





- Automated Synthesis of Carbohydrates
- Synthetic Tools for Glycobiology
- Synthetic Carbohydrate Vaccines
- Biochemistry of Infectious Diseases
- Glycoimmunology
- Continuous Flow Microreactors as Tools for Organic Chemists

# BIOMOLECULAR SYSTEMS



## Research in the Department of Biomolecular Systems



The Department of Biomolecular Systems, founded in 2009, conducts research at the **interface of chemistry, engineering, biology, immunology and medicine**. The core focus is the development of **synthetic methods** for the chemical synthesis of defined oligosaccharides. The compounds are the basis for **chemical tools** that aided **biochemical investigations** into the fundamental roles complex

carbohydrates play in biological processes that underlie disease. The findings helped create diagnostic carbohydrate arrays to begin to understand **immunological aspects** of malaria epidemiology. **Vaccine development** of several infectious disease carbohydrate vaccine candidates is becoming increasingly more important for the laboratory. We are actively pursuing different aspects of glycobiology including the structure, function and biological role of sugars found on the surface of mammalian and bacterial cells particularly in the areas of immunology, biochemistry and human disease. Other areas of interest include ways to automate chemical synthesis and novel means to conduct chemical reactions using continuous-flow microreactors. Vaccine programs against infectious diseases including malaria, leishmaniasis, as well as a host of bacterial infections are currently progressing from synthesis to the preclinical stage.

Three major classes of polymers are responsible for the storage of information and signal transduction processes in biological systems. Nucleic acids make up the genetic material that transfers information from generation to generation. Proteins constitute the catalytic machinery carrying out most of the reactions in the cell. Carbohydrates, the third class of biopolymers, are branched, most complex and diverse. Access to pure carbohydrates was exceptionally difficult and therefore, all aspects of glycomics are less well understood than genomics and proteomics. A general, straightforward method for the procurement of oligosaccharides was needed to jump-start glycobiology the way molecular biology was impacted by the automated methods for DNA and peptide synthesis.

### Automated Synthesis of Carbohydrates

The Department of Biomolecular Systems developed prior to the arrival in Potsdam, by solving a host of chemical problems, the **first automated oligosaccharide synthesizer [1]** as a platform to pursue glycomics as the next frontier in biology and medicine. This instrument provides now **access to many complex carbohydrates in days rather than years [2]**. Prototype instruments have been built to achieve these syntheses in a fully automated manner. This platform is currently being expanded to all classes of carbohydrates including glycolipids, glycoproteins, and heparin. All aspects of automated synthesis are being improved as novel methods resulted in excellent efficiency, selectivity and versatility of the synthetic process. The Department is closing in on the ultimate goal of creating a commercially available instrument that uses a defined set of monosaccharide building blocks to

assemble most oligosaccharides reliably. Thus, non-specialists will be able to access defined sugars for biological or medical applications.

### Synthetic Tools for Glycobiology

Rapid access to usable quantities of defined oligosaccharides has enabled the creation of **synthetic tools** that have been commonplace in genomics and proteomics research. These tools include **carbohydrate microarrays**, carbohydrate affinity columns to isolate carbohydrate-binding proteins and labeled carbohydrates for *in vitro* and *in vivo* imaging. The tools permitted us to explore fundamental aspects of glycobiology. The Seeberger group pioneered the use of carbohydrate microarrays to:

- 1) define HIV oligosaccharide antigens for the development of potential AIDS vaccines;
- 2) determine the ligands for carbohydrate-binding proteins;
- 3) understand the specificity and resistance problems of aminoglycoside antibiotics;
- 4) screen blood for disease patterns; and
- 5) **detect pathogenic bacteria in blood** and other body fluids. Particularly the ability to detect bacteria very sensitively in biological samples holds applications in food safety and the detection of blood poisoning. These more applied avenues are currently being expanded.

### Synthetic Carbohydrate Vaccines

Based on the synthetic chemistry and tools platform, the Department has developed several applications. The presence of specific oligosaccharides on the surface of particular cell types including parasites, bacteria and cancer is the basis for the creation of synthetic carbohydrate vaccines against a host of diseases. An anti-toxin malaria vaccine candidate we identified **[8]** is currently in late preclinical development at a spin-off company and is expected to enter clinical trials in 2011. Carbohydrate arrays have provided the basis to demonstrate in epidemiological studies malaria resistance in endemic areas in Africa. It has been clearly shown that anti-toxin antibodies protect people in endemic areas after age two **[15]!** This finding strongly suggests that our vaccine candidate will provide protection for infants and naïve individuals much like that enjoyed by resistant individuals in endemic areas. Other vaccine candidates against infectious diseases are currently at differ-

