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Hot from the press!

10th Wädenswil Day of Life Sciences Hosts 2nd CCBIO Symposium 'Industrial Biocatalysis'

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Abstract: The chemical industry is under increasing pressure to manufacture chemicals that match not only economic targets but also fulfill societal and environmental objectives. These requirements necessitate the adoption of new approaches and consequently the pace of application of biocatalysis in the chemical industry is increasing. The 10th Wädenswil Day of Life Sciences on June 7th, 2018 focused for the second time on 'Industrial Biocatalysis'. Upon invitation of the Competence Center of Biocatalysis (CCBIO) international experts in the field gave an update about their current research interests and attracted more than a hundred guests from industry and academia.

Keywords: Bioprocess engineering · Chemo-enzymatic cascade reactions · Computational design · Enzyme discovery · Enzyme engineering

Biocatalysis is the application of enzymes and microbes in synthetic chemistry to make products of interest and has been part of our everyday life for several thousand years. We use yeast to make bread, beer and wine in whole cell biotransformations, employ lab-ferment to produce cheese using crude enzyme preparations or depend on washing powder, which contains lipases or proteases, to improve washing performance even at low temperatures.

Thanks to their exquisite chemo-, regio- and enantioselectivity enzymes can make accessible or improve the synthesis of numerous added-value chemicals by increasing production yields, shortening process routes or providing alternative to toxic and dangerous reagents. Additionally, biocatalysts work under environmentally friendly reaction conditions, are biodegradable and can help avoid the generation of waste. Recent key advances in DNA sequencing, gene synthesis and data analysis are now enabling scientists to tailor biocatalysts according to industrial needs rather than engineering the industrial process to fit the enzyme requirements. Products generated by enzymatic transformations are being used in the food, feed, chemical, pharmaceutical and cosmetic industries and further expansion is expected as enzymes have proven to be excellent catalysts for the sustainable production of chiral and highly functionalized asset molecules.

Remaining challenges for the industrial application of enzymes can be the long(er) development times for biocatalytic processes compared to classical organic chemistry, the limited range of accessible enzymatic transformations as well as the need for experts with transdisciplinary expertise in the fields of chemistry, biotechnology, micro-and molecular biology and engineering.[1]

Collaborations between academia and industry will thus be an important driving force in fueling the field of biocatalysis. The Competence Center of Biocatalysis (CCBIO) at the ZHAW in Wädenswil aims to help bridge the gap between academic laboratories and the production plant in Switzerland. One initiative is the network project "Innovation in Biocatalysis" led by CCBIO (Infobox 1).

Infobox 1
'Innovation in Biocatalysis' at the ZHAW

The network project is supported by the Swiss Higher Education Council and aims to establish a transdisciplinary biocatalysis network within Switzerland. Between 2017 and 2020 projects within three areas are funded: Within the frame of '*Research Projects'*, new enzyme toolboxes and methods for biocatalysis are being developed. The objective of '*Curricular Elements'* is to design teaching tools and practical courses to integrate biocatalysis in life sciences education and prepare students to work at the interface of chemistry/life sciences and engineering. '*Sustainability Projects'* will evaluate sustainability, economic and social aspects of biocatalysis and open up a dialogue within the community and the public. Thus, 'Innovation in Biocatalysis' will foster collaborations between industry and academia and promote the long-term implementation of biocatalysis in industry.
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Fig. 1. The 10th Wädenswil Day of Life Sciences attracted guests from industry and academia. Photo Beat Gautschi (ZHAW).

Another approach is to foster scientific exchange with experts in the field. The 10th Wädenswil Day of Life Science gave participants from industry and academia the possibility to network and exchange ideas on topics such as enzyme discovery, optimization and computational design as well as bioprocess engineering strategies and application of biocatalytic principles in industry (Fig. 1).

Twelve speakers from academia as well as from industry, from Austria, Germany, Sweden, UK, USA and Switzerland accepted the invitation to come to Switzerland for this one-day meeting (Fig. 2).

