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Hot from the press!

Innovation in Biocatalysis – A Swiss Network Project Coordinated by the Competence Center for Biocatalysis (CCBIO)

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Abstract: Biocatalysis – the application of enzymes or microbes in chemistry – has developed into one of the key technologies of the 21st century. Enzymes in isolated form, as a cell extract or whole cell biocatalysts can be used to replace or supplement purely chemical process routes with the goal to make chemical synthesis more efficient, environmentally friendly, sustainable and potentially more cost-effective.

Keywords: Biocatalysis · Enzymes

Academic and commercial interest in biocatalysis arouse over a century ago but it is the recent developments in molecular biology – often referred to as the third wave of biocatalysis – which have truly fueled the industrial use of enzymatic biocatalysts.[1] More efficient cloning techniques, decreasing costs for synthetic DNA, new hosts for the efficient expression of heterologous proteins as well as new purification strategies have decreased costs for biocatalyst production. Immobilization techniques increase stability of enzymes and allow them to be reused. Co-factor recycling systems have been developed for the use of isolated enzymes. Advances in bioinformatics (DNA mining, protein modeling) combined with state-of-the-art mutation and selection strategies allow to identify, design and produce enzymes optimized for a certain application. Thus, not only natural enzymes and variants thereof are now available but even enzymes to catalyze reactions not found in nature have been produced.[2–4] New concepts and developments in designing proteins as well as high-throughput screening methodologies reduce development times even further.[5] Obviously, a fourth wave of biocatalysis is approaching.[6]

Biocatalysis – From the Academic Bench to Industrial Application

Several prominent examples of successful application of biocatalysis in industry exist, many of which can be found in the pharmaceutical industry. Here, critical steps in the synthesis of active pharmaceutical ingredients were improved considerably by including biocatalytic steps, for example in the synthesis of Sitagliptin[7] and Atovarstatin.[8] Generally, however, it seems that industry is not yet taking full advantage of the potential biocatalysis offers[9] and in particular small and medium companies lack in-house competences to develop biocatalytic processes. Consequently, the set-up of economic viable biocatalytic process steps requires a close collaboration between academia and industry and experts with transdisciplinary skills and an extensive training at the interface of chemistry/life sciences and engineering are essential.

CCBIO – The Swiss-based 'Competence Center for Biocatalysis'

Despite hosting headquarters and research facilities of many major global players in the chemical and pharmaceutical industry, an academic contact point to help solve biocatalytic questions was only recently established in Switzerland. Today, the Competence Center of Biocatalysis (CCBIO) at the University of Applied Sciences in Wädenswil is closing this gap. The center started operation in 2016 under the leadership of Prof. Dr. Rebecca Buller and tackles multidisciplinary research projects combining tools of chemistry and biology using the expertise of its members (*www.zhaw.ch/ccbio*). Additionally, CCBIO works on establishing networks of researchers from both academia and industry within Switzerland making use of the platform 'Biocatalysis and Biosynthesis' supported by the National Thematic Network (NTN) Swiss Biotech™.

To advance CCBIO's mission further, support was granted by the Swiss Higher Education Council. CCBIO was awarded CHF 2 Mio in the frame of project-based contributions 2017–2020 to establish a Swiss biocatalysis network with the aim to fuel the development of bio-based sustainable production in Switzerland.

'Innovation in Biocatalysis': A Toolbox for Sustainable Bio-based Production

The project 'Innovation in Biocatalysis' aims to create a network for dynamic and innovative biocatalysis in Switzerland and to develop transdisciplinary expertise between the fields of chemistry, biotechnology, micro- and molecular biology and engineering. To do so, three areas of particular importance, namely 'Research Projects', 'Curricular Elements' and 'Sustainability', were identified for support by the program between 2017 and 2020 (Fig. 1). A scientific committee composed of experts in the field from academia and industry (Fig. 2) supervises and supports the program and selected the projects to be funded.