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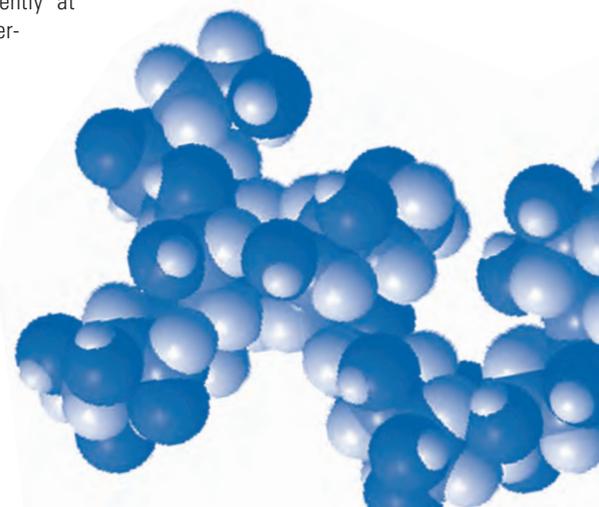
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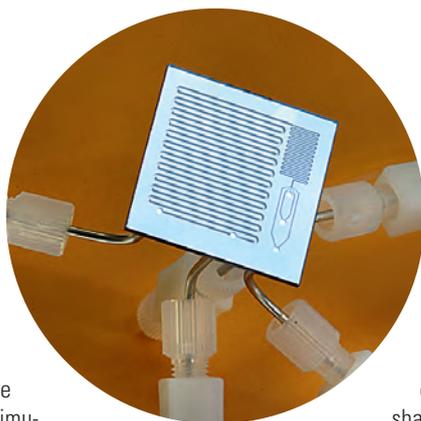
ent stages of development: *anthrax* (animal tests), *leishmaniasis* (animal tests), tuberculosis (synthesis completed), avian flu (synthesis completed), and a host of bacterial diseases that are at different stages of development. Synthetic glycolipids have been found to be powerful immunostimulants for use as vaccine adjuvants.

### Biochemistry of Infectious Diseases

The identification of the malaria toxin as a glycosylphosphatidyl inositol (GPI) anchor provided the basis for more detailed biological studies into the role of these complex molecules. In this context the department has been able to identify new signaling and entry mechanisms that are of crucial importance in malaria pathogenesis. These studies have provided the basis for different modes of intervention to fight this devastating protozoan parasitic disease.

Synthetically derived GPIs aid the quest to understand the role of **glycolipid signaling** in the inflammatory cascade, insulin independent signaling in diabetes and nerve growth. The past year has seen breakthroughs in the assembly of complete GPI-anchored prion proteins, an area that is now rapidly expanding. Biological investigations aiming at understanding **prion infectivity** *in vivo* are currently being initiated.

With the development of powerful synthetic tools in the department to generate carbohydrates the situation is increasingly changing leading to a better design of carbohydrate-based drugs and vaccines. A research group focuses on the development of peptide mimotopes of carbohydrates for vaccine development and to inhibit lectin-glycan interactions. Structural characterisation of peptide mimotopes of carbohydrates has provided important insights into the molecular mechanism of mimicry. Based on this information we will design phage-display libraries to improve the binding affinity of peptide mimotopes.



### Glycoimmunology

The immunology group investigates the role of C-type lectin receptors (CLRs) in infections and autoimmune diseases. CLRs are carbohydrate-binding proteins of the innate immune system that share a conserved calcium-dependent carbohydrate recognition domain and include many endocytic receptors, collectins and selectins.

CLRs belong to the innate immunity since they recognize conserved carbohydrate structures on pathogens and thus play a crucial role in the initiation of a protective immune response and for the maintenance of tolerance to autoantigens.

Animal models to analyze the function of CLRs during malaria infection and in autoimmune diseases such as colitis and encephalomyelitis have been established. The goal is to provide answers to the following questions: How is the expression pattern of CLRs altered during the course of infections and autoimmune diseases? Are CLRs involved in the induction of pathology during infection/inflammation? Do CLRs represent valuable drug targets to modulate ongoing immune responses *in vivo*?

### Continuous Flow Microreactors as Tools for Organic Chemists

Traditionally, organic chemists have performed chemical transformations in batch mode. Our department has pioneered the use of continuous flow microreactors for use by synthetic organic chemists. The department has utilized commercially available as well as internally developed microreactor systems to develop an automated reaction screening platform for organic chemists. Using these microreactor systems a host of chemical transformations has been rendered more efficient. In particular, dangerous, highly exothermic reactions as well as radical chemistry and photochemistry have benefited from the new way to run synthetic organic chemistry. Currently, these systems are being expanded to a host of applications in the area of total synthesis, methods development but most importantly, also to the preparation of organic and inorganic nanoparticles and colloids.

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