Fig. 2. Speakers at the 2nd Symposium on Industrial Biocatalysis: Prof. Dr. Thomas Ward, University of Basel (CH); Prof. Dr. Uwe Bornscheuer, University of Greifswald (DE); Prof. Dr. Rebecca Buller, ZHAW (CH); Dr. David Pearlman, CyrusBio Seattle (USA); Prof. Dr. Anett Schallmey, TU Braunschweig (DE); Assoc. Prof. Dr. Selin Kara, Hamburg University of Technology (DE), now Aarhus University (DK); Dr. Radka Snajdrova, Novartis Pharma AG Basel (CH); Dr. Emil Byström, SpinChem Umeå (SE); Prof. Dr. Robert Kourist, TU Graz (AT); Prof. Dr. Andreas Schmid, Helmholtz Centre for Environmental Research Leipzig (DE). Not on the picture: Prof. Dr. Nicholas Turner, University of Manchester (UK), Dr. Rita Correro, INOFEA AG Basel (CH). Photo Beat Gauchi (ZHAW).

Discovery and Engineering of Enzymes for Biocatalytic Applications

Professor ***Uwe Bornscheuer*** from the University of Greifswald (Germany) has coined the term the "three waves of biocatalysis"[2] which have shaped the field of biocatalysis during the last century and were driven by specific technological advances. Today, so he is convinced, the scientific community may approach a fourth wave[3] facilitated by recent developments in molecular biology, gene synthesis, bioinformatics and the possibility to design more focused enzyme libraries. As Uwe Bornscheuer pointed out "Whatever took 3 years only 15 years ago, now can be done in less than 6 months".

Next to their interest in advanced biocatalytic tools, the Bornscheuer group focuses on the discovery and improvement of industrially valuable enzymes. Pure chiral compounds are important intermediates in the synthesis of active pharmaceutical ingredients. Consequently, amine transaminases (ATA), which catalyze the conversion of ketones into chiral amines, have drawn substantial attention in the field. A limitation of this enzyme class thus far, however, is their limited substrate scope in particular with respect to the acceptance of bulky substrates. Starting from the scaffolds of three (*S*)-ATAs from Fold Class I which showed essentially no activity towards bulky amines, extensive protein engineering was performed and a common motif identified and optimized. Mutations at five residues resulted in enzymes which exhibited up to 8,900-fold higher activity than the starting scaffold with high stereoselectivity (up to >99.9% enantiomeric excess) in the asymmetric synthesis of a set of chiral amines bearing bulky substituents. The distinct motif derived could be transferred to novel sequences resulting in an ATA enzyme toolbox converting bulky ketones.[4]

A 'holy grail' in industrial biocatalysis is the functionalization of non-activated carbons, leading researchers to look into the discovery of novel CH-activating enzymes such as cytochrome P450 monooxygenases. The Bornscheuer group identified new marine P450 monooxygenases, which show little phylogenetic homology to previously known P450s. Interestingly, these enzyme exhibit a previously unknown biological function namely the oxidative demethylation of 6-O-methyl-D-galactose which is catalyzed in the presence of appropriate redox-partner proteins. This extends the group of carbohydrate-active enzymes to include the class of cytochrome P450 monooxygenases.[5]

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Biocatalytic Reductive Amination

Many drugs contain one or more chiral amine building blocks, a fact which has driven the development of new and efficient chemo- and biocatalytic methods. Nevertheless, reductive amination remains a challenge as Professor ***Nicholas Turner*** (University of Manchester), an expert in industrial biocatalysis, pointed out and further exploration of this reactivity is thus a research priority of his group. Imine reductases (IREDs) are an enzyme class capable of catalyzing reductive amination reactions and they have attracted immense attention since their discovery only 8 years ago. Today members of this enzyme family are used in industrial applications, such as in cascade reactions together with ω-TAs, in tandem reactions or in one-pot biocatalytic cascades for example for the synthesis of chiral piperidines.[6] A promising novel IRED variant discovered by the Turner group is the so-called AspRedAm, a NADP(H)-dependent reductive aminase from *Aspergillus oryzae* which shows sequence similarity and structural homology to known imine reductases (IREDs).[7] This enzyme, a first eukaryotic IRED homolog, catalyzes the reductive coupling of a broad set of carbonyl compounds with a variety of primary and secondary amines in up to >98% conversion and with up to >98% enantiomeric excess. Steady-state kinetic studies of AspRedAm suggest a mechanism involving ordered binding of substrates and release of products, consistent with an enzyme capable of catalyzing imine formation as well as reduction. A cascade reaction using ADH or oxidase together with AspRedAm was developed for redox neutral amine alkylation in the synthesis of heterocycles (unpublished).

