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## Meeting report: Protein Design and Evolution for Biocatalysis

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**Meeting report: Protein Design and Evolution for Biocatalysis**

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**Meeting report: Protein Design and Evolution for Biocatalysis**

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October 25-30, 2008, Sant Feliu de Guixols, Spain

The third event of this conference series was held at the beautiful city of San Feliu de Guixols north of Barcelona in the hotel Eden Roc being directly located at the Mediterranean Sea. In contrast to the previous meeting held in Greifswald [1], it was this time organized under the umbrella of the European Science Foundation and the European Molecular Biology Organization as an ESF-EMBO symposium and Professor **Jiri Damborsky** (Brno, Czech Republic) was responsible for the scientific program. The meeting was attended by 149 participants from 30 countries with the majority coming from Europe. Notably, many young scientists joined the meeting and there was also a good mix between academia and industry.

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The scientific program comprised of 24 invited lectures and 14 short talks subdivided into several sessions dealing with (i) fundamentals of enzymatic catalysis, (ii) computer modelling in protein design, (iii) bioinformatics in protein design and (iv) directed evolution (and engineering) of biocatalysts. Thus, the conference represented an excellent forum to exchange the latest achievements and theories on our current understanding of how enzymes function, how their relationship can be identified and interpreted, and how computational methods can be used to support these studies or even to tailor-design novel enzymes. Furthermore, it became obvious that directed (molecular) evolution has become a robust and state-of-the-art tool in protein engineering. It is impossible to cover all lectures in this report, but certain trends and highlights should be mentioned:

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((quote))Directed (molecular) evolution has become a robust and state-of-the-art tool in protein engineering

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A clear trend was the increasing importance of computer modeling and software tools in protein engineering. **Daniela Grabs-Roethlisberger** (University of Washington, Seattle, USA) and **Dan Tawfik** (Weizman Institute of Science, Rehovot, Israel) exemplified this with their outstanding work on the *de novo* computational design of an enzyme able to catalyze the Kemp elimination – a reaction for which no natural protein is known to be active. A completely different approach was presented by **Burckhard Seelig** (University of Minnesota, St. Paul, USA), who created a catalytically active protein from scratch using mRNA display. Yet another alternative is the design of artificial metalloenzymes, which was demonstrated by **Marc Creus** (University of Neuchatel, Switzerland). Using avidins as protein hosts, the designed proteins can catalyze for instance enantioselective hydrogenation, allylic alkylation and sulfoxidation.

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*In silico* screening of the vast information available in public databases of protein sequences and structures is increasingly facilitated due to the development of software and advanced modeling tools. This was exemplified for instance by **Adrian Mulholland** (University of Bristol, Bristol, UK) for the application of QM/MM methods and **Henk-Jan Joosten** (Bio-Product, Wageningen, [The Netherlands](#)) for a database to identify key residues for mutagenesis. These developments were supported by many examples of various proteins, where the engineering of a given protein was substantially facilitated as computation significantly reduces the number of variants to be created and increased the probability to find the enzyme with desired properties. Furthermore, these methods allow for a much better understanding of the sequence-function relationship of proteins.

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The second half of the symposium was much more [focused](#) on biocatalysis and hence the application of enzymes was in the foreground, but also novel methods for mutagenesis were presented. For instance, **Manfred Reetz** (MPI, Mülheim, Germany) showed that iterative saturation mutagenesis and CASTing enabled the rapid creation and identification of a highly enantioselective epoxide hydrolase (where previous directed evolution experiments using error-prone PCR led only to a modest increase in selectivity) and he could show that several routes exist, which can lead by step-by-step mutation to a useful enzyme. **Aurelio Hidalgo** (University of Madrid, Madrid, Spain) reported on a new method (OSCARR), which enables a facile cassette mutagenesis to modify a set of amino acids rather than single mutations and already led to the creation of an esterase with lipase-like chain-length profile. The flexibility of proteins was also demonstrated in the talk by **Stefan Lutz** (Emory University, Atlanta, USA), who performed circular permutation on lipase CAL-B and could show that even alternative N- and C-termini can result in a functionally active protein.