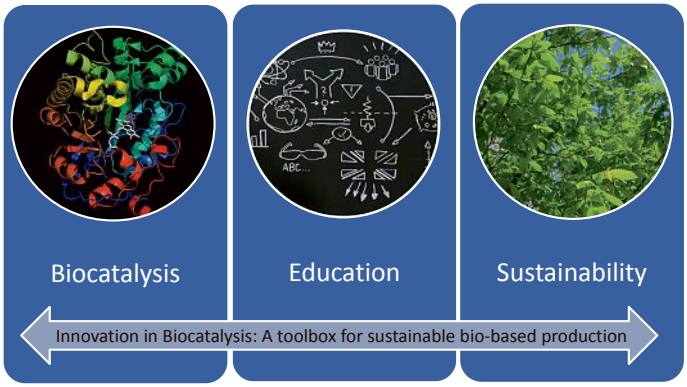

Fig. 1. The network project 'Innovation in Biocatalysis'

Fig. 2. Scientific Board (from left to right): Prof. Dr. Donald Hilvert (ETHZ), Dr. Steven Hanlon (Roche), Dr. Roland Wohlgemuth (Merck), Prof. Dr. Gerhard Grundler (FHNW), Dr. Jan Lucht (Scienceindustries), (Photo Beat Gautschi).

Research Projects

To integrate biocatalytic and chemical processes for the sustainable production of added-value chemicals, new biocatalytic tools and methods need to be developed and implemented in applications. Thus, the program supports research projects concerned with biocatalysis, *i.e.* chemical transformation catalyzed by one or multiple enzymes in any form, and platforms enabling the discovery, application and optimization of biocatalysts.

Curricular Elements

To give insights into the potential of biocatalysis and to educate multi-disciplinary experts for the life science sector, the design of classes and practical courses in biocatalysis will be targeted for the tertiary level. Toward this goal, the program supports projects concerned with the development of curricular elements aiming at a long-term integration of biocatalysis in life sciences education to facilitate the use of enzyme systems for modern production processes.

Sustainability

To generate a better understanding about the sustainability aspect of biocatalysis, economic and social implications of this scientific field will be examined and communicated within the community and to a larger audience. Projects in this category will also focus on the sustainable implementation of biocatalysis in industry and collaboration between academia and industry beyond 2020.

Research Projects

The call 'Research projects' was announced in Spring 2017 and communicated to all eligible academic partners. Proposals were evaluated by a working group composed of experts in the field from academia (Dr. Valentin Köhler, Basel University; Prof. Dr. Sven Panke, ETH Basel; Prof. Dr. Patrick Shahgaldian, FHNW; Prof. Dr. Manfred Zinn, HES-SO Valais-Wallis, Prof. Dr. Regine Eibl, ZHAW and Prof. Dr. Rebecca Buller, ZHAW) as well as industry (Dr. Eric Eichhorn, Givaudan; Dr. Marco Mirata, Lonza; Dr. Kirsten Schroer, Novartis). Based on the recommendation of the Working Group the Scientific Committee selected seven research projects for funding.

In the frame of the selected projects the development of new enzyme toolboxes and methods for biocatalysis will be tackled. Examples range from the implementation of halogenases, cytochrome P450 reductases and squalene-hopene-cyclases for industrial applications, the design of nanobiocatalysts capable of asymmetric catalysis, biocatalytic solutions for preparative methylation reactions, the biocatalytic functionalization of biopolyesters and the assessment of catalytically active enzyme inclusion bodies.

The projects are introduced below based on excerpts from the applicants' project summaries.

Improved Whole Cell Biocatalysts for P450 catalyzed API Metabolite Synthesis

Martin Held (ETHZ, Basel)

Cytochrome P450s monooxygenases (P450s) catalyze the regio- and stereoselective hydroxylation of non-activated carbon skeletons. No homologous reaction can be found in the world of organic chemistry, which makes P450 monooxygenases an indispensable tool for many applications. In particular, the pharmaceutical industry frequently employs these enzymes to reconstitute the metabolism of xenobiotics and pharmaceuticals and their elimination from the body, which is mainly enabled by human P450s, particularly those found in the liver.[10] This re-enactment is important as due to the high structural homology of the P450's hydroxylation products to the original drugs, these substances can either contribute to the pharmacodynamics in a similar or even larger extent than the API itself or alternatively may affect off-targets, with the risk of triggering undesired side effects.