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Engineering Strategies towards more Efficient Biocatalytic Cascades

Assoc. Professor ***Selin Kara*** (recently moved to Aarhus University) studies the design and engineering of biocatalytic cascades in aqueous and in non-conventional media. She presented two different systems: A multi-enzymatic cascade to synthesize lactones, and a chemo-enzymatic cascade for the production of aroma compounds (Fig. 3). Both systems were investigated at the Institute of Technical Biocatalysis (Prof. Dr. Andreas Liese) at Hamburg University of Technology (TUHH). Lactones are building blocks for the production of flavors, fragrances and pharmaceuticals as well as for the synthesis of biodegradable polymers. ε-Caprolactone (ECL), for example, is a building block for the synthesis of poly-ε-caprolactone. The two-step enzymatic reaction sequence toward the lactones involves an alcohol dehydrogenase (ADH) and a cyclohexanone monooxygenase (CHMO) for the oxidation of cyclohexanol

(CHL) to ECL which is followed by a third step: hydrolysis of ECL to 6-hydroxyhexanoic acid (6-HHA) by an immobilized CALB. The set-up overcomes previously experienced kinetic limitations of CHMO: Inhibition by CHL is prevented by feeding the substrate, whereas product inhibition by ECL is avoided by hydrolyzing the product with CALB. Acidification, extraction with organic solvent and solvent free polymerization of 6-HHA with an immobilized CALB (a different enzyme preparation than the former step) resulted in bimodal form (high and low molecular weight) of poly-ε-caprolactone (PCL) with an average molar mass of 63500 g/mol and a polydispersity index of 1.1 of the higher molecular weight.[8] In a complementary approach, chemical and biocatalytic reaction steps can be connected allowing access to, for example, alkyl- and phenylguaiacols, important aroma compounds found in various types of food and beverages. The chemo-enzymatic cascade studied in the Kara group optimizes the production of 4-ethylguaiacol from ferulic acid (FA), an abundantly available platform chemical from lignocellulosic biomass *via* the design of a sequential two step – two pot system. Here, the decarboxylation of FA by phenolic acid decarboxylase (PAD) in aqueous solution is coupled with a hydrogenation reaction catalyzed by palladium on charcoal (Pd/C) in an organic solvent without intermediate isolation.[9]

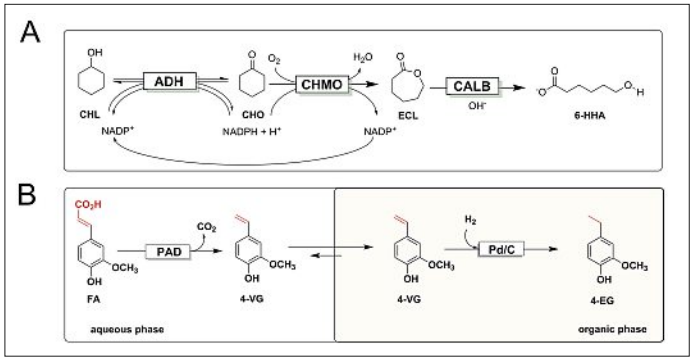

Fig. 3. Improving the efficiency of enzyme cascades by A) reaction engineering: a multi-enzymatic linear cascade for the synthesis of lactones (building blocks)[8] and B) medium engineering: a sequential two step – two pot chemo-enzymatic cascade for the synthesis of guaiacols[9]

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Biocatalysis in Drug Discovery and Drug Development at Novartis