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A strong link to organic synthesis was obvious in the lectures by **Dick Janssen** (University of Groningen, Netherlands) and **Nick Turner** (Manchester Interdisciplinary Biocentre, Manchester, UK). Janssen showed that halohydrin dehalogenase represent highly versatile biocatalysts in the synthesis of a broad set of enantiopure  $\beta$ -substituted secondary and tertiary alcohols and by far exceed the synthetic utility of epoxide hydrolases. Turner also introduced new enzymes useful for synthetic purposes such as amine oxidases, alcohol oxidases and ammonia lyases. From all lectures in this area it became obvious, that protein engineering is now state-of-the art technology to tailor-design biocatalysts for a given target.

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Hence, the use of computer [modeling](#) for rational protein design and of directed evolution with high-throughput screening/selection tools appear to be generally used tools to solve synthetic problems.

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Still, basic research to support our understanding on how proteins function has its place and is of high importance to solve issues in applied biocatalysis. This was exemplified for example in the lectures by **Stephen Benkovic** (Pennsylvania State University, University

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2 Park, USA) and **A. Warshel** (University of Southern California, Los Angeles, USA) both  
3 using the 'bench-mark' protein dihydrofolate reductase (DHFR) as model enzyme. **Gregory**  
4 **Petsko** (Brandeis University, Waltham, USA) described general rules for identification of  
5 binding sites on protein surfaces using experimental studies (crystallographic analysis in the  
6 presence of small organic molecules) as well as theoretical calculations (theoretical solvent  
7 mapping and QM calculations of titration curves of ionisable groups).  
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11 Recent trends and a possible outlook on protein engineering was the focus of a **plenary**  
12 **discussion** chaired by Stephen Benkovic, Dick Janssen, Romas Kazlauskas, Dan Tawfik  
13 and myself with Jiri Damborsky as the moderator. The participants agreed that great  
14 progress has been made in terms of tools and data generation as such, but an in-depth  
15 understanding of the data is still lacking. A combination of computational and experimental  
16 data sets within one project is necessary to broaden our understanding of structure-function  
17 relationships. The general trend in protein engineering is a combination of directed evolution  
18 and rational design, for which experimentally the need for high-throughput screening  
19 methods is still important to identify interesting hits in large mutant libraries. The *de novo*  
20 design of enzymes from scratch is still far off as current designs do not match natural  
21 enzymes in their catalytic efficiency. This is clearly a 'higher order problem'. Also, how  
22 enzymes work in cells is not well understood. Hence, more research is needed for improved  
23 production of enzymes and new host organisms are needed to be developed for production  
24 of difficult-to-express proteins. It was also commonly accepted, that there is an increasing  
25 gap between large amounts of data and how to understand them. For instance, annotations  
26 of some data stored in genomic and proteomic databases is wrong, and thus the use of  
27 statistical analyses is becoming increasingly important. Another point which was intensively  
28 discussed was artificial life: one of the great challenges of synthetic biology is to design and  
29 construct the living cell and protein engineering may provide useful molecular tools for this  
30 difficult task. For protein engineering, the understanding and design of loops was considered  
31 highly important as loops are known to play an important role for binding of ligands to the  
32 active sites and are involved in the evolution of new substrate specificities. Thus, the  
33 development of novel methods for engineering of loops will promote construction of enzymes  
34 with novel substrate specificities or functions. Finally, the holy grail in protein engineering  
35 was identified as the prediction of the protein tertiary structure from the primary amino acid  
36 sequence.  
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46 ((quote))

47 Cell and protein engineering may provide useful molecular tools for synthetic biology  
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2 In addition to the excellent lectures, the conference also featured almost 100 posters  
3 demonstrating highest quality science, which created a perfect platform for extensive  
4 discussions among the participants.