The detailed characterization of the effects of such so-called drug metabolites in the course of pharmacokinetic and pharmacology studies require gram or (multi-)gram amounts[11] of these substances. Unfortunately, preparative scale synthesis is not trivial with any of the currently, typically recombinant, systems or liver tissue preparations. Regarding the former, one major thrust is the recombinant expression of P450s in microbial hosts, which has been impeded by enzyme instability in these systems.[12] At least part of the poor operational stability is due to oxidative damage caused by the so-called 'uncoupling reaction'.[13] 'Uncoupling' refers to the unspecific breakdown of the P450's heme-Fe(II)-oxygen complex, *i.e.* at the enzyme's active site, or to the escape of electrons during transport from the cytochrome P450 reductase (CPR) to the P450. In both cases, highly reactive oxygen species (ROS, mainly hydrogen peroxide (H_2O_2), but also superoxide ions ($O2^-$) are formed instead of the desired hydroxylated products. These ROS can then react with other oxidizable substance available close by, including parts of the enzyme itself, and thus severely damage the (whole cell) biocatalyst. (…)

We will develop a high-throughput screening assay that will allow measurement of the degree of uncoupling directly in a recombinant *E. coli* cell by quantifying the concentration of hydrogen peroxide *in vivo*. The assay system will find broad application for assessing and modulating the coupling efficiencies of oxygenases in general. Within this project, the system will be applied for reducing unproductive reductase-P450 electron shunts for the most prominent P450 enzyme involved in xenobiotic degradation, CYP3A4 from human liver[10], and concomitantly for reducing the degree of uncoupling. To this end, (i) the metagenome will be screened for new heterologous reductase partners, (ii) performance of the enzyme system will be improved by means of protein engineering of the reductase component, and, (iii) artificial self-sufficient reductase-CYP fusions will be generated with already known and novel CPRs isolated from the metagenome.

Engineered Halogenases for the Late Stage Functionalization of Added-Value Chemicals

Rebecca Buller (ZHAW, Wädenswil), Radka Snajdrova (Novartis Pharma AG, Basel), Olivier Loiseleur, Régis Mondiere (Syngenta Crop Protection AB, Basel)

Halogenation is a biocatalytic transformation which is not often explored for industrial processes. However, in the context of the discovery of a range of novel halogenases, this type of biotransformation is being reconsidered as a greener, more sustainable and more regio- and enantiospecific alternative to chemical halogenations. To tackle the challenge of harnessing halogenases for industrial processes, a collaboration between Novartis, Syngenta and the Competence Center of Biocatalysis at the ZHAW was initiated with the aim to implement bio-halo-

genation processes for substrates of pharmaceutical and agrochemical interest.

Current halogenating enzymes very often suffer from instability and very narrow substrate scope. Within this project those drawbacks will be addressed by enzyme engineering. Modern tools for enzyme discovery, combined with increasingly reliable strategies for protein engineering will be applied to the design of novel halogenases for a regioselective green synthesis, addressing the shortcomings of chemical methods and providing Syngenta, Novartis and the wider academic and industrial community with access to high-value low-molecular-weight intermediates, APIs, or agrochemicals.

Success in this field will lead to a wider uptake of halogenating enzymes, and biocatalysis in general. Having access to robust, regioselective and scalable halogenases will result in significant time and cost savings in synthesis of novel drugs and agrochemicals and will allow the preparation of novel compounds either impossible or difficult to manufacture with conventional chemical methods.

Construction of a simple S-Adenosylmethionine Regeneration System for Preparative Enzyme Catalyzed Methylation

Florian P. Seebeck (Universität Basel)

The third wave of biocatalysis has established the versatility of *in vitro* reconstituted enzyme cascades for the production of market-relevant organics. Enzymes that catalyze group transfers to and from complex molecules are of particular interest because such reactions are often challenging to achieve by chemical means. For example, S-adenosylmethionine (SAM) dependent methyltransferases (MTs) can methylate natural products with exquisite regio-, chemo- and stereoselectivity (Fig. 3). Given the large number of known MTs with defined substrate specificities, the even larger number of putative MTs annotated in today's genome data bases, combined with the increasing possibilities to redesign substrate specificities of enzymes by computational design, it seems possible to engineer biocatalytic solutions for any preparative methylation reaction. Currently the biotechnological application of MTs is limited due to the very high costs of the stoichiometric methyl donor SAM. To mitigate this problem we plan to develop a simple catalytic system for *in situ* regeneration of SAM.

