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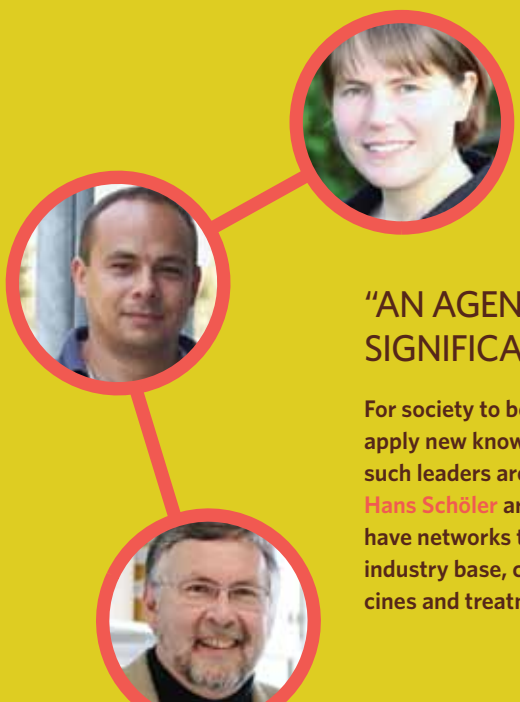

"AN AGENT THAT PROVOKES OR SPEEDS SIGNIFICANT CHANGE OR ACTION."

For society to benefit from science, we need leaders who can apply new knowledge to solving big problems. Here, three such leaders are profiled. Julia Bandow, Günter Schwarz and Hans Schöler are outstanding academic researchers; they also have networks that reach deeply into the region's life science industry base, contributing to the development of new medicines and treatments for disease. They are R&D catalysts.

Tackling the Antibiotic Crisis

An academia-biotech consortium led by Ruhr-Universität Bochum's Julia Bandow is racing to find new compounds to combat drug-resistant bacteria. By Richard Gallagher

Julia Bandow is a proponent of collaborative research. "If you want to bring an antibiotic from an idea to the clinic you need so many different skills," she explains. "I specialize in microbiology and proteomics, which is a small part. You have to collaborate with partners that have the complementary skills that are needed."

So, not long after her 2008 move from Pfizer's proteome research center in Ann Arbor, Michigan to start her own group as a Junior Professor in Bochum, Bandow began to stitch together academic and biotechnology teams. "I contacted the different partners that might be interested in working with me. Within two months we had put together a proposal, the one that would fund our entire project." That project, called Innovative Antibiotics from NRW, or "InA aus NRW" for short, integrates groups from three universities and two biotechnology companies, all based in North-Rhine Westphalia. It is one of nine consortia funded under a 2009 scheme called "Bio.NRW" that is funded by the European Framework for Regional Development program (EFRE). "Our goal is to follow different ideas of where new antibiotics might come from, to generate a range of lead compounds, throw out everything that's toxic to human cells and elucidate the mechanisms of action so that we know how the compounds work," Bandow says.


Julia Bandow

The initiative to develop new antibiotics has come not a moment too soon. Drug-resistance is causing "huge problems," according to Bandow (See Table, page 19). "Gram-negative bacteria are already creating major problems in the clinic," she says. "For instance, in the last few years *Pseudomonas aeruginosa* strains have been reported which are not susceptible to any marketed antibiotic. Luckily for us these pandrug-resistant strains haven't spread very widely yet." But this is just the tip of the iceberg. "I don't think that it will take too long for other organisms to become so resistant that we cannot treat them any more," Bandow says. "We are close to this with other Gram-negatives and *Staphylococcus aureus*. You could get to a situation where hospitals can't do invasive medicine because the risk of infection is too high. It really is that serious."

Adding to the sense of foreboding, many of the major pharmaceutical companies have given up on antibiotic research and exited the field altogether. This has been partly due to an unfavorable market environment—treatments for other diseases tend to be much more lucrative—and partly to strategic failures. "When the first bacterial organisms were sequenced, when we knew the whole genome, people were very excited," explains Bandow. Research changed. Companies abandoned natural compound studies and focused on identifying genes necessary for bacterial survival and inhibitors of those genes. "Pretty much everyone followed this strategy and so far it has not yielded a single clinical candidate antibiotic," she says. The current pipeline of antibiotics that are in clinical trails includes very few compounds that are radically different from the current molecules, meaning that resistance to them will develop quickly.

SEARCHING FOR NEW ANTIBIOTICS

FINDING INNOVATIVE DRUGS

"InA aus NRW" is starting with a clean sheet of paper in the search for novel antibiotics. The first objective was to accumulate a large collection of compound libraries to screen. Bandow approached Squarix biotechnology, a small company based in Marl, about 25 kilometers from Bochum. Squarix were not active in antibiotic research, says Bandow, "but I thought that they might be interested. And they were. They had several libraries of compounds that could be tested for antibacterial activity and were eager to expand those, opening a new field where they can develop compounds for a different purpose than they had before."

"(I have the) opportunity to work on molecular issues and to look very deeply into the physiology of bacteria, but also having the outlook that it might help mankind."

