The **development of resistance** to infectious pathogens poses an increasing **threat to our health**. But researchers from **InfectX** are on the right track to new therapeutic approaches.

Matthias Scholer

"There probably isn't a single 'magic bullet' that can solve the problem", surmises Professor Christoph Dehio. The microbiologist describes the best possible outcome of his research in precise phrases. "To find a therapeutic approach, which can contend with all bacteria and viruses. And without the development of resistance and side effects for the patient." It is unlikely a panacea will be found to combat all pathogens, but innovations to fight infectious diseases are urgently needed. "Because of increasing resistance, incidence of bacterial and virally caused diseases is rising significantly", says Dehio.

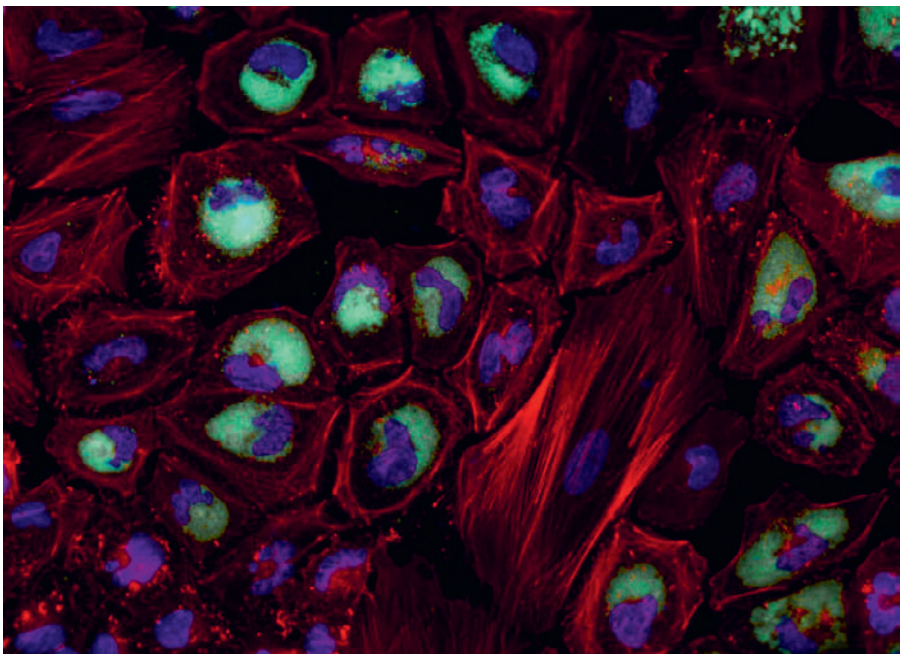
According to latest WHO estimates around 25 000 people die in Europe every year from infections that are caused by bacteria that can no longer be fought with the present range of approved antibiotics.

Fundamentally new strategies

Until now anti-infectives have worked by doing direct damage to the pathogen. To affect the host organism as little as possible, the targets of these drugs are only found in the pathogen. Penicillin, for example, targets only the unique cell walls of the bacteria, while other antibiotics block specific enzymes of the bacterial metabolism that do not occur in humans.

The disadvantage of this treatment approach is that, due to genetic mutations that change the corresponding structures, pathogens can emerge that are protected against the applied drug. Owing to the variety and variability of pathogens development of resistance to a new drug can follow close on the heels of its introduction.

"We need fundamentally new strategies to fight infectious diseases", stresses Dehio. This is why the main goal of the RTD "InfectX" project, which he has directed for the past three years, is to find innovative approaches. The team's focus is on so-called "intracellular pathogens". These comprise all viruses, but also bacteria, that are dependent on the structures and mechanisms of the infected host cells for their intracellular growth and can even tap into their host's metabolism for their food and energy supplies. "We are interested in what is happening at the molecular level between these pathogens and the infected host cells", explains Dehio.



Human cell after infection with the bacteria *Brucella abortus* (blue: nucleus, red: cytoskeleton, green: intracellular pathogens). *Photo: InfectX*

Restricting the host's capacity to assist infection

InfectX is investigating the infective development of five bacteria and four types of viruses. "The behavior of these nine pathogens is representative of the majority of intracellular pathogens. Basically, each of them makes use of a certain part of the host cell's basic machinery, regardless of the clinical picture it causes or the tissues it attacks", says the researcher. The team not only wants to investigate the infection of individual pathogenic agents, but also develop a broad-based model which will allow them to carry out computer simulations of the infection mechanisms of as many intracellular pathogens as possible. "This would then allow us to identify similarities between the pathogens and thus to define potential targets for therapeutics", is how Dehio summarizes the concept.

The spread of infection is limited by a restriction of the host's functions essential to permit infection. Therein lies the big difference compared to conventional drug treatment strategies. This disruptive intervention can happen, for example, at the start of infection, when the pathogen enters a cell, during the transport through the cell, or by means of multiplication with the help of the cell's own structures. The advantage of this approach is that the pathogen is unable to develop resistance.

Complex investigation

However, owing to the sheer variety of molecular interactions between invader and host cell, what sounds simple is, in practice, an extremely complex task. This is why InfectX's research teams are investing so much time in the development of appropriate methods and pro-

tocols. As parallel research is being carried out at multiple institutes, including the universities of Basel and Zurich as well as the ETH Zurich, the groups must also pay due regard to strict standardization. “Both the methodology used in the experiments as well as the computerized calculations had to be defined in detail. This is the only way to develop a comprehensive model applicable to all agents.”