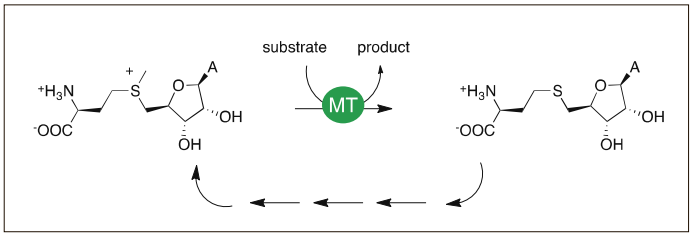

Fig. 3. S-Adenosylmethionine regeneration system for preparative enzyme catalyzed methylation (by courtesy of F. Seebeck).

Supramoleculary Engineered Nanobiocatalysts Capable of Asymmetric Catalysis in Organic Solvents [NanoBioCat]

Patrick Shahgaldian, Philippe F.-X. Corvini (FHNW, Muttenz)

A large number of high-value specialty chemicals and active pharmaceutical ingredients (APIs) are asymmetric; they are preferably produced as pure enantiomers. A large number of chemical asymmetric catalysts has been developed. However, the level of enantioselectivity of the reaction reached is always lower than that of natural or engineered enzymes.

Enzymes are therefore first-choice candidates for asymmetric synthesis, as they are potent natural catalysts that can operate under mild conditions and often display high chemo-, regio- and stereoselectivity, elevated turnover rates, and often good substrate selectivity. However, the use of the majority of natural enzymes is mainly limited to aqueous solvents in which many specialty chemicals are not or poorly soluble.

The *NanoBioCat* project builds upon recent results in nanobiocatalysts design;[14] it aims at developing stable nanobiocatalysts capable of asymmetric catalysis and cofactor regeneration in organic solvents.

In more detail, the nanobiocatalysts will be designed in way that two different enzymes are immobilized and shielded by a protection layer at the surface of mesoporous silica nanoparticles. In the aqueous nano-environment of the nanoparticle, the first enzyme will catalyze an asymmetric reductive amination on a apolar substrate molecule diffusing through the protection layer and concomitantly consume a reduced cofactor molecule ($NADPH,H^+$).

Biocatalytic Production of (R)-α-ionone

Rebecca Buller, Dieter Eibl (ZHAW, Wädenswil)

In this project, a streamlined and efficient biocatalytic process for the selective production of (*R*)-α-ionone will be developed. To this end, Nature's Brønsted acid catalysts, the squalene-hopene cyclases (SHCs)[15] will be evaluated to identify enzymes capable of generating (*R*)-α-ionone with a high level of regio- and stereocontrol. Optimization of enzyme activity (*e.g.* activity, selectivity, thermostability, solvent tolerance) will be achieved through laboratory evolution to create enzyme variants suitable for use in manufacturing processes.[1] Following development of improved enzyme candidates, enzyme production will be optimized *via* fermentation engineering to create a cost-effective and environmentally benign route to (*R*)-α-ionone.

Our work on SHCs will not only open up practical and environmentally friendly routes to the high-value chemical products, but also help to elucidate the underlying catalytic mechanisms of this important and under-developed enzyme family, thus advancing our fundamental understanding and our ability rationally reengineer these systems.

In situ Immobilized Biocatalysts – Production and Characterization of Catalytically Active Enzyme Inclusion Bodies

Lukas Neutsch, Christian Adlhart (ZHAW, Wädenswil)

A more detailed investigation of intracellular protein deposition processes in the recent past has led to a paradigm shift in the classical perception of inclusion bodies (IBs) as inactive agglomerates of misfolded polypeptides. As a consequence, catalytically active IBs are currently coming to the focus of attention as a cost-effective, one-step strategy for enzyme *in situ* immobilization, thereby facilitating the rational development of biocatalytic production chains (Fig. 4).