The consortium is looking for antibiotic leads from multiple sources—natural compounds, synthetic compounds and peptides. In the latter case, "We want short antibacterial peptides of no longer than six amino acids, to act as a scaffold to produce peptidomimetics," Bandow explains. Synthesis of the peptides is outsourced as fee-for-service work, with the resultant compounds being screened in Bandow's lab. Nils Metzler-Nolte's bioinorganic chemistry group, also at Bochum University, then modifies promising candidate peptides by introducing metals into their scaffolds to modify antibacterial and pharmacological properties.

The project was up and running by October of 2010. A bioinformatics component, which predicts antibacterial peptides, has been completed and peptide synthesis has begun. Screening of the Squarix libraries for antibacterial activity is ongoing and already several active compounds have been identified, ready to enter the toxicity screening. The ultimate targets for new antibiotics are bacteria that are among the most critical in the clinic—*Staphylococcus aureus, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Screening is done against those organisms but non-pathogenic *Escherichia coli* bacteria and *Bacillus subtilis* are used for studies of the mechanism of action.

After screening for toxicity in mammalian cells, the elucidation of the mechanism of action of lead compounds is shared among three labs. There aren't countless ways to stop bacteria. The main mechanisms are to inhibit protein biosynthesis, DNA synthesis, RNA synthesis, folic acid synthesis, cell wall synthesis or bacterial membrane synthesis. A new idea involves inhibition of fatty acid biosynthesis and cell division. "All of us have different specialties," Bandow says. "My group works on proteomics. Hans-Georg Sahl in Bonn University specializes in cell wall biosynthesis and cell membranes. And Heike Brötz-Oesterhelt, from the University of Düsseldorf, has developed a lot of in vitro and cell-based assays to investigate the mechanism of action of antibiotics."

Bandow enjoys the fact that the project combines the generation of new insights into the biology of bacteria with the possibility of developing new therapies. "It gives me the opportunity to work on molecular issues and to look very deeply into the physiology of bacteria, but also having the outlook that it might help mankind," she says. This dual interest originated during her PhD research with Professor Michael Hecker at the Ernst-Moritz-Arndt-University in Greifswald in which Bandow investigated the impact of antibiotics on the microbial proteome. The work was done in collaboration with Bayer in Wuppertal.

Her further experience of industry, gained with Pfizer in the United States, has influenced how Bandow approaches research. "I learned about making tough decisions in terminating projects that don't yield anything. In academia you tend to just work harder at something if it doesn't work, and sometimes you keep trying way too long. This might take up years and may never bear fruits. Being able to let go of a project that isn't working was a valuable thing to learn. It doesn't mean that if something doesn't work at the first try you drop it. It's just having in mind that you want to get to a final goal and that there's not just one route that you could take."

Bandow expresses her hopes for "InA aus NRW" succinctly: "What we'd really like are antibiotics that have one or more of three properties. One is that they hit a novel target in the bacterial cell. The second is that they work via a new mechanism—even if they hit an existing target. The third is that we have a structurally novel compound that doesn't have any pre-existing resistance."

REACHING THE CLINIC

For the most promising candidates, the second industry partner, AiCuris, awaits to take on pharmacological evaluation and, potentially, testing in animal models of disease. AiCuris whose name is derived from 'anti-infective cures', is a Wuppertal-based pharmaceutical company focused on the discovery, research and development of novel antiviral and antibacterial agents. Its involvement means that the consortium can take a compound from the idea all the way through pre-clinical phases.

With funding for just over three years from the Ministry of Innovation, Science and Research of North Rhine-Westphalia, that's as far as the current project will take things. For the next step—human trials, which requires much larger investments—the consortium member that owns the intellectual property on the compound is free to move ahead as they see fit. "We don't have an exclusive deal," says Bandow, "there are several possibilities for moving ahead." A lot will depend on how attractive the antibiotics market is to the pharma industry. If the landscape has changed sufficiently that companies want to develop antibiotics, "Then, of course, we would like to work with them. We hope that's the case," Bandow says. What if that isn't possible? "In that event," Bandow says, "We could apply for public funding for those trials."

Time is short. In a recent resolution, the EU Commission stated that in the next 5-10 years clinical needs will not be met by existing antibiotics and compounds currently in development. "It's really bad news for people undergoing chemotherapy, or who are immune suppressed for whatever reason, such as transplant patients," Bandow explains. "Already, there are some strains of *Pseudomonas* that, if you are infected with them, the doctor can only hope that the immune system will take care of it, there's nothing he or she can do. That's really scary."

It's also energizing to Bandow. "As program coordinator you have to provide a vision for the entire project; you have to coordinate multiple partners and multiple work streams at different levels." While this might seem stressful to some, Bandow is positive. "Most of the stress comes from within from the feeling that I want to achieve something in a certain timeframe," she says. "It's more a healthy stress. We're in the green zone!"

WHY DO WE NEED NEW ANTIBIOTICS? ANTIBIOTIC RESISTANCE DEVELOPMENT

Antibiotic	Clinical Approval	Resistance in Clinic
Penicillin	1943	1940
Streptomycin	1947	1947
Tetracycline	1952	1956
Methicillin	1960	1961
Nalidixic acid	1964	1966
Gentamicin	1967	1969
Vancomycin	1972	1987
Cefotaxime	1981	1981
Linezolid	2000	1999