

JUNE 2011

NEWSLETTER 5

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Kick-off Meeting for the Granted Projects of the 2nd Joint Call, Warsaw, Poland, April 2011

FOREWORD

Dr. Maarten de Zwart | Coordinator of ERA-IB
NWO Division for Chemistry & Physical Sciences
The Hague, June 2011

With great pleasure I present to you this newsletter that shows the outcome of the 2nd joint call for proposals of ERA-IB. After a successful 1st call in 2008, partners in ERA-IB once more joined forces to fund excellent cross-border partnerships between industrial and academic industrial biotechnology research. This time we were able to fund 10 project consortia, with a total budget of 11.1 million euro, and in which in total 56 research groups participate.

The preparations for the joint calls in ERA-IB started in 2007, resulting in an integration of national and regional funding procedures which made a commonly executed programme possible. At that time, ERA-IB invited stakeholders from both the academic and industry sectors to discuss the topics that should be addressed in the calls. In January 2010, the 2nd jointly coordinated, transnational call for project proposals in Industrial Biotechnology was launched, once more with the subject: "Industrial biotechnology for Europe: an integrated approach".

The 10 2nd call granted projects will present themselves in this newsletter which they also have done during the kick-off meeting for granted projects in Warsaw, Poland, on 14 April 2011.

I hope you will enjoy reading about the granted projects in our 2nd call and that you will stay connected to the future activities of ERA-IB.

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ERA-IB 2ND JOINT CALL FOR PROPOSALS

ERA-IB has launched Europe's second jointly coordinated transnational call for multilateral research projects addressing: "Industrial biotechnology for Europe: an integrated approach".

With this call ERA-IB aims at establishing cross-border partnerships between industrial and academic IB research, improving and accelerating technology transfer, and strengthening European efforts to achieve sustainable industrial development. These goals should be achieved by implementing common calls for transnational R&D projects. The transnational collaboration on research as well as on funding level will contribute to strengthen the still fragmented European Industrial Biotechnology funding landscape.

In this call innovative and industrially relevant R&D research projects have been granted. The 2nd call was open for researchers in Belgium, Croatia, Finland, France, Germany, Poland, Portugal, Spain, Romania and The Netherlands.

To enable researchers to form project consortia, ERA-IB organised a partnering event on 2 February 2010 in Frankfurt, Germany.

On 31 March 2010 ERA-IB received 46 pre-proposals. After a selection by the ERA-IB expert panel, 25 full proposals were received on 30 June 2010. These full proposals were evaluated through peer review, resulting in 10 funded projects. The participating ERA-IB funding organisations allocated a total of 11.1 Million €. The projects will run at least 3 years.

Grants were awarded using a "virtual common pot" model. Through this model the call was jointly organised. There was a central call secretariat and the evaluation and selection processes were executed via commonly agreed procedures. The funding follows national or regional rules and each funding organisations funds only the research consortium members from its own country or region.

On 14 April 2011 ERA-IB organised a kick-off meeting for the granted projects in Warsaw, Poland. During this meeting all granted projects presented their research plans. Participants had the opportunity to meet other ERA-IB partners and thereby enhance their networks.

The ERA-IB partners have agreed to continue their work, to expand the ERA-IB network and to start preparations for future activities and new joint calls. We keep you updated in next editions of this newsletter. For the most recent developments and news regarding ERA-IB, also visit the ERA-IB website: www.era-ib.net

TOPICS INTEGRATED IN PROPOSALS

The title of the call was "**Industrial biotechnology for Europe: an integrated approach**".

ERA-IB wants to foster knowledge transfer from invention to innovation, i.e. from fundamental research into technically realisable and cost-effective products and technologies. Applicants needed to integrate several of the below given topics into the research proposal:

- * Novel enzymes and microorganisms for new and more efficient bioprocesses
- * Metabolic engineering for the improvement of industrial microorganisms, including synthetic biology approaches
- * Enzyme design combining rational and or evolutionary methods
- * Development of multi-enzyme processes and modular enzymes
- * Microbial stress under process conditions
- * Development of new platform chemicals, including biomonomers
- * Development of new and functionalised biopolymers
- * Process analytical technologies for improved bioprocess understanding
- * Scale-up of bioprocesses
- * Innovative down-stream processing and biocatalyst recycling
- * Biotechnological upgrading and valorisation of biorefinery byproducts

