think the validation in a clinical setting is becoming a very important part and that's where we would like to find ourselves in using a comparative mouse-human system.

"Once they have made a commitment they stick to it."

So you're going to test biomarkers in mouse first?

Balling: It's going both ways. The mouse will be a "hypothesis-generator" as well as a "hypothesis-validator". In some cases, the ideas are derived from human genetics and genomics, in other cases, the ideas will come from the mouse but then have to be validated in clinical trials in humans.

Now you're advertising for scientists?

Balling: Right now I'm the only employee. So I'm really starting from scratch. Within 2-3 years I'd like to employ up to 80 or 100 people with very different skills and backgrounds. Of course we need biologists but also chemists, geneticists, mathematicians or people like physicists, who know how to bring biological systems into abstract mathematical descriptions and develop models. The building that is currently being constructed is in Esch-sur-Alzette. It is one of the first buildings on that new campus some 20 kilometres from Luxembourg city.

Do you expect to allure 100 specialists to that little country?

Balling: Yes. I'm optimistic. That's my job. Look, I moved and I like Luxembourg.

But you were born close by, in the Eifel. So for you, it's some sort of returning to your roots.

Balling: Right, and because I've often been in Luxembourg; I know the country and the people. But knowing them is not the reason for coming here. The reason is that I want to come and work in places that offer the chance to initiate and push forward interesting developments. Now Luxembourg has really made a commitment to science. And I have noticed that once they have made a commitment they stick to it. So I'm looking very optimistically into the future.

INTERVIEW: KARIN HOLLRICHER