Unfortunately, there is still little knowledge available on the bioprocess designs and parameter settings to best possibly accumulate catalytically active IBs, and on how to modify their relevant key attributes in a controlled fashion. This is also due to the fact that the analytical methods to characterize IBs, which may be regarded as 'endogenous biological nanoparticles', have not yet been explored in detail. (…)

In this project we will focus on bioprocess development and nanomaterial analytics to (i) generate essential practical knowledge on the formation kinetics of catalytically active IBs in microbial host systems, (ii) establish relationships between process conditions and IB properties to allow for target-specific process optimization and real-time control, and (iii) develop best practice guidelines for monitoring enzyme IB manufacturing in industrial biocatalysis applications. In combination with the constantly evolving technologies for genetic enzyme engineer-

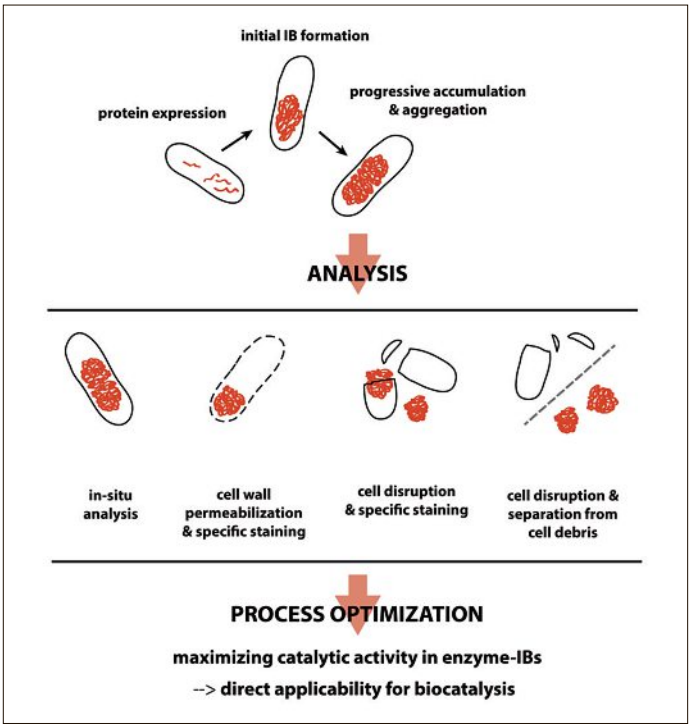

Fig. 4. Characterization of IB properties in dependence of process conditions (by courtesy of L. Neutsch).

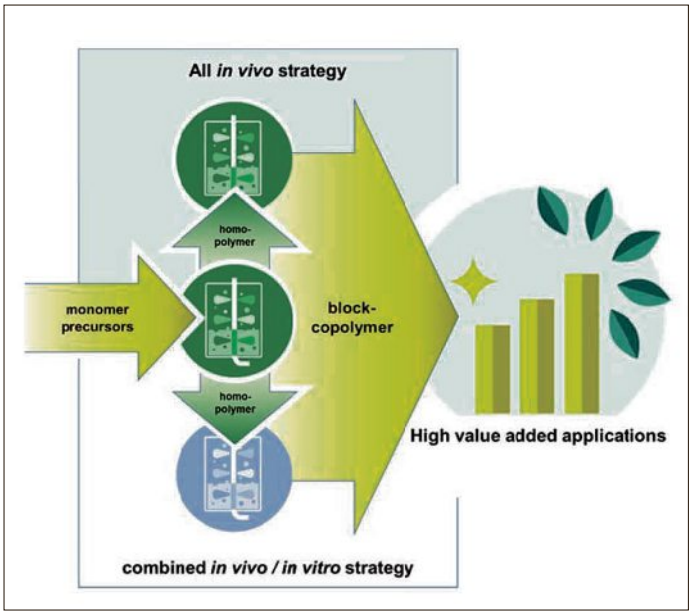

Fig. 5. Biocatalytic functionalization of biopolyester (by courtesy of M. Zinn)

ing and synthetic biology, this will further pave the way towards well-controlled enzyme self-assembly and the production of multifunctional, *in situ* immobilized biocatalysts *via* coexpression and deposition of multiple enzymes.

The results obtained in this project will help advance the emerging field of direct IB utilization to a platform technology with a broad range of applications, and provide innovative solutions to Swiss biocatalysis industry and R&D initiatives on carrier-free enzyme immobilizates.

Biocatalytic Functionalization of Biopolyesters

Manfred Zinn (HES-SO Valais-Wallis, Sion)

The proposed project aims at the enzymatically catalyzed modification of biorenewable and biodegradable polyhydroxyalkanoates (PHA) and the formation of well-defined block-copolyesters. Such materials are recognized to increase available PHA properties and architectures (*i.e.* viscosity, flexibility, rigidity, crystallinity, block-copolymer systems, cross-linkable systems) and have gained increased attention due to their recognized potential for high-value added applications (*e.g.* bio-implants, tissue engineering, drug delivery and smart materials). While current chemical synthesis strategies encumber economically realistic access due to reaction complexity, a distinct need for new methods of their preparation has been identified.