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Project coordinator

Dr. Steffen Rupp

Fraunhofer-Gesellschaft zur Förderung der
Angewandten Forschung e.V. | Germany

Project leaders

Prof. Christoph Syldatk

Karlsruhe Institute of Technology | Germany

Dr. Thomas Greiner-Stöffe

c-LEcta GmbH | Germany

Prof. Ludo Diels

Flemish Institute for Technological
Reserach | Belgium

Dr. Eddy Laeremans

Tomans Engineering Noord BVBA | Belgium

Dr. Dirk Develter

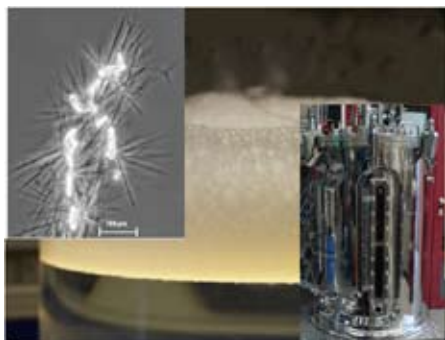
Ecover Belgium NV | Belgium

Prof. Michael O'Donohue

LISBP/INRA/CNRS/INSA | France

Novel Production Strategies for Biosurfactants (BioSurf)

Surfactants form an integral part of our everyday life with applications reaching far beyond our hygienic needs ranging from asphalt over food to fuel additives all the way to compounds with antibiotic activities. We aim at an increased replacement of petro-based surfactants by biosurfactants generated from renewable resources. Central topics are the identification of novel enzymes and microorganisms for new and more efficient biosurfactant production, understanding of cellular regulatory processes involved in biosurfactant production and consequent metabolic engineering for the improvement of the respective microorganisms also with respect to stress resistance during production, enzyme design combining rational and or evolutionary methods for enzymatic synthesis of surfactants and scale-up of bioprocesses including innovative down-stream processing using membrane technologies and biocatalyst recycling. These objectives will be achieved by connecting five technical work packages that address the entire biosurfactant value chain. The expected results include the identification of new, patentable microbial and enzymatically synthesized biosurfactants with significant economic exploitation potential for industrial applications. The construction of new production strains of biosurfactants with better productivity is envisaged as well as new enzyme products with advantageous properties towards the synthesis or modification of biosurfactants. In addition new technologies for fermentation and downstream processing of surfactants will be developed, including immobilized enzymes and *in situ* product removal from fermentations or biochemical conversions. By coupling of fermentation and separation technology we do not only expect to improve the down-stream process, but also envisage the improvement of surfactant production by avoiding product inhibition conditions. Exploitation is ensured by three companies. Ecover is a producer and supplier of detergents as well as biosurfactants. Ecover has both the marketing and distribution power to further develop the achieved R&D results into products and place them at the market. Enzymes and strains developed in the consortium will be commercialized by c-LEcta and engineering developments of *in situ* product recovery (ISPR) by Tormans, both SMEs.



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Project coordinator

Prof. Bruno Moerschbacher

Westfälische Wilhelms-Universität
Münster | Germany

Project leaders

Prof. Antoni Planas

Universitat Ramon Llull | Spain

Prof. Wim Soetaert

Bio Base Europe Pilot Plant vzw | Belgium

Dr. Katja Richter

Heppe Medical Chitosan GmbH | Germany

Prof. Wim Soetaert

Ghent University | Belgium



Scar-free wound healing promoted through high quality speciality chitosan (courtesy of Dr. Dominique Gillet, Mahtani Chitosan, Veraval, India)

Metabolic and Enzyme Engineering for the Biotechnological Production of Partially Acetylated Chitosans (ChitoBioEngineering)

Just as people have to communicate to build a community and, eventually, a society, cells need to communicate to build a tissue and, eventually, an organism. Cells have evolved a sophisticated molecular language, and complex sugar molecules form key words of this language. One example are sugar structures on the cell surface that inform cells of their neighbors and that lead to the distinction between self and non-self as a basis of our immune system and successful defense against pathogens. Understanding this molecular language of sugars is a prerequisite for the molecular understanding of many diseases such as cancer which in fact results from failed cellular communication. Recent advances in glycosciences suggest that subtle patterns of substitution, such as the pattern of sulfation in heparin, are the bearers of crucial information, e.g. for blood coagulation. And evidence is accumulating that related sugar molecules such as chitosans with a specific pattern of acetylation may interfere with this cellular communication, allowing us to influence cellular behaviour in a targeted manner.

