**Report on a**

# CERC3-Brainstorming Workshop

**on**

# Biological aspects of chemistry (Chemistry for Life)

Toulouse, 12th and 13th of April 2002

## Introduction

The key question that was addressed during the meeting was: Is the time ready to start CERC3 supported research projects in the area of the biological aspects of chemistry, which by the opinion of most participants is Chemistry for Life?

To investigate this key question CERC3 invited about 25 scientists from 8 countries. Several of the participants are active in their national research councils and panels. Missing countries were the United Kingdom, Italy and Spain. Each participant lectured for 30 minutes. The lecture contained a brief overview about the research topic in general, covered own results in the research field and discussed potential future developments. Each lecture was followed by a short discussion, which addressed in particular the challenges for the next decade in the particular areas.

Almost all contributions stressed the fact that two main ultimate goals exist for chemical research at the border to biology. 1. The development of new medical treatments, which at the end requires in most cases the discovery and synthesis of a molecule that can cure a particular disease. 2) The usage and optimization of new enzymatic methods for the production of chemicals in order to make chemistry more environmentally friendly.

## Results of the CERC3 Meeting

The research areas discussed during the CERC3 meeting that are thought to require active funding in order to reach the two outlined goals can be sorted into four main areas: 1) Proteins and proteomics. 2) Nucleic acids and genomics. 3) Carbohydrates and carbohydrate recognition. 4) Catalysis.
In all four areas is chemistry today a major component. This, however, is currently not sufficiently realized by the public due to the dominance of the discipline biology in all current scientific discussions.

Proteins and Proteomics:
In the proteomics area the development of new chemical analysis tools, like the so called molecular beacons, for the profiling of protein function *in vitro* and *in vivo* is an extremely important topic. These new chemical analysis techniques, together with

mass spectrometry may allow in the future to analyse the complete proteom of cells. Worldwide leading research groups and a number of small start-up companies, particularly in the US, are currently active in the field.
Protein research requires in addition the investigation of protein function. Here chemists will clearly focus on the analysis of small molecule protein interactions, which is also essential for drug development.
Overexpression of the newly discovered proteins and elucidation of their function, in particular with the help of protein crystallography, are the key steps that have to follow. This functional analysis has to be followed by the synthesis of molecules able to interact with the proteins. This in turn requires hand-in-hand research of computational chemists and synthetic medicinal chemistry. The computational chemist has to perform *in silico* screening of compounds databases to select promising compound candidates. The medicinal synthetic chemistry has to take on the challenge to synthesise even the most complex chemical structures and to analyse, in collaboration with biologists, the interaction of the chemical compound with the biological target. Multinational groups targeting protein identification, structure elucidation, *in silico* screening of compound libraries and chemical synthesis will clearly set up scientific knowledge platforms onto which pharmaceutical companies can establish strong drug discovery programs. Research consortia in this field will in addition educate students in a way that will increase the competitiveness of the European pharmaceutical industry.

Nucleic Acids and Genomics:
Genomics requires the parallel analysis of gene sequences, which is today the basis for modern drug development programs. Drug discovery is becoming more and more unthinkable without DNA-chips, which are constructed from chemically modified and immobilized oligonucleotides. Almost all DNA-chips and chip-reader, used in Europe have to be imported from the US, where the world leading companies Affymetrx and Nanogene are localized.
In the field of DNA research it became clear during the CERC3 meeting that the development of gene chips of the next generation, which may allow even more rapid and more reliable genome analysis, as well as genome analysis based on electrochemistry, requires strong synthetic programs in the field of oligonucleotide chemistry. Oligonucleotide chemists have to team up with surface chemist to develop new DNA chip technologies. Both could interact with molecular biologist to develop gene chips for the direct analysis of particular diseases.

The multiplexing approach requires chemical synthesis of highly modified oligonucleotides, which contain fluorescence donors and acceptors at various points in the oligonucleotide. Chemistry in this area, together with photochemists and molecular biologist could start to develop new oligonucleotide tools for the rapid analysis of gene sequences in order to pinpoint down even small genetic differences (SNPs). Novel oligonucleotide chemistry is in addition required for the synthesis of compounds that enable in the future efficient antigene and antisense therapies as well as gene delivery. Antigene, antisense and gene delivery, however, still face the problem of inefficient cell penetration. New smart molecules able to deliver DNA and DNA-analogs into cells have consequently to be developed.

DNA chemistry holds further promises for the field of nanotechnology. Groups around the world use currently DNA and DNA-like materials as connectors and organizers for chemical nanostructures. E. g.: Gold clusters and Proteins are oriented and organized in one, two, and three dimensions using oligonucleotide tags, which guide the self-assembly process. In this field, oligonucleotide chemists, protein scientist, surface chemists and supramolecular chemists could join in programs aimed to construct protein chips or folded and functional nanosystems.

