

CeBiTec – Quarterly

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6th International CeBiTec Research Conference on New Techniques, Substrates and Products for Bioprocesses

From September 26 to 28, 2016, the CeBiTec organized the 6th International CeBiTec Research Conference (ICRC) on Advances in Industrial Biotechnology at the Center for Interdisciplinary Research (ZiF) of Bielefeld University which was chaired by Prof. Volker F. Wendisch (CeBiTec & Biology). The ICRC started as a series of annual alternating conferences on industrial biotechnology in 2010 focusing on important research areas in the life science fields of Microbes and Industrial Biotechnology, Cell Culture Technology and Microalgae Biotechnology. Industrial biotechnology is firmly established in several industries such as food and feed, and is a central pillar of the knowledge-based bio-economy. There is currently considerable interest in applying novel technological advances such as 'omics, systems biology or synthetic biology approaches to develop the field further, particularly with a goal of increasing the



sustainability of chemical production. New Techniques, Substrates and Products for Bioprocesses in the field of Microbial Biotechnology took center stage in the 6th ICRC 2016. Technological advancements covered genetic techniques such as CRISPR/Cas or biosensors, synthetic biology approaches to developing microorganisms as cell factories or microfluidics for screening and characterizing enzyme and cell functions. The utilization of C1 carbon sources such as methanol, formate and carbon dioxide by natural and metabolically engineered bacteria was discussed in the opening session. The product class of the terpenoids was covered in a number of presentations that highlighted how plant biosynthetic pathways may be characterized with the help of yeasts, algae and bacteria that subsequently can be developed as production hosts for terpenoids. Various classes of fine chemicals and their biotechnological production were discussed with a focus on *Corynebacterium glutamicum* as host. To illustrate how research breakthroughs may lead to commercially successful products examples of the industrial production processes in the chemical and food industries were presented. 87 scientists from academia and industry from 9 countries also discussed the newest developments in all covered thematic subjects as poster presentations.

Meeting of the Scientific Advisory Board

After a strategical reorientation and reorganization of the CeBiTec a new Scientific Advisory Board (SAB) has been elected by the *Rektorat* of Bielefeld University. The board members are Dr. Rolf Apweiler (EMBL – European Bioinformatics Institute, Cambridge, United Kingdom), Prof. Dr. Sabine Flitsch (The University of Manchester, United Kingdom), Dr. Ralf Kelle (Evonik Industries AG Halle/Westfalen, Germany), Prof. Dr. Dr. Thomas Lengauer (Max-Planck-Institut für Informatik, Saarbrücken, Germany), Prof. Dr. Ralf Reski (Universität Freiburg, Germany), and Prof. Dr. Bettina Siebers (Universität Duisburg–Essen, Essen, Germany). On December 5 and 6, 2016, the SAB visited the CeBiTec for a constitutive board meeting and used the opportunity to get an overview about actual developments and future strategies of the institute. The scientific director Prof. Dr. Olaf Kruse started with an overview talk providing essential developmental steps during the last years, the actual structure of the CeBiTec and illustrated the scientific activities within the two main research areas on the basis of selected exemplary projects. Finally O. Kruse emphasised on the high level performance statistics of the CeBiTec. The visit of the SAB also included a guided tour of the CeBiTec, presentations of the technology platforms and future research strategies, as well as a poster session with young scientists. The SAB is going to summarize its statements and recommendations in a report to the *Rektorat*.



New SAB of the CeBiTec (left to right): Dr. Rolf Apweiler, Prof. Dr. Sabine Flitsch, Prof. Dr. Bettina Siebers, Dr. Ralf Kelle, Prof. Dr. Ralf Reski (missing: Prof. Dr. Dr. Thomas Lengauer); and representatives of Bielefeld University: Prof. Dr. Martin Egelhaaf, Prof. Dr. Thomas Noll, Prof. Dr. Olaf Kruse.