The ChitoBioEngineering project aims at establishing, through genetic, metabolic, and enzyme engineering, biotechnological ways of producing fully defined, partially acetylated chitosan oligomers. Today's commercially available chitosans are produced chemically from chitin isolated from shrimp shell wastes. They can be well defined concerning their degree of polymerisation and degree of acetylation, but they are invariably characterised by a random pattern of acetylation (PA). We have recently hypothesised that the biological activities of chitosans, such as their antimicrobial, plant strengthening, immuno-stimulatory or wound healing activities, should be greatly influenced by their PA. However, no methods are available today for the production of chitosans with defined non-random PA.

Microbial genes will be used to drive the biosynthesis of chitosan oligomers with defined architecture, i.e. with a specific, non-random PA. We will use novel chitin synthases and chitin deacetylases stemming from our extensive gene discovery projects for heterologous expression in suitable micro-organisms to drive the production of a range of such oligomers which will be fully characterised using state-of-the-art analytical tools. Advanced genetic and enzyme engineering will optimise the expression of the genes and fine-tune the properties of the enzymes, respectively, and metabolic engineering will maximise the yield of the well defined chitosans. We will use our extensive experience as well as our wide-spread network within the chitosan scientific and industrial community to analyse the biological activities of these chitosans and to explore their potential applications in different market sectors, with a focus on cosmetics and pharmaceutical applications.

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Project coordinator

Prof. Lutz Heide

Eberhard Karls Universität Tübingen | Germany

Prof. Wolfgang Wohlleben

Eberhard Karls Universität Tübingen | Germany

Project leaders

Prof. Carmen Méndez

University of Oviedo | Spain

Prof. Jolanta Zakrzewska-Czerwińska

University of Wrocław | Poland

Dr. Francisco Moris

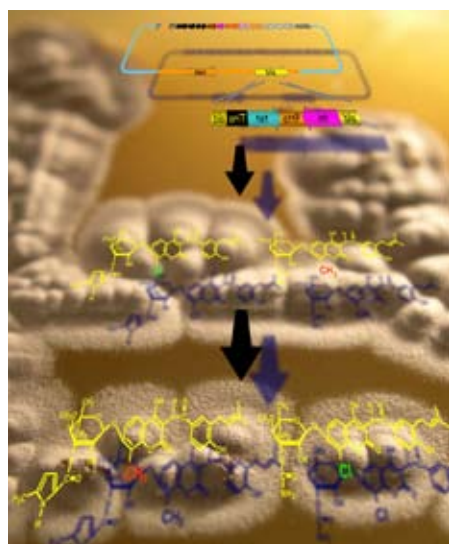
EntreChem SL | Spain

Maria Holmbäck, Kristiina Ylihanko

Galilaeus Oy | Finland

Prof. E. Takano

University of Groningen | The Netherlands



Genome mining for drug discovery: Activation of silent biosynthetic gene clusters (GenoDrug)

The GenoDrug proposal aims at the development of a new technology for drug discovery, i.e. the activation of previously silent biosynthetic gene clusters of microbial genomes. Microbial natural products have an outstanding track record as drugs and drug leads since more than sixty years. However, conventional screening programs increasingly result in the re-discovery of already known compounds. Sequencing of many microbial genomes, especially from actinomycetes, has now revealed that the genome of each strain contains gene clusters for the formation of 10-30 bioactive compounds ("secondary metabolites"). This implies that for any actinomycete strain most of its potential as producer of bioactive compounds is yet undiscovered. An economy which can harness this potential is likely to take an international lead in the development of new antibiotics, anticancer drugs and other pharmaceuticals in future. The bottleneck in the economical exploitation of this strategy is the development of technologies which allow the utilization of DNA sequence data of secondary metabolic gene clusters to generate the encoded compounds, in quantities sufficient for characterization, pharmacological testing and preclinical drug development. The GenoDrug proposal will develop such technologies and demonstrate their applicability in drug discovery by the identification of several novel bioactive compounds.

The principal objectives of the GenoDrug proposal therefore are:

Bioinformatic analysis of the available genome sequences of five actinomycete strains, expected to result in >100 new gene clusters which code for the biosynthesis of new bioactive compounds. Approximately 10 of these clusters will be selected for further investigation.