Carbohydrates:

Carbohydrates are responsible for cell-cell recognition processes. They trigger the immune response for example against cancer cells and are hence of fundamental importance for the development of vaccination strategies against cancer. Since the biochemical synthesis of carbohydrates is up to now not possible, all new developments in the carbohydrate field will critically depend upon the development of new and efficient chemical synthesis methods. Again worldwide leading groups and start-up companies are mostly localized in the US.

Carbohydrate chemistry was not particularly covered by the CERC3 meeting. However, the field appeared in several talks and was also during the discussion recognized as an emerging research area that requires particular attention. It was stressed that the field is currently hampered by the lack of reliable and efficient synthetic methods that allow preparation of complex carbohydrates. If synthetic carbohydrate chemists and protein crystallographer would join to decipher in detail protein carbohydrate interactions, the field could start to develop into a new fascinating phase. New synthetic methods for carbohydrate preparation has most surely also to include enzymatic synthesis and bacterial engineering approaches. Teams made up of biochemists and carbohydrate chemists, concentrating at the development of synthetic and semi-synthetic methods for the preparation of carbohydrates could have a major impact on the hole field.

Catalysis and metals in biology:

Another major direction intensively discussed during the CERC3 meeting was catalysis. Particularly enzyme catalysis was identified to be of major importance for the hole field of chemistry at its interface to biology.

In this context it is becoming increasingly clear that evolutionary principles of protein engineering or protein selection using technigues like phage display provides a basis for the tayloring of enzymes to specific functions. The sequential redesigns of proteins will be increasingly possible by combinations of rational structure-based modifications and stochastic variations based on the generation of combinatorial libraries. Identification of variants with novel functional properties can be performed with various screening and selection strategies. The evolutionary optimization of enzymes has to be accompanied by detailed mechanistic studies.

Particular focus has to be placed onto metal ion, because most enzymes that perform complex and highly valuable chemistry contain a metal atom at the active site, which is responsible for catalysis. These enzyme are for example able to perform CH-activation reactions, which are considered to be the "holy grail" of organic chemistry. Groups working in enzyme chemistry, or enzyme evolution could team up with groups of inorganic chemists to decipher complex enzyme mechanisms and to create tailor made enzymes.

Since metals play also a major role as active anti-cancer drugs similar teams addressing the question of how these metals in their interplay with nucleic acids and proteins help to cure diseases could form. In the whole area the synthesis and evaluation of organic and inorganic model compounds, which may in the future allow to mimic the enzymatic function with smaller molecules is of paramount importance and should not be underestimated.

Enzymes perform chemistry with high efficiency and in many cases unreachable selectivity. Harnessing the properties and function of enzymes for the large scale production of fine chemicals is in many companies a major theme. The ability of handle enzymes for fine chemical production could in the future even determine the fate of the fine chemical industry in Europe. The CERC3 participants agreed that it is consequently of paramount importance to set up strong European collaborations aimed i) to discover new enzymes with fascinating catalytic potential, ii) to decipher the mechanism of enzyme catalysis, iii) to mimic the enzymatic reaction with model compounds and iv) to establish evolutionary methods to optimize the catalytic potential and the substrate specificity of these enzymes or to create even new enzymes. Catalysis is clearly the key theme for chemists' ongoing effort to make chemical procedure more environmentally friendly (green chemistry).

## Conclusion

Catalysis and medicine are the two areas in which the field that is covered by the expression: “The biological aspects of chemistry” could make a major impact. Research in both areas is essential for the development of chemistry as a science. Chemical breakthroughs in both areas will have important impact on the development of our European society.

In both areas faces Europe fierce international competition. In medicine it is clearly the United States which possesses a leading position. The lack of proper scientific support of chemistry in this area allowed the US to overhaul Europe as the major discoverer and developer of new medicines. European wide collaborations and funding is needed to stay in touch with the US and to make up lost ground.

In catalysis Japan is one of the leading nations that e. g. uses extensively enzymes to produce fine chemicals. Here Europe is still in a very strong position but new financial efforts and European wide collaborations are clearly needed to stay in a competitive position. This is particularly important because catalysis and among it enzymatic catalysis will determine the future of the European fine chemical industry.

In addition: The public demands increasingly more environmentally friendly synthesis and production processes. This request can only be fulfilled if chemistry invests consequently in the development of "green" enzymatic synthesis methods.

Now that the 6th framework program hints strongly to huge consortia, an option for smaller, strongly focused collaborating teams in basic research appears to be particularly desired. Teams of about 3 - 5 groups from different countries, which are complementary operating are highly desired. The teams should also include younger European scientist, which are not yet organized enough to be part of one of the huge networks put together under the 6th framework program.

The CERC3 report about “The biological aspects of chemistry“ closed in the believe that the four topics: 1) protein chemistry and proteomics, 2) nucleic acid chemistry and genomics, 3) carbohydrate chemistry and carbohydrate recognition, 4) catalysis are today hot scientific areas with outstanding importance for the development of Europe.