"Biocatalysis has gained tremendous relevance in industry over the last decade as a green, atom efficient and economically viable route towards active pharmaceutical ingredients (APIs) in particular compounds inaccessible to traditional synthetic chemistry" says Dr. ***Radka Snajdrova***, head of the Bioreactions Group at Novartis in Basel (Fig. 4). Using Cipargamin as an example, an experimental synthetic antimalarial molecule with a novel mechanism of action, she gave an insider view of biocatalysis at Novartis. In the initial synthesis strategy, a racemic variant of the API could be obtained with moderate yields after a five-step chemical synthesis. To improve the process, a new chemo-enzymatic route involving a transaminase was developed and successfully scaled-up to 44 kg scale/batch size (high ee/high purity/quantitative yield). To study the metabolism of Cipargamin in the human body, the Bioreactions group produced potential Cipargamin metabolites using recombinantly expressed hydroxylating enzymes. Another focus of the Bioreactions group at Novartis is the development of enzyme toolboxes. Chemical hydrolysis of nitriles, for example, often leads to unwanted byproducts and consequently hydrolysis by nitrilases has become an interesting alternative. Using a combined approach of sequence data analysis including new biological material and high throughput experimental activity screening of a nitrile substrate panel a biocatalytic toolbox of nitrilases useful for chemical synthesis was set up.[10]

Fig. 4. Dr. Radka Snajdrova talks about Biocatalysis at Novartis. Photo Beat Gauchi (ZHAW).

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Artificial Metalloenzymes: Challenges and Opportunities

In 2016, Professor ***Thomas Ward*** (University of Basel) received an advanced ERC grant to realize his DrEAM, the 'Directed Evolution of Artificial Metalloenzymes'. Artificial Metalloenzymes (ArMs) combine features of organometallic and enzymatic catalysis and are composed of a catalytically active metal complex, which is introduced into a macromolecule (protein or DNA). The protein environment controls the second coordination sphere and thus the selectivity of the reaction. Reactivity can be modulated by either varying the metal itself, the spacer *via* which the metal is anchored within the macromolecule or the protein environment around the location of the metal.

In order to generate improved ArMs, the Ward group made use of the well-known biotin-(strept-) avidin-technology coupled with directed evolution.[11] Using a chemo-genetic optimization strategy, imine reductase mutants with opposite enantioselectivity for the reduction of cyclic imines were constructed. Interestingly, the inversion in enantioselectivity was induced by a single amino acid mutation, whereas variant S112A was selective for the (*R*)-product (96% *R*), variant S112K preferably generated the the (*S*)-product (78% *S*).

Going one step beyond, the Ward group targeted *in vivo* catalysis by artificial metalloenzymes. Using *E. coli* periplasm as a reaction compartment, the directed evolution of an artificial metalloenzyme for ring-closing metathesis was achieved *in vivo*.[12] In another approach *E. coli* surface display was employed for the directed evolution of an artificial allylic deallylase and used for high-throughput screening.[13] Recently, an intracellular reaction cascade was assembled in mammalian cells, which linked an artificial metalloenzyme to a hormone-responsive gene switch.[14]

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Linking Photosynthesis and Whole Cell Biocatalysts for C–H Functionalization

C–H functionalization is a key reaction required in many chemical processes performed to produce specialties (*e.g.* pharma), fine or bulk chemicals. The Department of Professor ***Andreas Schmid*** (H*elmholtz*-Centre for Environmental Research) explores the use of oxygenase-driven biocatalysis for synthetic chemistry. Enzymatic processes are an interesting alternative to chemical methods, yet gas–liquid mass transfer of gaseous reactants in aqueous media is a major limitation regarding space time yields. The novel concept developed in the groups of Bruno Bühler, Katja Bühler and Andreas Schmid thus relies on light-driven water oxidation for the homogenous supply of O_2 to a catalytically active oxygenase enzyme.[15] Two reaction model systems use cyanobacterium *Synechocystis sp.* PCC6803 as a biocatalyst for the production of oxyfunctionalized compounds from hydrocarbons (Fig. 5).

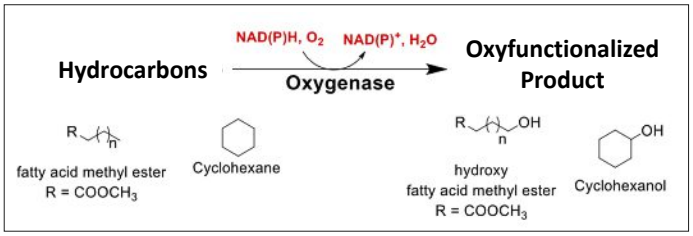

Fig. 5. Model reaction systems in the phototrophic organism *Synechocystis sp*. PCC 6803. Source: A. Schmid.