Development of molecular genetic strategies for the activation and expression of silent or low-expressed biosynthetic gene clusters. These strategies will focus on the use of:

- * global and pathway-specific regulators;
- * introduction of artificial (constitutive and inducible) promoters;
- * heterologous expression of gene clusters in genetically engineered host strains.

Production of new compounds from the engineered strains and testing for bioactivities and toxicities. The resulting compounds may represent valuable new drug leads, especially in the field of antibiotics and anticancer drugs.

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Project coordinator

Dr. Ton van Maris -

Delft University of Technology | The Netherlands

Project leaders

Prof. Isabel Sá-Correia

Technical University of Lisbon | Portugal

Prof. Elke Nevoigt

Jacobs University Bremen | Germany

Prof. Joaquín Ariño

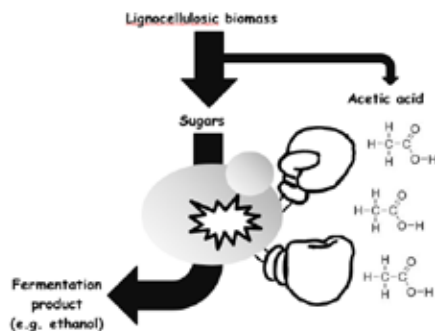
Universitat Autònoma de Barcelona | Spain

Integral Engineering of Acetic Acid Tolerance in Yeast ([INTACT])

Carbon efficiency and food security dictate that a substantial replacement of current petrochemical production by industrial biotechnology should be based on crude plant biomass hydrolysates as feedstocks rather than on refined, food-grade carbohydrates. The presence of acetylated polymers in these crude hydrolysates implies that acetic acid tolerance of industrial microorganisms is and will remain a key issue in the implementation of sustainable, non-food feedstocks in industrial biotechnology. The yeast *Saccaromyces cerevisiae*, one of the most important microorganisms in industrial production and in metabolic engineering, already has an innate degree of tolerance to weak organic acids and low pH. However, better understanding and improvement of the tolerance to acetic acid is essential for development, diversification and intensification of yeast-based bioprocesses in industrial biotechnology. Finding solutions to this problem is urgent, since the first full-scale factories for yeast-based production processes from lignocellulosic feedstocks (the first products will be biofuels) are anticipated within the next 5 years. Our highly complementary consortium will integrate classical genetic mapping, comparative genomics, genome-wide expression analysis, evolutionary engineering and global transcription machinery engineering with targeted genetic modification, with the aim to understand and rationally improve acetic acid tolerance in *S. cerevisiae*.

Key deliverables from the project will include:

- Target genes for functional analysis and metabolic engineering through the integration of classical genetic mapping and comparative genomics
- Selection procedures to improve acetic acid tolerance
- Metabolic engineering strategies to rationally improve acetic acid tolerance
- S. cerevisiae* strains with improved acetic acid tolerance



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Project coordinator

Prof. Karl-Heinz van Pée

Technische Universität Dresden | Germany

subcontractor: Prof. Philippe Jacques

University of Lille 1 | France

Project leaders

Prof. Jutta Ludwig-Müller

Technische Universität Dresden | Germany

Prof. Willem van Berkel

Wageningen University | The Netherlands

Dr. Jean-Yves Berthon

Greentech | France

Prof. Kaarina Sivonen

University of Helsinki - Finland

Prof. Wolfgang Wohlleben

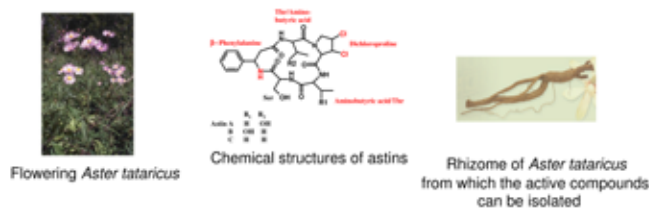
Eberhard Karls Universität Tübingen | Germany

Multi enzyme systems involved in astin biosynthesis and their use in heterologous astin production (MESIAB)

