Universität Bielefeld

CeBiTec
Center for Biotechnology

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In this Issue

9th CeBiTec Symposium: Molecular Biotechnology

From April 3-4, 2014, the 9th CeBiTec Symposium was held at the Center for Interdisciplinary Research (ZiF), Bielefeld University. The thematic focus was on Molecular Biotechnology and researchers from the universities of Paderborn, Münster and Bielefeld presented insights into cutting edge developments of Molecular Biotechnology. This regional focus – also documented by a joint welcome address of the vice-rectors of Bielefeld and Münster – was chosen deliberately to showcase the strength of these neighbouring universities in the field of Molecular Biotechnology. According to Prof. Dr. Volker F. Wendisch, one of the organizers, 'Biotechnological processes deliver important contributions to the grand challenges of our society, such as sustainable nutrition or the change from a petrol-based to a bio-based economy'. Examples of research developments in this field ranged from enzyme catalysis to white or industrial biotechnology and to green biotechnology and were presented in five sessions.

The application of genome and transcriptome analyses to Bacterial and Environmental Biotechnology is relevant for production hosts and also for the analysis of natural or man-made habitats such as drinking water. Biodegradation processes may benefit from enzyme catalysis or the use of synthetic bacterial communities. Insight into the analysis and application of Biopolymers was demonstrated for chitin, xanthan and rubber. Bacterial as well as mammalian hosts for the production of various proteins including antibodies were compared in the session Protein Production. Another focus was put on Biocatalysis with examples of combining enzyme catalysis with chemical catalysis ranging from pharmaceutically relevant compounds to biological halogenation, enzyme coatings and chemical protein labelling. One session was dedicated to metabolic engineering for the production of biomonomers and bio-isoprenes using bacterial and plant hosts as well as on potential applications of hydrogels. Finally, Green Biotechnology applications and characterizations of algae like *Chlamydomonas reinhardtii* and plants like the beet *Beta vulgaris* using proteomics and genomic approaches were presented.

'We are looking forward to intensify current collaborations between researchers of these three universities and develop new joint projects in the future' concluded Prof. Dr. Thomas Noll, the scientific director of the CeBiTec.

12th Bioinformatics Research and Education Workshop

More than a decade ago, five European PhD programmes in bioinformatics agreed to organize a series of Bioinformatics Research and Education Workshops (BREW). The BREWs address first-year PhD students in bioinformatics and were designed to combine a maximum of educational impact and scientific stimulation with a minimum of financial and administrative effort. The 12th BREW conference was held from May 12–14, 2014, at Bielefeld University and the CeBiTec and was organized by Kai Stadermann, Linda Sundermann, and Prof. Dr. Robert Giegerich.

Active BREW partners are currently PhD programmes from universities in Bergen (Norway), Berlin (Germany), Bielefeld (Germany), Helsinki (Finland) and Tartu (Estonia). BREW maintains a certain bias towards northern Europe, to keep travel budgets small. However, some recent BREWs also had guests from Novosobirsk University (Russia).

The BREW activity is organized in a distributed, low-budget fashion, which could easily be adopted by other providers of PhD education [1]. The site of the annual workshop rotates through the participating programmes, and local students do the local organisation. The first call for papers goes to all first year students in the participating programmes; the local PhD programme responsibles decide who should submit an extended abstract to BREW. Students from different sites crosswise peer-review their papers, and all will be presented in their final version at the workshop. In this way, PhD students gain experience not only in writing and presenting, but also in reviewing and conference organisation.

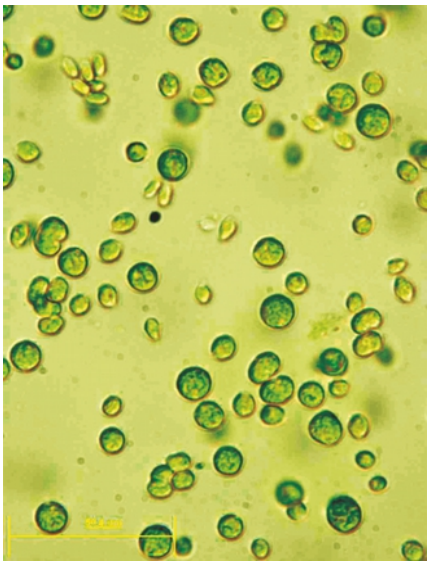
The BREW in May 2014 was the third held in Bielefeld after the workshops in 2003 and 2008. This year, 18 students from Bergen, Berlin, Helsinki, Tartu, Novosibirsk and Bielefeld took part. A wide rage of bioinformatics topics was covered including topics like metagenomics, applications of re-sequencing, mathematical modelling and the use of machine learning algorithms. Invited speakers at BREW are normally recruited from researchers at the hosting site. This year, one invited talk was provided by Prof. Dr. Jörn Kalinowski (CeBiTec) on "Why we sequence". An exception from the above rule was the invited talk by Prof. Dr. Alice McHardy (Düsseldorf). She returned to BREW 2014 as a professor after having been a BREW participant at the first workshop in 2002. She gave an overview of her recent projects in metagenomics. During the whole conference and the social programme, the students have the possibility to get in touch with each other and to exchange their experiences from different PhD programmes and countries. Next year's BREW will meet in Tartu, organized by two students participating in this year's BREW in Bielefeld.