Identifying essential factors

The research activities are in full swing. The scientists are currently looking into the entire human genome to identify essential factors for occurrences of infection.

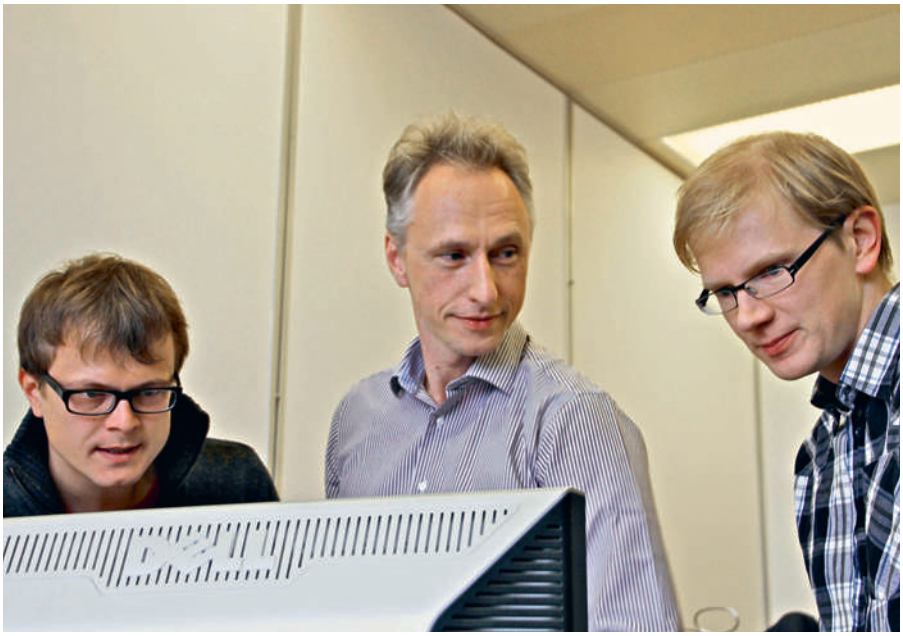
Here, special cell culture plates with arrays of small wells come into play. At the beginning of an experiment, all these wells are supplied with human cells. With the aid of the “RNA interference” method, one of the approximately 20 000 known human genes is inactivated in each of the individual wells. Subsequently, a bacteria or virus of a given species is added to all wells. “In each of these wells the infection process can run its course under standardized conditions. If the multiplication of intracellular pathogens in a particular well runs faster, slower or even comes to a complete standstill, we can draw conclusions about the role of the inactivated gene or its product in that particular well”, explains the microbiologist.

In order to quantify the spread of the pathogen, activities in each compartment are recorded pictorially. “We use infectious agents that, due to a genetic trick, produce a fluorescent protein. This allows us to track the route of infection and the multiplication rate of the pathogen”, explains Dehio.

Basic research, modeling and future visions

What the scientists capture is very important basic data, such as the condition of the cytoskeleton, the size of the nucleus, and about 250 other measurements. “So far, only about one third of the human genome has been allocated to a known function. Our data should help to close this gap”, says Dehio.

This combination of basic biomedical research, the modeling of complex relationships and the development of innovative therapies also neatly represents the field of systems biology research in an exemplary way. “The cooperation between different specialists and institutions is what makes it possible to cover such a wide area, as well as finding new ideas that interest industry.”



The team also includes computer science specialists, who, together with SyBIT, are developing specialized software for the analysis of millions of microscopic images (left to right, Mario Emmenlauer, Christoph Dehio and Pauli Rämö). *Photo: msc*

This means that we also have good reason to hope that in a few years time, our lives will no longer be threatened by resistant pathogens.

The InfectX-team

InfectX comprises a consortium of eleven research groups, ten of which work in Switzerland.

- **Prof. Christoph Dehio,** Biozentrum, University of Basel (coordination), bacterial infection (brucellosis and bartonellosis)
- **Prof. Cécile Arrieumerlou,** Biozentrum, University of Basel bacterial infections (shigellosis)
- **Prof. Niko Beerenwinkel,** ETH Zurich, Basel, modeling
- **Prof. Peter Bühlmann,** ETH Zurich, modeling
- **Prof. Pascale Cossart,** Pasteur Institute, Paris, bacterial infections (listeriosis)
- **Prof. Urs Greber,** University of Zurich, viral infections (adenovirus, rhinovirus)
- **Prof. Wolf-Dietrich Hardt,** ETH Zurich, bacterial infections (salmonellosis)
- **Prof. Ari Helenius,** ETH Zurich, viral infections (vaccinia)
- **Prof. Pelkmans,** University of Zurich, viral infections (rotavirus)
- **Prof. Christian von Mering,** University of Zurich, modeling
- **Prof. Bernd Wollscheid,** ETH Zurich, proteomics

InfectX
Systems Biology
of Pathogen
Entry into Human Cells

InfectX Overview

Project Director: Prof. Christoph Dehio (Biozentrum, University of Basel)
Number of research groups: 11
Researchers/Administration ratio: 56:2
Biologists/non-biologists ratio: 40:18 (incl. administration)
Total budget (2010–2013): CHF 10.3 million, of which CHF 5.1 million from SystemsX.ch