Astins are cyclic peptides isolated from the roots of the plant *Aster tataricus* and root extracts show antibacterial activity. Astin derivatives possess also a high anti-tumour potential. Since only very low amounts of astins can be isolated from plants and they are difficult to synthesise chemically without negative impacts on the environment. Therefore, this project aims at enhancing the production of astins using molecular genetic tools. Thus we will detect and clone the genes required for astin biosynthesis. To allow the detection of these genes, bioinformatic tools and sequence information from microbial nonribosomal peptide synthetases will be used to develop primers for peptide synthetases specific for the amino acids found in astins. Specific primers will also be constructed for the prolyl dehydrogenase and halogenase(s) catalysing the halogenation of prolyl residues. After detection, the genes will be cloned, sequenced and expressed in heterologous hosts such as bacteria or yeast. Alternatively, cell or organ cultures of aster can be used for homologous expression. After cloning and successful expression of the individual genes in heterologous hosts, the activity of the resulting nonribosomal peptide synthetases will be analysed using assays established in the groups working on this part of the project. Analogously, the gene(s) for the halogenase(s) and prolyl dehydrogenase will be expressed and analysed for activity. The genes of the individual enzymes will be combined in a "gene cluster" and will be introduced into heterologous host for over-expression. Over-expression of the astin biosynthetic "gene cluster" should result in enhanced production of astins. To allow the biotechnological production of astins, *Streptomyces* strains or alternatively plant cells will be used and a fermentation process will be developed by changing various

fermentation parameters. With larger quantities of astins available, screening using DNA arrays can be performed to analyse the influence of astins on gene expression. Special attention will be given to oncogenes and "vital" genes. The study of the genes highlighted by this method and their implication in the biological functions can bring new perspectives for the development of new pharmacological or cosmetic applications of astins.

Multi enzyme systems involved in astin biosynthesis and their use in heterologous astin production (MESIAB)



We will detect and clone the genes of

- non-ribosomal peptide synthetases
- flavin-dependent dehydrogenase
- flavin-dependent halogenase(s)

- express the genes and characterise the enzymes
- combine the genes and heterologously express them in plant cell cultures and in microorganisms for astin production
- analyse the various biological activities of astins



Project coordinator

Prof. Đurda Vasić-Rački

University of Zagreb | Croatia

subcontractor: *Mr. W. Bolt*

Micronit Microfluidics BV | The Netherlands

Project leaders

Prof. Martina Pohl

Forschungszentrum Jülich GmbH | Germany

Prof. Pere Clapés

Instituto de Química Avanzada de Cataluña-CSIC | Spain

Mr. Sergi Pumarola

Bioglane S.L.N.E. | Spain

Microreactor technology for continuous enzymatic reactions catalyzed by C-C-bond forming enzymes (MicroTechEnz)

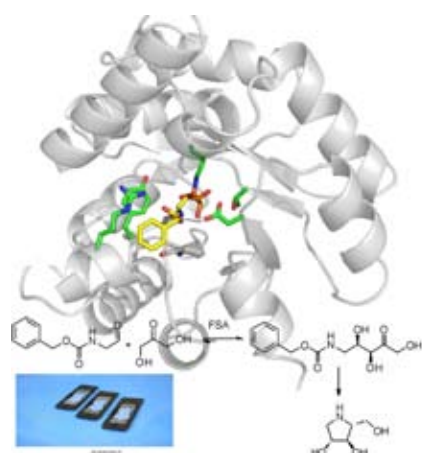
The present project deals with the evaluation of microreactor technology for enzymatic carbonylase reactions using thiamin diphosphate (ThDP)-dependent enzymes (TDEs) and D-fructose-6-phosphate aldolase from *E. coli* (FSA).

The main goal for the TDEs is to develop micro-reactor technology as a screening tool to identify the appropriate enzyme for a desired carbonylation reaction of two aldehydes yielding chiral 2-hydroxy ketones. Here, the prediction of the process relevant data concerning e.g. optimal substrate concentration, selectivity, enzyme stability and productivity with very small amounts of enzymes and chemicals will be tested using micro-reactor technology in comparison to conventional lab scale reactors.

The main advantage of FSA is that it dispenses with the need for laborious preparation of a sensitive phosphorylated reagent, dihydroxyacetone phosphate (DHAP), essential for DHAP-dependent aldolase, and it is currently used for the large scale production of D-fagomine. Notwithstanding the obvious advantages, some emerging issues limit its broad synthetic applicability while others can be significantly improved making them attractive from industrial point of view. Among them, are the following:

- A) Concerning the acceptor substrate selectivity, substrate inhibition, and the thermodynamic limitations of the catalyzed reactions.
- B) Improving performance by cascade reactions with in situ aldehyde generation.
- C) Improving molecular diversity by cascade two-aldol additions with in situ product formation. These issues can be effectively optimized in micro-reactors and/or in combination with protein engineering.

