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NEW WAYS OF THINKING

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Research Spotlight

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Drug discovery through a chemist's eyes

Professor Dr Rainer Riedl discusses his international and interdisciplinary research into the design of synthetic molecules to improve the development of drugs for a range of conditions

Why did you choose to pursue chemistry?

I have always been keen on synthesising molecules with biological function. This is visible throughout my whole scientific life starting as a student in organic chemistry, advancing as a postdoctoral scientist in biomedical research and as a medicinal chemist during my industrial career. As a medicinal chemist, I can do exactly what thrills me most: making molecules by organic synthesis for the treatment of diseases. Besides the synthetic part of medicinal chemistry, I enjoy the design aspect of drug discovery, as the three-dimensional structure of the biological target guides our creativity to design complementary small organic molecules. The principles of medicinal chemistry can be applied to a multitude of therapeutic targets and indications.

Who comprises your research group? What expertise do the members afford your research?

I am leading an international team of 20 enthusiastic scientists in different stages of their careers and with different expertise. I enjoy working with my group as we have a splendid mix of young and more experienced members, which creates a stimulating working environment. Our focus is obviously on medicinal chemistry, but as this is an interdisciplinary science, we cover organic synthesis, computer-aided drug design and cheminformatics as well as natural products and analytics. This mix of overlapping and complementary know-how allows us to tackle a variety of difficult problems in medicinal chemistry and related disciplines.

What impact is organic chemistry having on drug discovery? How does this discipline benefit from the input of other scientific domains?

Drug discovery means that you are designing, synthesising, testing and optimising organic molecules in order to find the optimal molecule for achieving a biological effect. Organic chemistry therefore plays a vital role in drug discovery because organic chemists have structural understanding and are capable of modifying a given chemical structure by organic synthesis.

However, you also need biological *in vitro* assays, *in vivo* efficacy studies and clinical trials in order to learn what chemical functionalities are needed and tolerated to improve the therapeutic effect of an organic molecule. It is this input from the biological sciences which makes drug discovery so attractive for organic chemists, as we have to respond to the biological effect of our molecules and make them better by modifying their chemical structure.

How do you foster enrolment in academic drug discovery programmes? What can students gain from your supervision at the Center for Organic and Medicinal Chemistry at the Zurich University of Applied Sciences (ZHAW)?

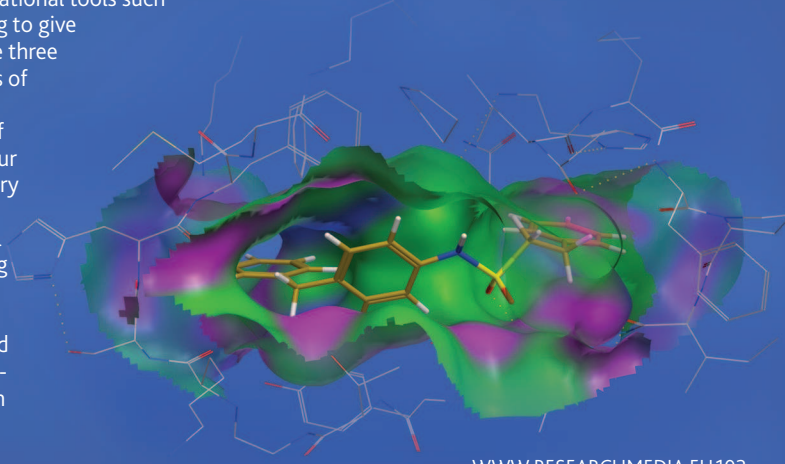
When I am teaching organic chemistry, I always try to show the students that this discipline is essential for creating new molecules with novel functions. In addition, I use computational tools such as molecular modelling to give students an idea of the three dimensional aesthetics of organic molecules. I have a large number of students enrolling in our academic drug discovery projects every year. Based on my industrial career I know how drug discovery works and how it will not. I pass this knowledge forward to my students and co-workers. Some of them picked it up very easily and have already made big leaps forward to becoming well-trained 'drug hunters'.

To date, what have been your greatest achievements?

I received several awards during my career including the Kurt-Alder award from the University of Cologne and a Feodor-Lynen fellowship from the Alexander von Humboldt foundation. An important scientific milestone was my first publication as PhD student. We published a paper in *Angewandte Chemie* about a fluorescence reporter which I had designed and synthesised that showed the intended biological effect. I was surprised how many people from all over the world asked us to send them our fluorescence reporter for their studies. During my industrial career I was delighted to see one of my molecules selected for clinical studies. This is the ultimate goal for a medicinal chemist and I am looking forward to seeing how this molecule performs in clinical studies.

What insights have you gained from your experience working with industry partners?

I have experience of drug development projects from my career in BigPharma, and from projects within academic research consortia with small biotech companies where there was a much smaller number of people and budget involved. I am pleased to see how much can be achieved if the right partners come together in such a consortium. I think these consortia should be run with the minimal critical size to have all required competencies on board. This keeps the team flexible and assures fast responses, which is a key component in reducing the costs of drug discovery.