Distinguished Lecture by Prof. Dr. Birger Lindberg Møller, Center for Synthetic Biology, University of Copenhagen



“Synthetic plant biology: Light-driven production of structurally complex diterpenoids” was the title of Prof. Dr. Birger Lindberg Møller’s talk in the CeBiTec Distinguished Lecture Series. On the invitation of Prof. Dr. Olaf Kruse, Prof. Møller, Director of the Center for Synthetic Biology, University of Copenhagen (Denmark) visited the CeBiTec on November 21, 2016. In the plenary hall of the Center for Interdisciplinary Research (ZiF) of Bielefeld University he reported about the manifold application of diterpenoids as pharmaceuticals, fragrances, natural plant growth promoters, as food ingredients such as flavours or as colourants and spices. After explaining the biosynthetic routes of these compounds Prof. Møller reported about the development of an integrated biochemical and func-

tional genomics approach to identify the genes encoding a desired pathway and gave examples of pathways elucidated with this approach.

iGEM Team Bielefeld–CeBiTec 2016: Evobodies – molecular speed dating

On October 31, 2016, the iGEM team from Bielefeld was rewarded with a gold medal for the seventh time in a row. The design of a system for binding protein development in *E. coli* was one of the best projects at the Giant Jamboree in Boston. Our team impressed the judges, which were composed of researchers from various fields in context of synthetic biology. Eleven students of different life science programs at Bielefeld University had the idea to replace the current development of antibodies in animals by a new bacteria-based system. Therefore, they produced a library of binding protein encoding plasmids. Candidates were selected from this library via selection. A bacterial two hybrid system (similar to a yeast two hybrid system) was implemented for the selection of high affinity binding proteins. The strength of the interaction is translated into a resistance against a selection marker. Only cells with strong binding proteins are able to survive the following selection. These initial binders are further optimized by *in vivo* mutagenesis of the corresponding protein encoding sequences on the plasmids. The submission and extensive characterization of this plasmid-specific mutagenesis system was one of the major achievements. The total system comprises a continuous cycle of mutagenesis and selection to find the optimal binding protein.

www.igem-bielefeld.de or 2016.igem.org/Team:Bielefeld-CeBiTec



iGEM-team Bielefeld–CeBiTec of 2016 at the famous Massachusetts Institute of Technology (MIT), (back, left to right): Judith Kampa, Fabian Roeloffs, Marius Schöller, Sebastian Perez Knoche, Niklas Hoffmann, Carsten Hain, Pascal Schmidt, Bianca Frommer, and Boas Pucker (supervisor); (front, left to right): Mikail Sahin, Marten Linder, Cassandra Königs, and Julian Droste (supervisor).

Project week “systems biology” for students from upper secondary school

From September 17 to 23, 2016, the project week “systems biology” took part in the students’ lab teutolab–biotechnology. The specialised project course of the Friedrich–v. Bodelschwingh–Gymnasium Bielefeld took the chance to put biological experiments combined with mathematical modelling into practice. The students received insights in the interdisciplinary field of systems biology, where maths, physics, informatics and engineering are applied to highly

developed biological methods for understanding complex biological systems.

In the beginning, the students got an introduction to systems biology and mathematical modelling by talks of a biologist and a mathematician. Subsequently, they worked out the theoretical background of gene regulation. For the practical part, they planned and conducted some experiments to measure the transcription activity of the lactose (*lac*) operon under different growth conditions by photometric measurement. The students used the data to generate graphs of bacterial growth and of activity of enzymes to derive mathematical rules of these biological activities. The goal of this method is the transfer to other systems, so that general conclusions and predictions can be drawn. In a second practical phase, the activity of a promoter was made visible by fluorescence microscopy. After the practical lab work and the mathematical modelling the students presented their experiments and results to the other students of their school by posters. The project was supported by the Joachim Herz Stiftung and will be offered to more students of different schools in the following years.

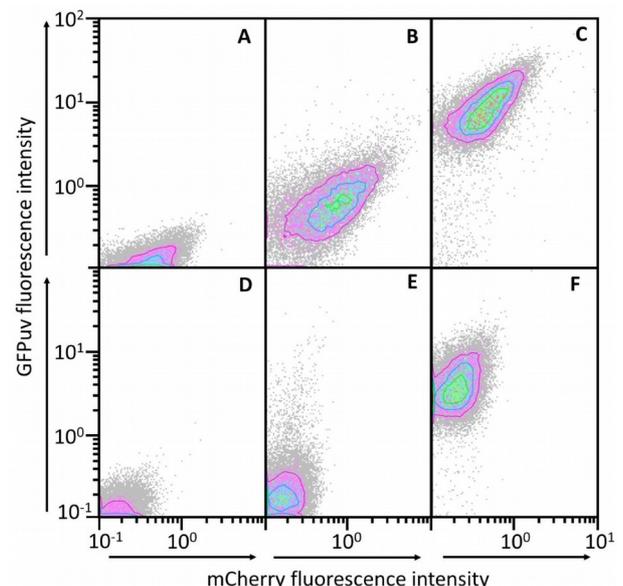


Genome-based genetic tool development improved methanol-based production by *Bacillus methanolicus*