The project would bring new insights into green chemical syntheses reactions which are of vital interest to the field of high technologies, such as industrial biotechnology and approve a new concept for the production of enantiomerically pure diols and iminocyclitols. Technology transfer to end users, who are involved in the project, will be realized. Micro-reactors integrating oxidation, aldol reaction, enzyme separation and downstream processing are of utmost importance to develop a competitive process and the present project will provide technological solutions and will represent the first real example of industrial biotechnology development of an active process using aldolases.



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Project coordinator

Prof. Martin Bertau

TU Bergakademie Freiberg | Germany

Project leaders

Dr. Antje Eichler / Dr. Thorsten Oeser

Junior Research Group Industrial Biotechnology
Germany

Prof. Wladimir Reschetilowski / Daniel Däumer MSc

Technische Universität Dresden | Germany

Dr. Thomas Greiner-Stöffele

c-LEcta GmbH | Germany

Prof. Andrzej Kolinski / Dr. Claudia Feller

University of Warsaw | Poland

Prof. Volker Hessel

Eindhoven University of Technology | The Netherlands

Combining efforts in enzyme and process engineering to improve access to multifunctional chiral intermediates (ProAChIm)

Most of the top-selling drugs today, like the cholesterol lowering "Atorvastatine", are chiral, i.e. they contain one or more stereogenic centres. To produce these chiral drugs, small chiral building blocks are required as a starting material. Hence provision and thus synthesis of the latter in an efficient, economical and preferentially ecological way is of increasing importance in order to ensure the supply of state-of-the-art drugs at a reasonable price.

This project addresses the latter issue by focusing on the synthesis of a certain group of chiral building blocks named α -amino-alcohols. These substances are known to be valuable in the synthesis of various β -sympathomimetics, anti-parkinsons-disease-drugs and even antibiotics.

Enantiomerically enriched α -amino-alcohols are theoretically accessible in an ecological and economical way by using enzymes. However, most of the amino-alcohol producing enzymes known today only accept a limited number of substrates and show unsatisfying stereoselectivity. Thus the first aim of this project is to identify new enzymes which are subsequently optimised and adjusted to the process needs using mutagenesis guided by in silico enzyme modelling.

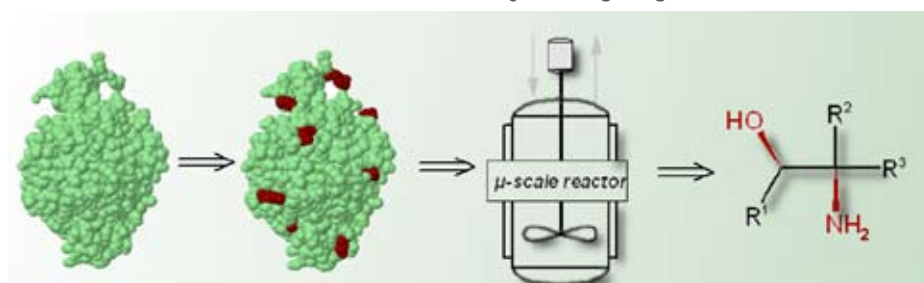
A further challenge which hampers application of enzymes in biocatalytic synthesis of chiral amino-alcohols lies in the reversibility of the reaction. As a consequence a high yield is only achievable if measures are taken to shift the equilibrium of the reaction towards the side of the products. The second aim of the project will attend to that by investigating consecutive reactions coupled to the primary one in order to make

the overall reaction practically irreversible.

This will also be facilitated by innovations in process chemistry. Thereby the project is aimed at running the process in micro-structured reactors allowing operation in novel process windows, in which the reaction is intensified and run continuously.

With the established project consortium

bringing together experts from various fields such as biochemistry, bioinformatics, industrial chemistry and micro-reactor engineering, the project is expected to yield new enzymes and a new process which together will improve access to enantiopure α -amino-alcohols. As enzymes and the process are expected to be commercially available, industry is enabled to benefit from the results of the project.



