targets with human diseases presents tremendous challenges for drug research. Nonetheless, advances in technology have enabled Pharma to explore multiple medicinal chemistry approaches in support of chemical biology efforts and to identify leads and optimize to drug candidates. These advances include improvements in structure-based design, integrating techniques of x-ray crystallography, computational chemistry and nuclear magnetic resonance spectroscopy, multivariate analysis, parallel synthesis and early pharmaceutical profiling. Additionally, application of these techniques, coupled with the growing field of biosynthetic engineering, precise synthetic methods and the use of high-resolution analytical tools has spurred renewed interest in natural product-based drug research.

The lecture will give a brief overview of the evolution of drug discovery and the various medicinal chemistry approaches from the past and present and with an outlook to the future.

AWARD LECTURES

AL01 - Nauta Award for Pharmacochemistry

CHANGING PARADIGMS IN DRUG DISCOVERY

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The strategies of drug design changed significantly over the past few decades. Whereas chemistry, biological activity hypotheses, and animal experiments dominated drug research, especially in its "golden age" from the 1960's to the 1980's of the last century, many new technologies developed over the past 20 years. A vast amount of new drugs was expected to result from combinatorial chemistry and high-throughput screening; however, the yield of new drugs was relatively poor. Molecular modelling, virtual screening and 3D structure-based design support the selection and rational design of high-affinity protein ligands. But high affinity to a disease-relevant target is only one condition; others are oral bioavailability, favourable pharmacokinetics, and a lack of unacceptable side effects and major toxicity; all these properties are most difficult to predict.

Despite the new technologies we observe a productivity gap in pharmaceutical industry: there is a sharp contrast between the increasing costs of drug research and development and the steady decline in the number of new chemical entities for human therapy. The presentation will shortly discuss the following questions:

- what are the reasons for the productivity gap between R&D costs and the number of new drugs (NCE's)?
- is there a "druggable genome"?
- is target focus always the best strategy?
- are we using the right virtual screening tools?
- is poor ADME the major hurdle in clinical development?
- what are the reasons for poor performance of ADME and toxicity predictions?
- what are the main problems in clinical studies?
- offers pharmacogenomics a hope for the future?

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AL02 - UCB-Ehrlich Award for Excellence in Medicinal Chemistry

AUTOMATED OLIGOSACCHARIDE SYNTHESIS AS PLATFORM FOR VACCINE DEVELOPMENT

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Cell surface oligosaccharides and glycosaminoglycans are important for signal transduction processes but also are markers for infectious agents and disease.[1] Described is the development of a fully integrated platform[2] based on automated oligosacharide sythesis[3] and carbohydrate arrays to address biological problems. Particular emphasis in this lecture will be placed on the new automated synthesis platform that will be made available to laboratories around the world. Microreaction systems constructed from etched silicon complement this automated synthesis system and are used for rapid reaction optimization as well as scale up for production.[4]

Based on the automated synthesis platform, carbohydrate arrays an be accessed for use in screening of proteins and blood sera.[5] These diagnostic tools are now beeing applied to correlate glycan expression and disease.

A general approach to semi-synthetic carbohydrate vaccines that are currently at different stages of development will be discussed. vaccine candidates against malaria,[6] Leishmaniasis,[7] and anthrax[8] as well as several other bacteria are currently being developed. The malaria vaccine candidate is now in preclinical development and we are investigating the molecular mechanism of the infection in detail. The process that enables merozoites to enter red blood cells is not completely understood and the search for a receptor on host cells continues. We show that glycosyl phosphatidyl inositol (GPI) glycans, present on the apical surface of merozoites, interact with a protein on the surface of the host cell. The protein-GPI interaction is essential for merozoite entry into erythrocytes and mediates the inflammatory response via human macrophages.

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AL03 - GlaxoSmithKline Award for Outstanding Achievement in the Field of Chemical Biology

EXPLORING CHEMICAL SPACE WITH APTAMERS

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Small molecule inhibitors of proteins are invaluable tools in Chemical Biology. Their identification can be tedious, because most screening methods have to be tailored to the corresponding drug target. We have developed modular assays based on aptamer displacement or protein-dependent reporter ribozymes for the screening of small-molecule inhibitors. As aptamers can be generated for virtually any protein, the assay potentially identifies inhibitors for targets or individual protein domains for which no functional screen is available. Thereby, chemical space is explored in a rapid, focused, and modular manner, by indirectly taking advantage of the highest molecular diversity currently amenable to screening, namely that of 10^{16} different nucleic acid sequences. I will discuss the application of these approaches to find new inhibitors for target proteins. Examples showing that these modulators can be used as tools for gaining novel biological insight are provided.