Organic chemistry: the heart and soul of drug discovery

The Center for Organic and Medicinal Chemistry at the Zurich University of Applied Sciences in Switzerland is collaborating with partners across industry and academia to create novel treatment options for patients

TO TREAT NEW diseases or make existing treatments more effective, there is a constant need for new molecules with specific biological properties. This enables better therapies and reduces ever-increasing healthcare costs. The Center for Organic and Medicinal Chemistry at the Zurich University of Applied Sciences (ZHAW) in Switzerland carries out cutting-edge research into the organic synthesis and medicinal chemistry of novel bioactive molecules at the interface between chemistry and biology. The Center aims to bridge the gaps between these disciplines to enable the development of new and improved treatments for a range of conditions.

At the heart of the Center's research activities are investigations into medicinal chemistry, organic synthesis, natural products, molecular modelling and cheminformatics. An important element of its work is cooperation with both industry and academia, to foster a collaborative, interdisciplinary approach to the development of new clinical candidates.

COVERING THE COMPLETE CHEMISTRY-DRIVEN VALUE CHAIN IN DRUG DISCOVERY

The Center's medicinal chemistry activities span from hit identification, through hit to lead development and lead optimisation to delivering active pharmaceutical ingredients for *in vitro* and *in vivo* studies. Their work includes the structural analysis of the target proteins and their complexes, resulting in the delivery of novel and patentable drug molecules for clinical trials by using a combination of classical structure activity relationship (SAR) profiling and state-of-the-art computer-aided drug design as well as natural products derived and fragment based synthetic approaches.

Hit compounds, lead compounds and clinical candidates are defined stages during the drug development process. Generally speaking, a lead compound is further advanced in terms of potency, selectivity and absorption, distribution, metabolism and excretion (ADME) properties compared to a hit compound. For clinical candidates additional efforts are needed to achieve beneficial pharmacological profiles, *in vivo* efficacy and to provide a non-toxic compound for the patients. "During the hit to lead to candidate optimisation process the molecules are chemically fine-tuned in order to fulfil all the above mentioned requirements," explains Professor Rainer Riedl, Head of the Center for Organic and Medicinal Chemistry at the Zurich University of Applied Sciences (ZHAW). "Therefore it needs creative, skilled and experienced organic and medicinal chemists. Every target and indication has different requirements for a drug molecule which makes this process a novel scientific adventure every time."

FOCUS ON RATIONAL STRUCTURE-BASED DESIGN

A core competence of Riedl's research is the rational structure-based design and synthesis of novel bioactive molecules. This allows for the targeted discovery of new compounds with defined biological properties. Compared to conventional methods such as high-throughput screening, this process delivers much more efficiently potent compounds. Riedl's international group received several scientific awards for the discovery of protease inhibitors with excellent activity against targets involved in rheumatoid arthritis and cancer as well as for novel molecules for the treatment of antibiotic resistance by using structure-based design techniques. Those novel molecules have great potential to be developed into clinical drug candidates. This would be of great benefit to the patients, both as a medicine in therapy and as tool compounds to generate knowledge of the mode of action of the underlying pathogenic processes.

TARGETED DEVELOPMENT

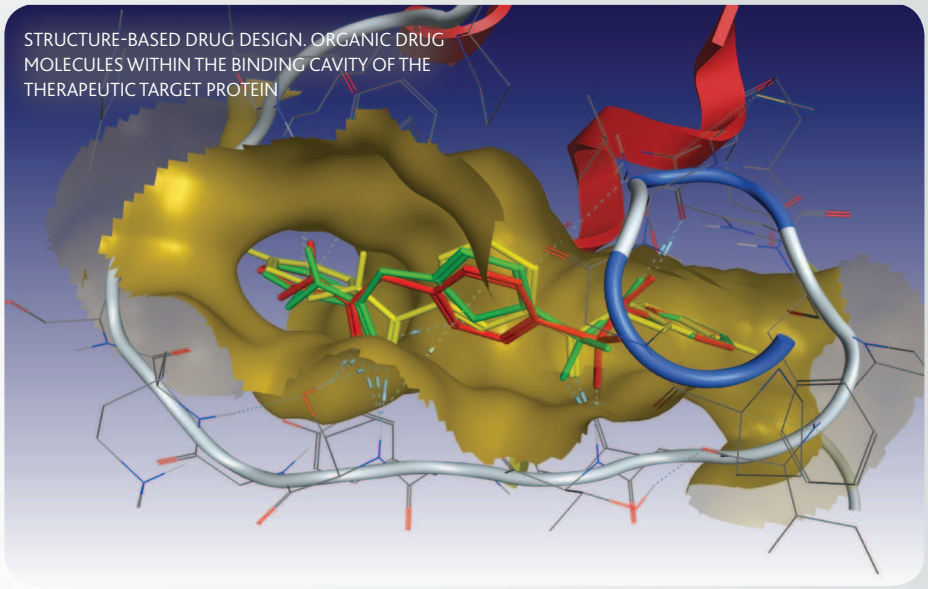
The structure activity relationship (SAR) guides the medicinal chemist during the process of optimising the organic drug molecule. The more modifications the chemist has performed on a given chemical structure, the more precise the understanding of the interaction between the organic molecule and the biological target. The researchers employ several techniques in order to establish a detailed understanding of these central interactions. "The analysis of X-ray crystallographic data, for example, gives us an idea of the shape and properties of the biological target molecule," Riedl states. "This can be seen as a blueprint for the design of organic molecules to bind to the target." NMR studies give an additional set of binding data of organic molecules which bind to their target protein in solution. Using this structural information allows the researchers in combination with computer-aided drug design techniques to accelerate the discovery of novel drug molecules.