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Project coordinator

Prof. Christian Wilhelm
Leipzig University | Germany

Dr. Gerhard Kerns
Leipzig University | Germany

Project leaders

Dr. Martina Bremer
Technische Universität Dresden | Germany

Prof. Martin Bertau / Dr. Michael Katzberg
TU Bergakademie Freiberg | Germany

subcontractor: *Dr. Carmen Boeriu*
Wageningen University | The Netherlands

Dr. Tarja Tamminen
VTT - Technical Research Centre Finland | Finland

Prof. Mircea Ioan Popescu
Applied Biochemistry and Biotechnology Center
Romania



Development of a process for the utilization both the carbohydrate and the lignin content from lignocellulosic materials of annual plants for the production of valuable products (Products from lignocellulose)

The general aim of the project is the development of a process for the utilization of both the carbohydrate and the lignin content from lignocellulosic materials of annual plants, particularly wheat or maize straw. The investigations basically concern (i) the development of a pre-treatment process, which allows the separation of both the lignin and the carbohydrate content of lignocellulosic raw materials, (ii) the development of a fungal enzyme complex optimized for the saccharification of the carbohydrate content of lignocellulose in a simultaneous saccharification and fermentation (SSF) process, (iii) investigations on the SSF-process, using model microorganism-strains for the production of platform chemicals, like fermentation alcohols, and (iv) the modification of the separated lignin for the production of fibre-reinforced biopolymers as well as for the production of fine chemicals.

Results from subproject i, ii and iii will be invaluable as the projects furthermore aims for investigating the performance of the SSF-process and the developed enzyme-complex not only at lab but also up to pilot scale.

For the planned investigations concerning the production of fibre-reinforced biopolymers on the basis of wheat straw lignin we are going to include expertises from the ERA-IB-project *VOC reduction of lignin containing materials* (ERA-IB first call) in which the utilization of kraft lignin for the production of fibre-reinforced biopolymers is investigated. Lignin-modifying enzymes and invaluable knowledge concerning reduction of VOC emissions in kraft lignin have already emerged from the latter project thus providing a strong basis for this new project. Finally the resulting processes will be evaluated economically in order to show whether it is commercially viable. As the main risk for the commercial utilization of the project results are enzyme costs and the effectiveness of the pre-treatment process, special attention will be paid to these objectives.



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Project coordinator

Dr. Lars Blank

TU Dortmund University | Germany

Prof. Andreas Schmid

TU Dortmund University | Germany

Prof. Ralf Takors

University of Stuttgart | Germany

Dr. Susann Müller

Helmholtz Centre for Environmental Research UFZ
Leipzig | Germany

Prof. Han de Winde

Delft University of Technology | The Netherlands

Prof. Bruno Zelic

University Zagreb | Croatia

Prof. Victor de Lorenzo

Centro Nacional de Biotecnología, Consejo
Superior de Investigaciones Científicas | Spain

Dr. Marcel Wubbolts

DSM | The Netherlands

Dr. Andreas Karau

Evonik Rexim S.A.S. | France

Pseudomonas 2.0: industrial biocatalysis using living cells (Pseudomonas 2.0)

The potential of non-pathogenic *Pseudomonas* as a platform host for Industrial Biotechnology has been discussed for decades in Europe, mainly inspired by its metabolic versatility, ease of genetic programming and high solvent tolerance. These properties enable growth in the presence of a second phase of toxic solvents, such as styrene or octanol, or high concentrations of inherently toxic compounds originating from cheap renewable feedstocks (e.g., biomass hydrolysates), like furaldehydes. Furthermore, *Pseudomonas* displays an extensive enzymatic inventory (e.g., hydrocarbon degradation pathways), and the potential to regenerate redox cofactors at a high rate (Blank et al., FEBS J. 2008 275/20). On this background, it comes as a surprise that *Pseudomonas* strains are still a minor player as *genomic and metabolic chassis* for the Bio-Industry, where most key processes are still dominated by *Bacillus*, *Corynebacterium glutamicum*, and *Escherichia coli*. We argue that by tackling and overcoming the few molecular bottlenecks that still make non-pathogenic *Pseudomonas* less efficacious than bacterial alternatives, we can contribute to place European Bio- Industry into a prime position within the global Biotechnology scenario. Novel biocatalytic processes, must successfully overcome economic barriers before realization. This necessitates high solvent tolerance, a high rate of redox cofactor regeneration, carbon efficiency, and biocatalytic stability. Preferably, these parameters determining whole-cell biocatalyst performance are optimized simultaneously. Explicitly, this performance has to be transferable to industrial environments, including large scale fermenters, which will be a main focus of *Pseudomonas 2.0*. The transfer of excellent academic research findings into industrially useful technology will be achieved by truly cooperative work between the 6 academic partners and Rexim-Evonik and DSM, 2 of the major European chemical companies. The outcomes of the project *Pseudomonas 2.0* will propel the development of Industrial Biotechnology in Europe, supporting a bio-refinery approach in the chemical industry on the basis of the European Lead Market Initiative.

