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Hot from the press!

Preventing Antibiotic Resistance by Switching off its Activity

Elsbeth Heinzlmann, science + technology journalist

Abstract: In order to develop new approaches for effectively combating antimicrobial resistance, universities of applied sciences, teaching hospitals and biotechnet industrial partners are working together in a National Research Consortium supported by the Commission for Technology and Innovation, CTI.

Keywords: Antibiotic resistance · *Mycobacterium tuberculosis* · Nosocomial infections · Staphylococcal infections

The warning bells have been ringing for quite some time: Infections caused by resistant microorganisms no longer respond to conventional treatment, prolonging illness and increasing the risk of death. According to WHO, the mortality rate for patients with serious infections treated in hospitals is about twice that in patients with infections caused by non-resistant bacteria.

Looking for the ‘Miracle’ Solution

When infection becomes resistant to traditional medication, there seems to be an urgent need for more expensive therapies. Due to the longer disease and treatment phase, healthcare costs are escalating, placing a burden on families and society. A real headache is caused by gram-negative bacteria such as *Escherichia coli* or *Klebsiella pneumoniae*, which are developing previously unknown resistance mechanisms for which effective medication is lacking.

At the Department of Biosystems Science and Engineering of the ETH in Basle, Dr. **Marc Gitzinger** and Dr. **Marcel Tigges** have been reflecting about how to realize a ‘Transcription Regulator

Inhibiting Compound’ (TRIC) that would be capable of switching off, instead of just combatting, the activity of resistance. Their vision was to lessen emergent new resistance and to reactivate antibiotics that have lost their effectiveness. Their idea was so successful that the two researchers founded their own company, BioVersys AG, in Basle. In fact, they achieved a breakthrough with one of their leading compounds: BV-TB 6481 was able to make multi-resistant *Mycobacterium tuberculosis* bacteria, which causes tuberculosis, sensitive again to the prodrug ethionamide, an antibiotic discovered back in 1956. However, to enable the company to develop its tuberculosis drug, BioVersys depends on public funding and partnerships: Although one third of the world’s population, predominantly in the Third World, is chronically infected with TB, the relevant medicine has orphan drug status and is of little interest for profit-oriented entities.

One Single Platform – Various Applications

Based on the lessons learned from the TB experience, the BioVersys founders wanted to attack nosocomial, *i.e.* hospital-acquired infections. As the *US Centers for Disease Control and Prevention* have confirmed for 2013, every twentieth person is the victim of this type of infection, which can prove fatal and which costs the US healthcare system up to 10 billion dollars a year. With the support of the Commission of Technology and Innovation CTI, a National Research Consortium was launched with aim of developing a medicine for successfully holding antibiotic resistance in check.



Organic synthesis and medicinal chemistry lab of the group headed by Prof. Rainer Riedl, ZHAW. Photo: ZHAW

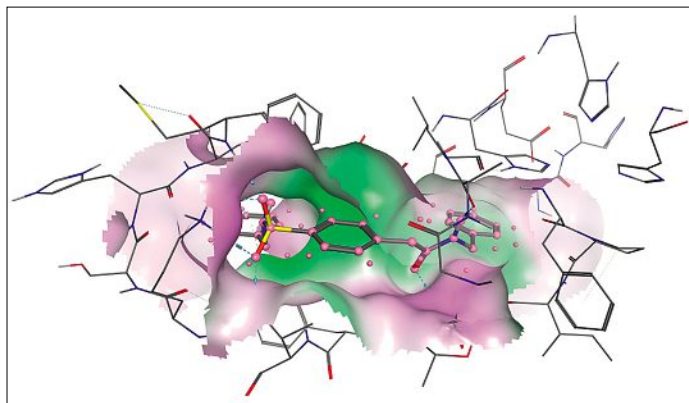


In the BioVersys labs. From left to right: Laboratory assistant Birgit Schellhorn, CEO Marc Gitzinger, CSO Marcel Tigges and Michel Pieren, Head of the described project. Photo: BioVersys

Part of the project involves the Life Sciences group headed by Prof. **Daniel Gyax**, FHNW Muttensz, and specialized in bioanalysis. The researchers want to determine the *in vitro* binding of the molecules – synthesized by their colleagues in Wädenswil – to the target protein with a biosensor system, label-free and in real-time. “This will enable us to quantify the binding performance of potentially new active substances and facilitate a rational selection of chemical compounds”, comments Daniel Gyax. “We also want to generate a high-resolution 3D structure

of the target protein. This will serve as a basis for medicinal chemists to synthesize improved drug candidates.”

The team directed by Prof. **Rainer Riedl** at the ZHAW in Wädenswil offers expertise in synthetic organic and medicinal chemistry. “We apply rational drug design approaches to generate new chemical structures with tailored biological activity”, explains Rainer Riedl. “Following *in silico* molecular modelling experiments, we synthesize the most promising structures and optimize their medicinal chemistry profiles by multi-step organic synthesis in order to develop a clinical drug candidate together with our research partners from biology and medicine.”



Rational drug design in the group headed by Prof. Rainer Riedl, ZHAW.
Photo: ZHAW

Only Together Can we be Strong

Prof. **Vincent Perreten** at the Institute of Veterinary Bacteriology in Bern, and Prof. **Jacques Schrenzel** at the Bacteriological Laboratory of the Hôpitaux Universitaires de Genève are working on the gene expression analysis in clinical

pathogens. The DNA microchip developed at the Bern Institute makes it possible to detect most of the known genes for antibiotic resistance, independently of their expression in gram-positive bacteria, within one working day. “The further development in the CTI project gives us the chance to also analyze – using the same microchip – the RNA of the resistance genes, leading to additional information regarding the expression”, says Vincent Perreten. “This, in turn, enables us to investigate the effect of a newly developed active substance on the gene expression of a multitude of resistance genes in an extremely fast way.”

Last, but not least, PD Dr. **Nina Khanna**, who works in the Infectious Diseases & Hospital Hygiene unit of Basle University Hospital, is working on infection models and pharmacokinetics. “Our aim is to produce therapeutic options for staphylococcal infections”, she declares. “The focus is on extraneous infections which are characterized by biofilms and are resistant to therapies.”

The researchers at BioVersys will test the activity of the compounds and help to co-ordinate the resources and the expertise of the various partners. The project leader, Dr. **Michel Pieren**, puts it in a nutshell: “It is our aim to create, within the next two or three years, a candidate for a clinical molecule tailored to a new class of therapeutic compounds – known as TRICS – that will be capable of switching off bacterial resistance to conventional antibiotics.”

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Information:

Prof. Dr. Rainer Riedl
Organic Chemistry and Medicinal Chemistry
ZHAW Wädenswil
Tel.: +41 58 934 5618
E-mail: rainer.riedl@zhaw.ch

Received: February 15, 2014