The reaction is driven by oxygen from photosynthetic water splitting[15] and the reaction rate is dependent on the light intensity. The novel phototroph biocatalyst achieves similar production titers per 1 g H_20 as a heterotroph biocatalyst (*e.g. Pseudomonas sp*.) per 1 g glucose. Scaling-up photocatalysis depends on reactor design allowing the generation of high biomass while ensuring high oxygen availability. A micro capillary flow through reactor developed by the group of Katja Bühler contained a cyanobacterial biofilm of *Synechocystis sp*. PCC6803, which was stable and showed continuous long term photosynthetic activity.[16]

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Novel Enzymes for Biocatalytic Applications: Selective Epoxide Ring-opening and Lignin Depolymerization

"Public sequence databases are a rich source for novel enzymes displaying new catalytic properties" is the take-home message of Professor ***Anett Schallmey*** (TU Braunschweig), who is interested in the discovery and characterization of under-explored enzyme classes such as halohydrin dehalogenases (HHDHs) and β-etherases, lignin degrading enzymes.

HHDHs, versatile enzymes of biotechnological interest without the need of a cofactor, belong to the short-chain dehydrogenases/reductases superfamily. They catalyze the reversible dehalogenation of vicinal haloalcohols with formation of the corresponding epoxide. In a reverse reaction, the enzymes can utilize nucleophiles such as cyanide, azide or nitrite for irreversible epoxide ring-opening reactions and formation of novel C–C, C–N or C–O bonds.[17] To establish a HHDH toolbox, the Schallmey group carried out a database mining, which led to the identification of 67 novel HHDH sequences belonging to four new phylogenetic subtypes. Substrate spectra based on the conversion of vicinally di-substituted and cyclic epoxides were determined highlighting the exceptional substrate scope of the newly identified halohydrin dehalogenase HheG.[18]

Lignin, an aromatic polymer and part of lignocellulose, is regarded as a waste product but could serve as a feedstock for aromatic platform chemicals as well as for other biomaterials. Valorization of lignin would therefore enhance the economics of lignocellulose-based biorefineries. In nature, lignin degradation involves multiple enzyme activities. In particular, β-O-4-aryl ether bonds, the most abundant type of linkage present in lignin, is selectively cleaved by β-etherases.[19] However, as only few of these enzymes are known and no common sequence motif is available, the Schallmey group used a peptide pattern recognition (PPR) algorithm to screen databases and identify novel β-etherases. Utilizing these enzymes together with a laccase-mediator system and a glutathione lyase, a two-pot biocracking route to depolymerize lignin was developed.[20]

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Representatives of several companies gave an update on current technology interesting for setting up biocatalytic processes (Infobox 2).

Infobox 2
New Tools for Biocatalysis – Companies at the 2nd CCBIO Symposium

Dr. David Pearlman from the Seattle based ***CyrusBio*** introduced 'CyrusBench', a computational modeling tool based on the Rosetta software and showed approaches how to design proteins with increased stability. The software targets to make modeling tools – which have traditionally been difficult to use – accessible to a much broader protein community.
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SpinChemAB (Sweden), represented by Dr. Emil Byström, has developed a rotating bed reactor that retains immobilized enzymes, protects them from mechanical stress and allows high reaction rates while reusing the enzymes. The system is scalable from 10mL to 100L.
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Dr. Rita Correro introduced 'enzzen®', ***INOFEA***'s technology of protein immobilization in soft organo-silica layers. This platform technology developed by the Basel-based company shields enzymes from the solution, which improves their stability under harsh conditions, allows their reuse and increases the efficiency of cascade reactions.[21]
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The Culture Collection of Switzerland (***CCOS***) is the national public culture collection for microorganisms in Switzerland and provides genetic resources (plasmids, bacteria, fungi and cell lines) in compliance with the Nagoya Protocol. Recently the company has launched 'GMT', a gut metabolization test system that allows the simulation of fecal degradation of drugs *in-vitro*.
www.ccos.ch

Dr. ***Hans-Peter Meyer***, Expertinova, sums up positively: "Biocatalysis has developed enormously during the last decade – to further push the boundaries of what the field can achieve, the community needs to join forces to identify additional fields of application".

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