In a collaboration with Prof. Dr. Trygve Brautaset and colleagues from Trondheim, Norway, the group of Prof. Dr. Volker Wendisch developed genetic tools for the methanol utilizing *Bacillus methanolicus* in a genome-inspired manner. This thermophilic methylotrophic Gram-positive bacterium is able to overproduce amino acids from methanol. This C1 carbon source does not compete with use in human or animal nutrition. Our previous RNA-seq analysis together with the Technology Platform Genomics (Irla M, Neshat A, Brautaset T, Rückert C, Kalinowski J, Wendisch VF. *BMC Genomics*. 2015 16:73) helped to identify a mannitol inducible promoter and a putative mannitol activator gene *mtIR*. The mannitol inducible promoter was characterized and after changing the promoter sequence to the consensus and over-expression of *mtIR* used for controlled gene expression using fluorescent reporter proteins and a flow cytometry analysis.

In addition, the xylose-inducible system from *B. megaterium* was used. Four different replicons for expression vectors (rolling circle and theta type replication modes) were characterized with respect to their copy number and stability. A two-vector system for combinatorial gene expression control by mannitol and/or xylose was developed. As a biotechnological application example, methanol-based production of cadaverine was improved from 11.3 to 17.5 g/L. As another example, methanol-based production of γ -aminobutyric acid (GABA) that may be used as monomer for production of the biodegradable plastic polyamide 4 has been established using these tools (Irla M, Nærdal I, Brautaset T, Wendisch VF. *Ind Crops Prod*. 2017 in press, 10.1016/j.indcrop.2016.11.050). The developed inducible promoter systems and compatible theta- or rolling circle-replicating vectors are an important extension of the poorly developed *B. methanolicus* genetic toolbox and are valuable for genetic engineering and further exploration of this bacterium.

Irla M, Heggeset TM, Nærdal I, Paul L, Haugen T, Le SB, Brautaset T, Wendisch VF. *Front Microbiol*. 2016 7:1481



A new project addressing rapeseed protein quality started

With funding from the Federal Ministry of Education and research (BMBF) a three year grant has been awarded to the group of Prof. Dr. Bernd Weisshaar for a project with the title “Rapeseed as a domestic protein source of excellent quality for human consumption”. The project uses the acronym RaPEQ, has seven partners and one associated supporting company, and is coordinated at CeBiTec.

Rapeseed is an important oil crop cultivated in Germany. In addition to its high seed oil content, rapeseed also provides a high content of valuable protein. Currently, this protein is used mainly for feed. The aim of the RaPEQ project is the development of new options for the application of rapeseed protein which presents a high nutritional value in food production. To reach this aim, targeted approaches of molecular breeding will be used to increase rapeseed protein content, and to improve the quality of the protein fractions. The project part carried out at CeBiTec will focus on rapeseed genomics and mapping of relevant traits by high-throughput sequencing. In the longer term, the project will contribute to develop improved rapeseed varieties with variety protection as property right which due to the breeders privilege exhibits open source features. RaPEQ will contribute to strengthening Germany as an optimal place for science and economy, and it will strongly support the establishment of knowledge-based bio-economy.

Further information about the project on Pflanzenforschung.de

Continuation of the CLIB graduate cluster as PhD study program Industrial Biotechnology

The state North Rhine-Westphalia together with Bielefeld University, Dortmund University and Düsseldorf University funded a PhD program in Industrial Biotechnology, the CLIB graduate cluster (Chairman Prof. Dr. Jörg Pietruskza, Vice-Chairman-Research Prof. Dr. Volker Wendisch and Vice-Chairman-Teaching Prof. Dr.-Ing. Gerhard Schembecker). This unique program started as jointly coordinated collaboration between the three universities in 2009 and the second and final elongation period ended in December 2016. In total, 144 PhD fellowships were granted, some of which are still ongoing. Besides completion of their PhD thesis projects, the 48 CLIB graduates in Bielefeld published 211 scientific publications, filed four patent applications and founded a spin off company.

In Bielefeld, Dr. Iris Brune served as local coordinator through the whole funding period. We, the CLIB GC PhD students and faculty, are very grateful for having been guided perfectly through retreats, selection workshops, finding the right companies for internships, accounting of funding for fellows and associated PhD students and catalysing the career paths of many Bielefeld CLIB graduate cluster PhD students.