AL04 - The Prous Institute-Overton and Meyer Award for New Technologies in Drug Discovery

NEW TOOLS FOR MOLECULE MAKERS: EMERGING TECHNOLOGIES

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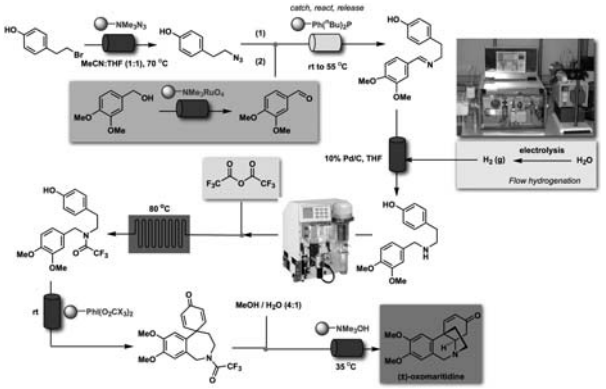
The search for new ways to assemble molecules continues to be an important driver for organic synthesis. The biological activity and exquisite structural diversity of many natural products stimulates invention by challenging today's synthetic methodology. However, preparing such materials from small and commercially available building blocks inevitably involves more than one synthetic step. For most modern drugs and other complex molecules, it is not uncommon for syntheses to require at least 10 steps, and sometimes many more.

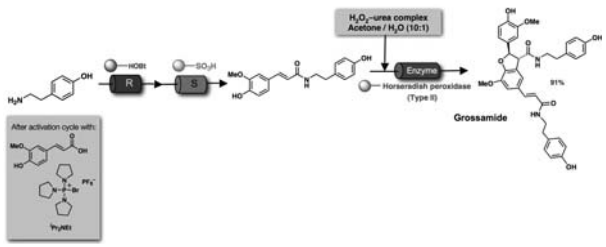
In order to make molecules more efficiently and economically, our group has developed and used solid-supported reagents in a multi-step fashion without the use of conventional work-up procedures. Now we have extended these concepts to make use of advanced scavenging agents and catch-and-release techniques, and combined these with the use of continuous flow processing to create even greater opportunities for organic synthesis.

As important examples of these developments, we have recently completed the syntheses of the natural products *grossamide* and *oxomaritidine* entirely by using these flow chemistry methods. The syntheses required the construction of a fully automated continuous flow reactor system (using a simple pumping arrangement) with immobilized reagents packed in columns to effect the synthesis steps efficiently. These examples illustrate the rapid and flexible nature of the methods for preparing compounds on demand and at various scales. The future vision of this emerging field could well cause a paradigm shift in the way chemical synthesis is conducted.

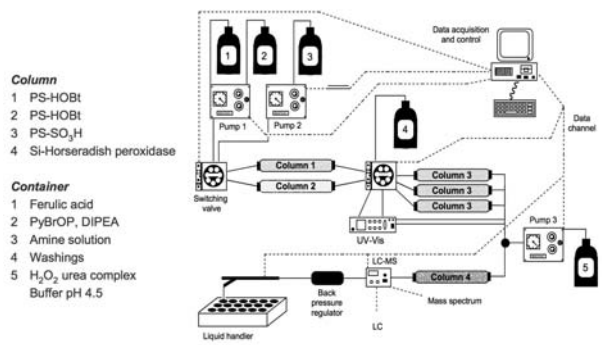
Flow Technology: The Synthesis of Oxomaritidine



Flow Technology: The Synthesis of Grossamide



Schematic diagram of the synthesis and equipment used for the preparation of Grossamide



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L01

INTEGRATION OF FRAGMENT DERIVED STRUCTURE-BASED DESIGN INTO THE DISCOVERY AND DEVELOPMENT OF SELECTIVE KINASE INHIBITORS FOR TREATMENT OF HUMAN CANCERS

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Rapid discovery and development of potent and selective targeted therapeutic agents depends critically on identification of viable starting points for lead optimization. There is a pressing need for more efficient approaches that complement conventional HTS strategies. The SGX platform utilizes high-throughput X-ray crystallography to guide fragment-based lead identification as a powerful drug discovery tool. This approach uses X-ray crystallography and complementary biophysical techniques to identify low molecular weight fragments