Until a few years ago **almost no new antibiotics** were being developed. In the intervening years the alarming increase in bacterial resistance to most drugs has scientists **feverishly looking for new therapeutic approaches**. The "BattleX" team is following **a promising route**.

"Please don't touch anything", warns Dirk Bumann before we enter the lab facilities at the Basel Biozentrum. And with good reason. Because, should we inadvertently take a few of his research objects back home, it could quickly become very uncomfortable. "What we're working with here is Shigella, the causative agent of bacterial dysentery. It's one of the most common diarrheal diseases", says Bumann justifying his warning. He is professor of biology at the center.

Each year, more than 80 million people suffer from the consequences of a Shigella infection and hundreds of thousands do not survive.

Most infections occur either through direct physical contact with infected persons or through the ingestion of contaminated food or water. First symptoms appear between one and four days after the initial infection. Typically, patients are brought down with bloody diarrhea, which results in a great loss of water and they weaken very quickly. This life-threatening development is especially dangerous for children, the elderly and people who are immunocompromised.

In principle, severe cases can be treated with conventional antibiotics. However, like many other species of bacteria, a lot of Shigellae strains are resistant to the most common drugs. This dramatic development has induced many researchers around the world to apply themselves to finding solutions.

The search for new defense strategies against infections is of huge interest to systems biologists as well. After all, the raison d'être for this forward-looking research discipline is to fully understand and recreate the molecular processes within and between biological systems, which, ultimately, is the basic requirement to develop any new therapies.

Dirk Bumann is the pivotman of the RTD-Project «BattleX».

Selective starvation

This is the area in which the RTD project "BattleX" led by Dirk Bumann and his team are working on. "Shigellae are among those bacterial species that penetrate their hosts' cells. They then steal the nutrients from the cells that they require for their replication and virulence. We are now trying to figure out which metabolites are essential to the invaders. Once we have identified these, we can look for ways to disrupt the invasion process". Or, in other words, the agent is to be starved by being cut off from supplies.

It may sound simple but is, in fact, extremely complex. "We chose the relatively well-studied Shigella organism as a study object. What's more, many metabolic pathways in human cells are already known. The molecular interactions between the two different sized networks are so complex that they are hard to understand", is how Bumann attempts to describe the starting position. Without the combination of laboratory experiments and mathematical models, the researchers would never get anywhere. As it is, there is a kind of roundabout-like action between the two methods. On the one hand, results can be interpreted from the studies and classified thanks to the models. On the other, possible associations between individual metabolic steps can first be calculated in models and then the resulting predictions can be checked for accuracy in experiments.

"To achieve its goal BattleX needs experts from a range of disciplines who work closely together", says Bumann. The complexity of the problem is apparent if one superimposes the maps of metabolic interactions that have been studied so far.

Substance pandemonium

Dirk Bumann sheds light on what is seemingly a jungle of countless meta-

bolic processes, "A cell extracts dozens of components from various body fluids in order to maintain its own metabolism, including substances like sugars, vitamins and amino acids". Barely arrived in the cell, a variety of enzymes separates them into their individual parts. In this way, a cell not only gains energy but also all the vital components to produce, for example, proteins for themselves. The result is the production of hundreds of end products and intermediates. "This pandemonium of substances is a paradise for bacteria. You can find just about anything you could possibly need in host cells", enthuses Bumann about the parasitic lifestyle of the Shigellae.

Searching for the ultimate breakdown

The team is focussing on the reactions and interactions that occur while the "nutrient heist" is taking place. Bumann explains, "We must first understand which substances Shigellae remove from the host cells, to what extent and at what stage. Only then can we attempt to interfere with a specific metabolic interaction". As if this task was not already complex enough, there is a further difficulty: "It's not enough to block a single pathway, hoping that this will deactivate the bacteria. If an agent can no longer procure a certain substance, it simply turns to an alternative component". So the search is on for the ultimate source of interference: "The aim is to trigger disastrous consequences for the Shigella with the smallest possible intervention into the cellular metabolic network".

If successful, the team will have found an approach to developing new therapeutics. Faced with the global increase in antibiotic resistance, however, Bumann puts the hope of any speedy solution into perspective. "Even if we succeed in disconnecting the bacteria from the host's metabolism, we are still years away from a clinical application". Because the next step will need to prove the effectiveness of this control strategy in other bacterial species. If it does succeed, however, a collaboration with the development department of a pharmaceutical company would be a future possibility.

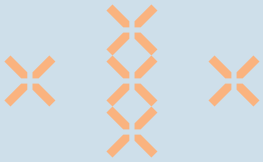
The BattleX-Team

BattleX includes a consortium of seven research groups, of which six are in Switzerland. The seventh member works alternately in Iceland and the USA.

- **Dirk Bumann** Biozentrum, Basel – Shigella Molecular Biology, Modeling, Coordination
- **Bernhard Palsson** University of Iceland, Centre for Systems Biology – Modeling
- **Vassily Hatzimanikatis** EPFL, Lausanne – Modeling
- **Amos Bairoch** CALIPHO, SIB, University of Geneva
- **Ralph Schlapbach** University of Zürich – Data management, Proteomik
- **Julia Vorholt** ETH, Zürich – Metabolomics
- **Cécile Arrieumerlou** Biozentrum, Basel – Shigella Infectional biology, RNAi

BattleX at a glance

Principal Investigator: Prof. Dirk Bumann (Biozentrum, Basel)
Number of research groups: 7
Researchers : Administrators 35:4
Biologists : Non-biologists 22:17 (Administration included)
Total budget (2010–2013): CHF 10.8 Mio, of which CHF 5 Mio von SystemsX.ch



BattleX
Manipulating the Fight between Human Host Cells and intracellular Pathogens

SystemsX.ch from an historical perspective

Alban Frei

At the Chair for the History of Technology at ETH Zurich a doctoral thesis is unfolding on systems biology research in Switzerland. The thesis examines the institutional organization of the richly endowed research initiative, SystemsX.ch, and the scientific and economic context in which it originated.

Among other things the thesis aims to determine how and to what extent research efforts in the field of systems biology change the long-term structures of the partner institutions. At the same time the thesis addresses the importance of paradigmatic change from the reductionist approach of molecular biology to systems biology that reflects the holistic. It also addresses the scientific culture of the new research direction. These four levels–institutional structure, socio-political constellation of epistemic change and cultural practices-furnish the framework of the project.

The knowledge-historical thesis thus offers an external view of the research achievements in the highly dynamic field of systems biology and analyzes these processes within a social and political context. The project is being funded for one year by ETH Zurich and SystemsX.ch initially. It should then be supported by the Swiss National Science Foundation for a further three years.

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