Two methods with a different range of combinations of PHA block segments will be developed in parallel (Fig. 5) The first method employs the enzymatic machinery of a mutant strain of *Pseudomonas putida* cultured in a multistage fermentation system to achieve an all *in vivo* approach to biocatalytically transform appropriate precursor molecules into chiral, block-copolymeric medium-chain-length PHAs. The second method will be developed within a transdisciplinary cooperation between the HES-SO Valais-Wallis, Switzerland and the BOKU University Vienna, Austria and utilizes the provided polymeric material from fermentative biotransformation as substrates for their enzymatically catalyzed conversion into novel block-copolymeric PHAs and thus omitting the use of bio-incompatible reagents, reactants or catalysts. Finally, the two novel methods will be compared with respect to efficiency and feasibility for the consideration of further scale-up, thus preparing the low barrier entry into subsequent industrialization processes.

Curricular Elements

The call 'Curricular Elements' was announced in Spring of 2017 and communicated to all eligible institutes of higher education. A working group with representatives from academia (Prof. Dr. Simon Crelier, HES-SO Valais/Wallis, Dr. Michal Dabros, HES-SO Fribourg, Dr. Martin Held, ETH Basel; Dr. Lukas Neutsch, ZHAW and Prof. Dr. Rebecca Buller, ZHAW) and industry (Dr. Kirsten Schroer, Novartis) reviewed the proposals and based on their recommendation the Scientific Board decided to fund four projects.

It is generally acknowledged that industrial biocatalysis suffers from the difficulty of finding staff with appropriate training to work in this highly interdisciplinary field.[9] Biocatalytic steps are best considered early in developing an industrial process, something which requires personnel with skills and background knowledge in the interface of chemistry/life sciences and engineering. Expertise, equipment and resources to cover the whole value chain (gene to product) of biocatalytic production concepts are available at Swiss universities; however, they are spread out among locations and between departments.

The four projects which qualified for funding propose new initiatives to foster interdisciplinary skills at various stages of education and extend collaboration between academia and industry. They are introduced shortly based on the abstracts provided by the applicants.

simCAT: A Mobile Aid to Recombinant Enzyme Production and Whole-cell Biocatalysis using Microorganisms

Verena Looser, Roland Gassmann (ZHAW, Wädenswil)

The simCAT mobile application will provide a novel tool to efficiently and effectively convey relationships between theory (*e.g.* use of mathematical formulas, differential equations, numerical computation methods) and practical experimentation, where appropriate planning and hands-on performance are required to carry out a specific biological experiment. This tool will comprise specific teaching materials and experience, to be shared

between different courses and universities and to complement traditional teaching with expert knowledge from academia and industry. The primary focus will be specifically on the field of microbial cultivation as the foundation of biocatalysis.

Features of the simCAT-application will cover the following three modes for use in the production of biocatalysts (*i.e.* recombinant or natural enzymes and whole-cell systems): (i) design and planning of a laboratory experiment, (ii) data collection and basic analysis, and (iii) interpretation of process data.

simCAT is not only a mobile application for future-oriented innovative didactics in university education and continuous training, but will also seamlessly combine the technical advantages of an intelligent (expert) system with daily work routines in bioprocessing and biocatalysis. Therefore, we envisage that former students will continue to use simCAT in their future professions in academic or industrial research or in industrial manufacturing. As a result, this mobile application, owned by CCBIO and ZHAW, may facilitate a paradigm change in prevailing manufacturing procedures from chemical synthesis to biocatalysis.