With respect to the synthetic challenges of drug discovery, the Riedl lab aims at efficient multi-step organic syntheses of novel scaffolds and focused libraries of organic drug molecules for validated therapeutic targets. Employing modern and powerful synthetic techniques such as microwave assisted, catalytic, automated and parallel syntheses as well as sophisticated chromatographic purification techniques ensures a constant flow of organic molecules from the chemist's lab to their collaborators for driving the projects forward quickly.

TACKLING ANTIBIOTIC RESISTANCE

The growing problem of antimicrobial resistance means that drugs are losing their power. More and more infections caused by resistant micro-organisms fail to respond to conventional treatment. Most malaria-endemic countries record a growing resistance to earlier generation antimalarial medicines. In the hospital environment, increasing numbers of patients are infected by highly-resistant bacteria such a methicillin-resistant *Staphylococcus aureus*.

Researchers at the Center are collaborating with the biopharmaceutical company BioVersys AG in order to tackle antibiotic resistance. They have identified the need for certain types of small organic molecules, called Transcription Repressor Inhibitory Compounds (TRICs), which are designed and synthesised by Riedl's lab and tested at BioVersys. "In contrast to a wide range of traditional antibiotics for which bacteria have developed resistance, the TRICs do not interfere with the bacterial metabolism but work on the bacteria's genetic level," Riedl enthuses. "These TRICs switch off the bacterial defence programme and the original antibiotic can kill the bacteria again." This has two beneficial effects: they disable the possibility for further development of antibiotic resistances and they reopen the door for conventional antibiotics. The formulation of



STRUCTURE-BASED DRUG DESIGN. ORGANIC DRUG MOLECULES WITHIN THE BINDING CAVITY OF THE THERAPEUTIC TARGET PROTEIN

those small organic TRICs could be a combination with conventional antibiotics in one pill.

FRUITFUL COLLABORATIONS

An important part of the Center's work is its research and development collaborations both with industry and other scientific disciplines. These collaborations stand to benefit both sides, as each has access to resources and expertise which they would not otherwise have. "For example, a spin-off company from a university usually has very strong expertise on a certain technique but for drug discovery it needs more than that. The collaboration between BioVersys with robust and innovative biological skills and my group covering the medicinal chemistry part is in my eyes a show-case for a very successful drug discovery and development programme between academia and industry," Riedl affirms.

In addition, they are networking as organic chemists with other academic groups to provide their proficiency in synthetic, analytical and computational chemistry to foster their research activities. This is especially fruitful in collaborations with groups with a strong biological background such as cell biology or microbiology. The process of drug discovery and development is very complex and requires the interplay between specialised scientists such as chemists, biologists, pharmacologists and physicians in order to be successful. Riedl's group also benefits from feedback from biology and pharmacology on their organic molecules' performance as drug molecules, in order to bring them up to the status of a clinical candidate: "These complementary arrangements of expertise serve as the basis for scientifically exciting projects and represent a win-win situation for all partners".

EDUCATION, RESEARCH AND DEVELOPMENT

Besides the education of students in organic and medicinal chemistry, the aim of the Center is to conduct research into both drugs for specific ailments and into the improved transition from bench to clinic. They are approaching this either directly through clinical candidate development projects such as the one with BioVersys, within significant research consortia, or by internal research projects. For example, the final compounds of the clinical candidate project with BioVersys will be specifically used for treating infections caused by multiple drug resistant pathogenic bacteria, whereas the activities on the rational design and synthesis of novel protease inhibitors represent the Center's independent research with the goal of discovering novel small molecule inhibitors in order to modulate a whole family of target proteins.

INTELLIGENCE

HIT TO LEAD TO CANDIDATE DEVELOPMENT OF A TRANSCRIPTION REPRESSOR INHIBITORY COMPOUND (TRIC)

OBJECTIVES

A new and highly innovative treatment will be realised by a novel and patentable orally available small molecule combinatorial drug candidate for the treatment of antibiotic resistance in multi-resistant, pathogenic bacterial strains. The consortium integrates medicinal chemistry with biological assays and screening for the development of a clinical candidate.

FUNDING AND KEY COLLABORATORS

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Professor Dr Martin Fussenegger, ETHZ, Basel, Switzerland

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RAINER RIEDL leads the Center for Organic and Medicinal Chemistry at ZHAW. For more than a decade he has successfully run academic and industrial drug discovery projects. His research is focused on the rational design and synthesis of novel bioactive molecules for the treatment of unmet medical needs.

Zurich University of Applied Sciences

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