After the ending of the final elongation period in December 2016, the cluster will live on as PhD study program Industrial Biotechnology offered both by the Technical Faculty and the Faculty of Biology at Bielefeld University. Funded by other sources and pursuing research projects in Industrial Biotechnology, PhD students may enrol in the PhD program Industrial Biotechnology. Their rights and obligations are detailed in the PhD study program and coincide with those of CLIB-GC students. We are looking forward to continue research in Industrial Biotechnology through successful PhD thesis projects.



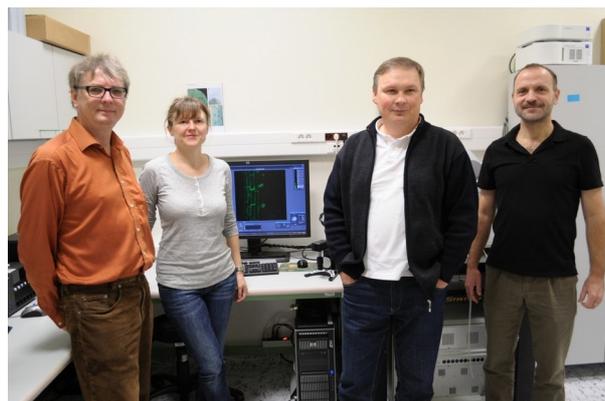
Agreement on scientific co-operation between the Palacký University Olomouc and CeBiTec

In 2016 an agreement on scientific co-operation was signed between the Palacký University Olomouc and the CeBiTec. The Palacký University Olomouc is a university with long-standing tradition. Founded in the 16th century, it is the oldest university in Moravia and the second-oldest university in the Czech Republic. With about 22,000 students, the Palacký University is of comparable size to the Bielefeld University.

The scientific partner of this collaboration is Prof. Dr. Jozef Šamaj who heads the Department of Cell Biology at the Centre of the Region Haná for Biotechnological and Agricultural Research. The Centre is comparable to the CeBiTec since it integrates different research activities in the field of plant biotechnology. The Centre of the Region Haná for Biotechnological and Agricultural Research is based on cooperation between the Palacký University in Olomouc, Institute of Experimental Botany, Czech Academy of Sciences and Crop Research Institute. Each partner has contributed their own specific know-how, their experts and top quality technologies.

The research group of Prof. Šamaj has two main research topics: “Plant signalling networks” and “Development of polarity in plants”, both depending on signal transduction cascades, cytoskeleton, and endomembranes. The research team is using integrated cell biological, proteomic, genetic, physiological, and biochemical approaches in order to better understand perception and transduction of information in plants in relation to the plant stress physiology (both abiotic and biotic stress). The group is studying interactions of plant with environment, as well as biotic interactions with soil bacteria (legume–Rhizobium symbiosis) in two plant model species; Arabidopsis and Medicago. Advanced cell biology techniques, including live microscopy, are well established to study the interplay between mitogen-activated protein kinases (MAPKs), endomembranes (endosomes), and the cytoskeleton during plant development and adaptation to stress. Both partners agreed to execute research concerning alfalfa and barley interactions with beneficial (Rhizobia) and pathogenic (Fusarium, Puccinia) microbes.

In October 2016 Dr. Hanna Bednarz and Prof. Dr. Karsten Niehaus (CeBiTec) visited the Palacký University in Olomouc to discuss results of an earlier research stay using the Zeiss Lightsheet Microscope Z.1 and different confocal systems. In addition, in 2017 the well-established co-operation in the field of Proteomics will be extended to metabolomics of barley.



Zeiss Reference Laboratory in the Department of Cell Biology at the Centre of the Region Haná for Biotechnological and Agricultural Research (Czech Republic). In front of the Zeiss Lightsheet Microscope Z.1 are (left to right) Prof. Dr. Karsten Niehaus, Dr. Hanna Bednarz, Prof. Dr. Jozef Šamaj and Dr. Miroslav Ovečka.

Cloud computing at the Bioinformatics platform of the CeBiTec

In the frame of the German Network for Bioinformatics Infrastructure (de.NBI) the Federal Ministry of Education and research (BMBF) selected – besides five other universities – the CeBiTec of Bielefeld University to establish the so-called de.NBI Cloud. Cloud computing is considered to represent a future-oriented compute infrastructure.