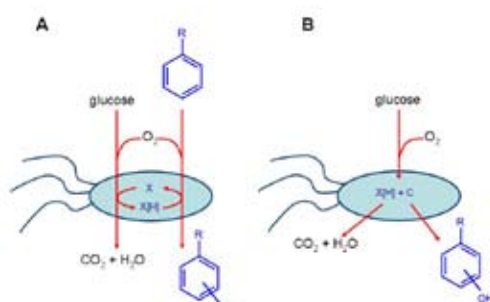


Figure 1: Biocatalytic aromatics production via A) biotransformation; B) fermentative. X[H]: reducing equivalents

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Netherlands Organisation for Scientific Research (NWO), The Netherlands



Spanish Ministry of Science and Innovation (MICYT), Spain



French Environment and Energy Management Agency (ADEME), France



Executive Agency for Higher Education, Research, Development and Innovation Funding (UEFISCDI), Romania



The Science and Technology Foundation (FCT), Portugal



Ministry of Science, Education and Sports (MSES), Croatia



Federal Ministry of Education and Research (BMBWF), Germany



Danish Agency for Science Technology and Innovation (DASTI), Denmark



Chief Scientist Office, Ministry of Health (CSO-MOH), Israel



Ministry of Science and Technology (MOST), Israel



The Spanish Science and Technology Foundation (FECYT), Spain



Belgian Science Policy (BelSPO), Belgium



Research Centre Jülich (FZJ), Germany



Agency for Renewable Resources (FNR), Germany



Saxon State Ministry of the Environment and Agriculture (SMUL), Germany



Finnish Funding Agency for Technology and Innovation (Tekes), Finland



National Centre for Research and Development (NCBiR), Poland



Technology Strategy Board (TSB), UK

ABOUT ERA-IB

ERA-NET "Towards an ERA in Industrial Biotechnology" ERA-IB www.era-ib.net is an ERA-NET funded from the European Community's sixth Framework programme. The objective of the ERA-NET scheme is to promote the cooperation and coordination of research and development activities carried out at national or regional level in the Member States and Associated States.

In the ERA-NET "Towards an ERA in Industrial Biotechnology" 18 partners from 13 different countries join forces to reduce fragmentation of national research efforts in the area of Industrial Biotechnology. ERA-IB started in May 2006 and will finalize in 2011.

ERA-IB's objective is to foster economic and academic Industrial Biotechnology players in sharing risks, costs and skills related to innovation in order to develop new knowledge, new products, technologies or supply services that could reach the market more efficiently. It is aimed at establishing cross-border partnerships between industrial and academic Industrial Biotechnology research, improving and accelerating technology transfer, and strengthening European efforts to achieve sustainable industrial development. These goals should be achieved by implementing common calls for transnational R&D projects. Other activities of ERA-IB include a systematic exchange of information and best practices between the involved national funding agencies.

ERA-IB closely collaborates with the Industrial Biotechnology section of the European Technology Platform for Sustainable Chemistry (ETP-SusChem) and the European Association for Bioindustries (EuropaBio).

Industrial Biotechnology

Industrial Biotechnology is a key technology to realise the Knowledge-Based Bio-Economy and to transform life sciences knowledge into new sustainable, eco-efficient and competitive products and technologies. Increasing our understanding of physiological and regulatory processes in cells and microorganisms will help to unlock the potential of biological systems for numerous industrial sectors including, amongst others, the chemical, pharmaceutical, textile, paper and food industries. In order to take innovation to a level where there will be economic benefit there are key technological challenges to be overcome by focused research investment. In particular, knowledge transfer from fundamental research into technically realizable and cost-effective products and technologies is a bottleneck.