SiBeC2 – Smooth Integration of Biocatalysis Elements into Chemistry Curricula

Simon Crelier (HES-SO Valais, Wallis), Roger Marti (HEIA-FR, Fribourg)

(…) Both schools decided to partner in order to develop teaching material and integrate it to the training of their respective students in chemistry and biotechnology, at both bachelor and master levels. (…). The SiBeC2 project (Smooth Integration of Biocatalysis Elements into Chemistry Curricula) will deliver teaching material with the following features and highlights:

- (…) a coherent set of chapters under various forms such as manuscripts, presentations, exercises, quizzes, laboratory protocols …
- The teaching elements will be based on existing material which shall be up-graded and reformatted to suit the requirement for state-of-the-art pedagogic approach
- Additional information and documentation will be obtained through numerous exchanges with contacts from industry, equipment suppliers, or other schools
- The course material will be made available on the HES-SO e-learning platform (...)
- The course will set a clear focus on active learning and hands-on approach (…)
- (…) provide an excellent opportunity to test electronic lab notebook (ELNs)
- Thanks to its modular nature, the material can be implemented at different timings and to different degrees in each partner school (…)
- The course material can be taught in different contexts: BSc, MSc and even continuing education (the latter would enable to directly approach target companies)
- The concept is in line with the trend for green chemistry, sustainable processes, natural ingredients, environmentally benign synthesis routes *etc.* … and hence fully compatible with other courses in biotechnology or food technology

VICAB – Blended Learning in Biocatalysis

Lukas Neutsch, Andrea Baier (ZHAW, Wädenswil); Simon Crelier, Manfred Zinn (HES-SO Valais, Wallis)

(…) Having a truly multidisciplinary orientation, biocatalysis as a training subject needs to be open for students from different scientific and professional backgrounds, *e.g.* chemistry, biotechnology, molecular biology or process engineering.

The goal of this project is to develop an innovative course format for biocatalysis in life science BSc curricula, which is able to meet the above-named challenges by utilizing a blended learning concept. The core element of the new course will be an online learning platform (*Virtual Campus Biocatalysis; VICAB*) that serves as a framework to guide students through a step chain of eLearning activities and interlaced practical exercise sessions in the laboratory.

The *VICAB* will offer a fully integrated training environment, including knowledge resources and simulation tools as preparation for practical work, as well as a cloud database to combine and collectively analyze experimental data. Communication forums and virtual meeting rooms will be available for online discussions among groups and interaction with lecturers and external mentors from industry. Emphasis will be placed on self-directed learning, with student teams designing their own experimental strategies under supervision of lecturers and applying data handling and teamwork routines according to the *Industry 4.0* principle.

In the first implementation stage, *VICAB* will cover the two course modules on biocatalyst production (*i.e.* bioprocess development and enzyme purification/characterization). In further expansion stages, additional course modules (*e.g.* molecular biology, directed enzyme evolution, special biocatalytic applications) and case studies provided by industrial partners can seamlessly be integrated into the platform.

'CAS- Biocatalysis' – A Novel Postgraduate Teaching Concept to promote the Transfer of Academic Knowledge from Investigative to Industrial Scale

Katrin Hecht (ZHAW, Wädenswil)

The competence center of biocatalysis (CCBIO) brings together academic and industrial partners within research projects to jointly develop biocatalytic processes for industrial application. Within this proposal (CAS – Biocatalysis), R&D efforts will be supplemented with a teaching concept which covers all aspects involved in setting up a biocatalytic process at industrial scale such as know-how in biology, chemistry, bioinformatics, process engineering as well as in law and economics.

The postgraduate Certificate of Advanced Studies course "CAS Biocatalysis" will consist of three modules:

- Basic biocatalysis and examples of industrial application (theory and experiments)
- Design of biocatalysts and evaluation of performance (theory and experiments)
- Legal/ economic aspects of biocatalytic processes (theory and case study)

Theoretical information will be provided in form of lectures as well as for self-study. Experimental work in the laboratory will give hands-on experience dealing with biocatalytic processes. The program will be open to university graduates in chemistry, biotechnology and related fields and employees with a long-term practical experience in these areas.

The initial CAS- Biocatalysis will be based on competences available at the ZHAW; further extension of the concept is planned by expansion of the module palette by involving other universities with experience in up-scaling, down-scaling or analytical methods. The final goal is to cover all aspects of the whole value-chain from gene to final product.

Symposium 'Industrial Biocatalysis'

Detailed Information on submitted proposals and their progress will be available on the CCBIO website (*www.zhaw.ch/ccbio/pgb*) and at the second symposium for 'Industrial Biocatalysis' which will take place on June 6–7, 2018 at the ZHAW in Wädenswil, Switzerland.

www.zhaw.ch/icbt/day-of-lifesciences

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