Advances in modern technologies pose huge challenges to research in life sciences. (Post-)Genomic or image based analyses generate enormous data sets, rapidly increasing with every new technology generation. Even small research labs can easily generate “big data”. However, the analysis becomes a major bottleneck for most labs, as local compute resources are often limited. Within de.NBI, the cloud will contribute to solve the bottleneck of compute resources. Germany-wide, the BMBF has spent 6 million Euro for the establishment of the de.NBI cloud, the CeBiTec participated with 1.2 million Euro. In addition, the BMBF supports the whole cloud initiative with six scientific positions which

were distributed amongst the selected universities. At the CeBiTec, Dr. Alexander Sczyrba is responsible for establishing the de.NBI cloud. Staff of the Bielefeld Bioinformatics Server and the Bioinformatics Resource Facility has already set up a prototype cloud together with Gießen University, CeBiTec's partner within the Bielefeld–Gießen (BiGi) service center. The environment is based on OpenStack, a widely-used software platform for cloud computing, offering Infrastructure as a Service (IaaS) to the de.NBI network. The de.NBI service centers will develop Platform as a Service (PaaS) and Software as a Service (SaaS) applications, providing bioinformatics developers and data scientists with powerful compute resources. The de.NBI cloud will also serve as a resource for training courses. In 2016, two de.NBI training courses made use of the cloud environment: the Joint de.NBI and German Center for Infection Research (DZIF) Training Course on Targeted and Untargeted Metagenome Analysis took place at Bielefeld University and the Cloud Computing Tutorial at the German Conference for Bioinformatics (GCB) in Berlin.



Contact persons for the establishment of the de.NBI cloud at the CeBiTec (left to right): Prof. Dr. Jens Stoye, Prof. Dr. Alfred Pühler, Dr. Alexander Sczyrba.

Research funds to promote transdisciplinary and medically relevant cooperations on research

The research funds *Forschungsfonds zur Förderung transdisziplinärer, medizinrelevanter Forschungsk Kooperationen in der Region OWL (Ostwestfalen-Lippe)* of the Bielefeld University was set up along with the establishment of the new university clinics in Minden and Herford. The aim of the funds is to encourage the area of medicinal research in the region and to support the network of the new facilities for medicinal education with the Universities of Bochum and Bielefeld. Within the first application round in December 2016, two projects from the CeBiTec succeeded in convincing the scientific panel. Both projects will start in 2017.

The research group Microbial Genomics and Biotechnology (Prof. Dr. Jörn Kalinowski) will cooperate with the Department of Dermatology, Johannes Wesling Medical Centre, Minden (Prof. Dr. Rudolf Stadler) on genomic analyses of cutaneous T-cell lymphomas. The goal of this project is the comparative study of genomic signatures in early and progressed states of this disease, especially with regard to the cell cycle and the JAK/STAT signalling pathway. Next-generation sequencing of disease gene panels and exomes as well as microarray expression analyses will be performed at the Technology Platform Genomics (CeBiTec) in order to identify disease-relevant mutations in patients suffering from cutaneous T-cell lymphoma. This data is then used in a systems biology-approach to reconstruct signalling and metabolic pathways to deepen our understanding on the molecular causes and the mechanisms involved. The project duration is three years and a PhD position is funded during this time.

The group Proteome and Metabolome Research of Prof. Dr. Karsten Niehaus will continue the research on molecular imaging of the tumor development by MALDI mass spectrometry imaging. Previously in 2016, this method for chemical imaging could be significantly enhanced enabling now for visualization of very small metabolites and molecules under 250 Da, after a novel matrix was designed, synthesized and successfully established (Giampà et al. 2016; *Chem Commun.* 52, 9801–9804). Along other molecules, several specific so called oncometabolites could be detected and visualized in single measurements in human brain tumour samples. Interestingly, these targets visualize *ex situ* the energy and hypoxia state of the tumor ("Warburg effect"), the defect in ion channels (local elevated chloride concentration), as well as the 2-HG metabolite (IDH1/2 mutation), which is relevant in the diagnosis and treatment decision making.

In the upcoming project, the potential of the MALDI mass spectrometry imaging method as a supporting tool for the pathologists in the clinical routine and for the basic research of cancer physiology and progression will be followed up and elevated “from-bench-to-bedside”. The new project will be coordinated by Dr. Hanna Bednarz (CeBiTec) in cooperation with Prof. Dr. Udo Kellner and PD Dr. Ulrich J. Knappe (Johannes Wesling Klinikum Minden).