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6 On the leisure side, participants had the opportunity to visit the beautiful city Girona during a  
7 half day excursion. The meeting closed with an excellent and delicious conference dinner  
8 framed by a very enjoyable professional performance showing classical Spanish and gipsy  
9 dances. Deleted: spanish

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11 Overall, the 3rd symposium, in this series was a great scientific meeting and an excellent Deleted: a  
12 opportunity to learn and discuss the latest developments in the rapidly developing field of  
13 protein engineering. I am sure that the participants are eagerly waiting for the next  
14 conference, hopefully taking place in 2010.  
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20 Uwe Bornscheuer (Greifswald University)

21 E-mail: [uwe.bornscheuer@uni-greifswald.de](mailto:uwe.bornscheuer@uni-greifswald.de)

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24 [1] Damborsky, J., *Biotechnol. J.* 2007, 2, 176-179 Deleted: ,  
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26 Complete set of pictures:

27 [http://loschmidt.chemi.muni.cz/peg/esf/esf\\_index.html](http://loschmidt.chemi.muni.cz/peg/esf/esf_index.html)

28 Popularization article about the conference: Deleted: ¶

29 [http://www.esf.org/research-areas/medical-sciences/news/ext-news-](http://www.esf.org/research-areas/medical-sciences/news/ext-news-singleview/article/computers-team-up-with-evolution-to-design-novel-enzymes-561.html)  
30 [singleview/article/computers-team-up-with-evolution-to-design-novel-enzymes-561.html](http://www.esf.org/research-areas/medical-sciences/news/ext-news-singleview/article/computers-team-up-with-evolution-to-design-novel-enzymes-561.html)  
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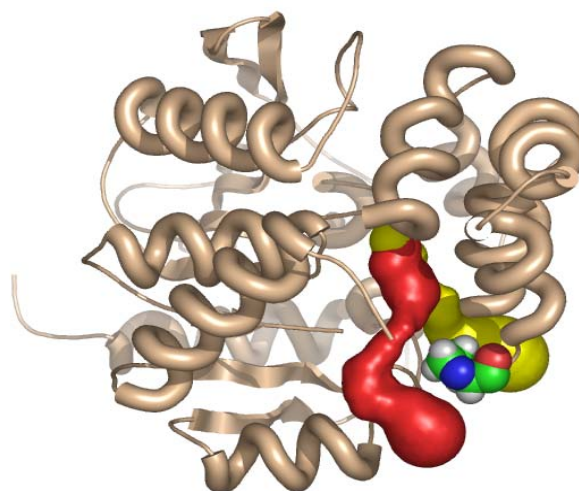


The meeting will bring together internationally renowned speakers who will review the current state of knowledge in the field of protein design and evolution for biocatalysis. The symposium will be the third event in a series held in Paris (2002) and Greifswald (2006). The main objective of the 2008 meeting will be to intensify discussion and collaboration between experimentalists with theoreticians, which is needed for development of novel biocatalysts by combining directed evolution with rational protein design. The meeting will be highly interdisciplinary through the participation of speakers with various backgrounds and research interests. The lectures will span the fields of mechanistic enzymology, biocatalysis, protein crystallography, computer simulations, phylogenetics, structural bioinformatics and synthetic biology. A substantial amount of time will be devoted to poster presentations and informal discussion to promote exchange of ideas and dissemination of information. Young scientists are encouraged to actively participate and a number of lectures will be reserved for their presentations based on originality and scientific quality of submitted abstracts.

## ESF-EMBO Symposium Protein Design and Evolution for Biocatalysis

Hotel Eden Roc, Sant Feliu de Guixols (Costa Brava) • Spain  
25-30 October 2008

With support from



**Chair:** Jiri Damborsky, Masaryk University, CZ

### Confirmed Speakers include

Stephen Benkovic, Pennsylvania State University, US	Stefan Lutz, Emory University, US
Uwe Bornscheuer, University Greifswald, DE	Adrian Mulholland, University of Bristol, UK
Janusz Bujnicki, Int. Institute of Molecular and Cellular Biology, PL	Sven Panke, ETH Zurich, CH
Federico Gago, University of Alcalá, ES	Gregory Petsko, Brandeis University, US
John Gerlt, University of Illinois, US	Juergen Pleiss, University Stuttgart, DE
Daniela Grabs-Röthlisberger, Uni. Of Washington, US	Manfred Reetz, Max-Planck-Institut für Kohlenforschung, DE
Philipp Holliger, MRC Cambridge, UK	Brian Shoichet, University of California - San Francisco, US
Karl Hult, Royal Institute of Technology, SE	Burckhard Seelig, Harvard Medical School, US
Dick Janssen, University of Groningen, NL	Dan Tawfik, Weizmann Institute, IL
Karl-Erich Jaeger, Heinrich-Heine-University Duesseldorf, DE	Janet Thornton, European Bioinformatics Institute, UK
Romas Kazlauskas, University of Minnesota, US	Nick Turner, University of Manchester, UK
	Rebecca Wade, EML Research, DE
	Arieh Warshel, University of Southern California, US