CeBiTec contributions to the data science initiative of Bielefeld University

A university-wide initiative with the working title “Bielefeld Center for Data Science” is connecting interests in data science in a wide range of disciplines: It combines existing competence in statistics and machine learning as well as in application areas in order to turn quantitative and qualitative data into knowledge and value. The 3rd Round Table of the initiative organized by Prof. Dr. Reinhold Decker, the vice-rector for Information Management, took place on December 12, 2016. It is obvious that the CeBiTec research area Large Scale Genomics and Big Data Bioinformatics should be a member of the initiative. This was the reason why Prof. Decker invited two representatives of the CeBiTec, namely Dr. Alexander Sczyrba and Prof. Dr. Alfred Pühler, to take part in the 3rd round Table meeting. As a first step, a short text describing the CeBiTec bioinformatics platform as well as the contribution of the CeBiTec to the German Network for Bioinformatics Infrastructure (de.NBI) was produced for inclusion into the initiative’s web page. It should be mentioned that the initiative is especially interested in the analysis of large data sets by cloud computing, which represents main parts of the CeBiTec bioinformatics platform. The Faculty of Technology is also involved in the initiative and plans to establish a new Professorship for Computational Data Science with the focus on bioinformatics.

iGEM Team Bielefeld–CeBiTec 2017 and the new iGEM Bielefeld website

The iGEM team Bielefeld–CeBiTec for the competition of 2017 consists of 15 highly motivated students from different life science programs. The team size was increased due to a sensational interest in iGEM among the students. All members are already working very hard on different specific tasks. Discussions about new and exciting topics are of utmost importance for the development of a new project. Moreover, the team is looking for interested sponsors and partners to finance the project and the trip to the Giant Jamboree in Boston next November.

Since the beginning of January 2017, the website of all iGEM Bielefeld teams (www.igem-bielefeld.de) is hosted at the CeBiTec. So far the new team is doing a very good job at extending the outreach about synthetic biology to the public – one of the aims defined in the iGEM competition. Please visit the new website to get more information about the fascinating and very successful iGEM projects at the CeBiTec.



The team Bielefeld–CeBiTec of 2017: (from left to right) Camilla März, Saskia Dymek, Michelle Liebers, Lennard Karsten, Markus Haak, Christina Drake, Denise Kerkhoff, Maximilian Edich, Yannic Kerkhoff, Svenja Vinke, Daniel Bergen, Sandra Syperek, Laura Schlüter, and Olga Schmidt. Not on this picture: Christopher Whitford, Julian Droste (supervisor), and Boas Pucker (supervisor).

CeBiTec Christmas Party

Since 2009 the students of the CLIB-Graduate Cluster Bielefeld as well as the students of the study program "Industrial Biotechnology" organize every year the CeBiTec Christmas party for the local working groups and friends to bring people together for festive cheer. In 2016 this event was held on December 20, in the well-proven location, the CeBiTec foyer. At this seasonal festive party, the students organized besides traditional Glühwein, Kinderpunsch and cookies also a comprehensive buffet with a large variety of delectabilities. The catering at this evening was completed by "Hot Dogs" and a variety of cold drinks, both sponsored by two faculty members of the CLIB-Graduate Cluster Bielefeld. At this point a great thank you to the faculty members and to all guests who participated in supporting this buffet and made this evening to a very lovely and enjoyable event.



Miscellaneous

The Administration Office of the German Network for Bioinformatics Infrastructure (de.NBI) at the CeBiTec has received additional three-year funding from the Federal Ministry of Education and Research (BMBF) to expand its administrative activities. The Administration Office provides a range of administrative and management services to the de.NBI consortium. Three positions are funded until February 2020 to manage the integration of new partners into the network, to establish a German node in the European life sciences infrastructure initiative ELIXIR and to support the governance of the de.NBI cloud at the national nodes in Bielefeld, Freiburg, Gießen, Heidelberg and Tübingen.

We published a new flyer briefly informing about our research areas, the technology platforms and further activities. The flyer is available on our [webpage](#) in the [downloads](#) section.

Upcoming Events

- September 11–12, 2017 | Landwirtschaftszentrum Haus Düsse, Bad Sassendorf
4th CeBiTec Retreat
- September 24 – 27, 2017 | Center for Interdisciplinary Research (ZiF), Bielefeld University
7th International CeBiTec Research Conference – Advances in Industrial Biotechnology: Prospects and challenges for the development of algal biotechnology
- October 23 – 25, 2017 | Center for Interdisciplinary Research (ZiF), Bielefeld University
de.NBI Symposium
- further events are announced on the [CeBiTec web page](#)

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