**Application Form & Programme** available from

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**Closing Date for Application 06 June 2008**

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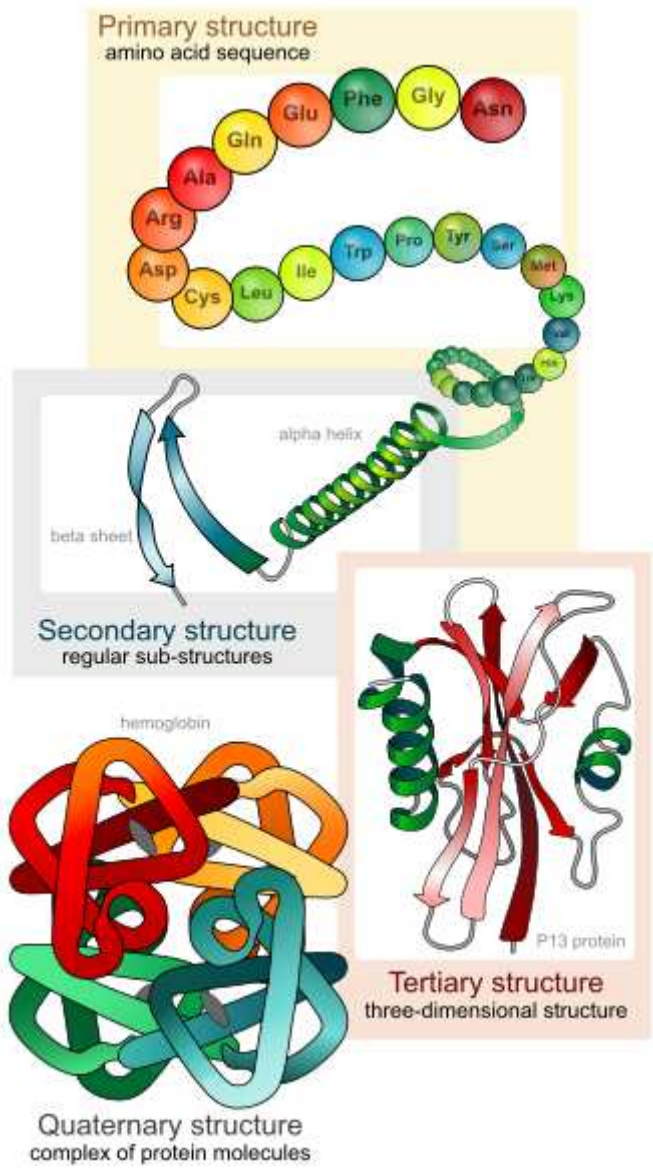
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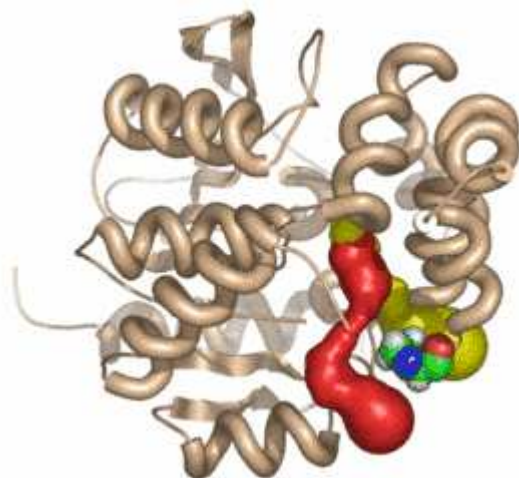
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