1. Giegerich R, Brazma A, Jonassen I, Ukkonen E, Vingron M (2008). The BREW workshop series: a stimulating experience in PhD education. Brief. Bioinform. 9:250–253.

Sun protection for algae

Researchers at CeBiTec together with colleagues from Italy and Australia identified a molecular mechanism that microalgae use to protect themselves from damaging environmental stress. According to the researchers, the results of their analysis could be used to speed up the cultivation of algae for the production of valuable products. An advance version of the study is now published online in the internationally renowned journal Plant Cell [1].

The key discovery for the study came from the Algae Biotechnology & Bioenergy Research Group headed by Professor Dr. Olaf Kruse at Bielefeld University's Faculty of Biology and the CeBiTec. The researchers isolated a protective protein in unicellular microalgae that is only expressed under certain environmental stress conditions. When activated, this pigment-containing protein scavenges excess solar energy. 'In this way, the protein blocks the formation of oxygen radicals, thereby preventing any potential long-term damage to the organism', says Professor Kruse. Oxygen radical can lead to damages of the DNA and eventually to cell death.

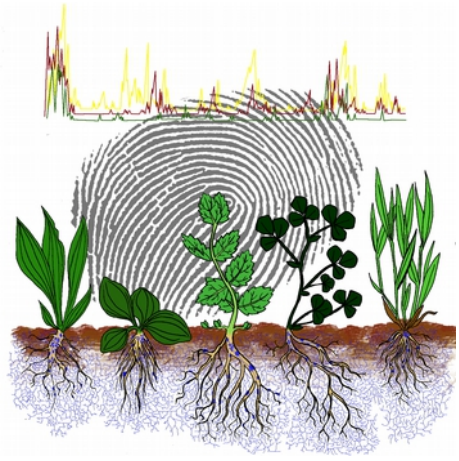


'In our analysis, we are engaged in basic research. Our primary concern is to understand the essential metabolic processes in algae', says Kruse. 'Nonetheless, the research findings obtained at Bielefeld University might also have a major biotechnological relevance', he explains. The biologist is working on large-scale cultivation of microalgae for use as "green cell factories" in biotechnology. Depending on their genetic apparatus, microalgae can produce not only energy such as biodiesel, biogas, or hydrogen but also other high value products for the pharmaceutical or cosmetics industries. 'Now that we have discovered this new protective mechanism in algae, we know which stress factors compel the algae to protect themselves against sunlight. If we want to grow algae outdoors, we can use this knowledge to make their conditions as stress-free as possible. This will avoid damage to algae cultures and thereby increase yields.' If necessary, it might even be possible to use molecular biology to optimize the protective mechanism. 'One approach would be to modify the protective protein so that the algae react more robustly than before to excess sunlight.'

When carrying out this study on microalgae, Olaf Kruse's Research Group cooperated with four international research institutes: Verona University (Italy), the Polytechnic University of Milan (Italy), the Italian Institute of Technology (IIT), and the University of Queensland (Australia).

1. Grewe S, Ballottari M, Alcocer M, D'Andrea C, Blifernez-Klassen O, Hankamer B, Mussgnug JH, Bassi R, Kruse O (2014) Light-Harvesting Complex Protein LHCBM9 Is Critical for Photosystem II Activity and Hydrogen Production in *Chlamydomonas reinhardtii*. Plant Cell. 26:1598–1611.

Many plants, one fungus – each marriage proceeds differently



The group of Prof. Dr. Caroline Müller in cooperation with the CeBiTec published their metabolomics study about the symbiosis between plants and fungi in Nature Communications [1].

The symbiosis of plants with arbuscular mycorrhizal fungi is ancient and dates back to the earliest land plants. In this marriage, the fungus extracts carbohydrates from the plant but delivers nutrients such as phosphate in return. This symbiosis does not only influence the chemical composition of the plant roots, which host the fungus, but can also affect the metabolites of the leaves. We could demonstrate that the chemical fingerprint of the leaves differs highly species-specifically between different plant species that are mycorrhized by the same fungus. Although all five investigated plant species share between 18 and 45% of their metabolites, only a very low percentage of metabolites responds in the same direction to mycorrhiza. This may be explained by the long time of coevolution of the individual plant species with the fungus. Our results highlight that research results found for one species cannot be necessarily transferred to other species such as, for example, crop plants. Changes in the chemical fingerprint, which are induced by the symbiosis with the fungus, are thus likely to have distinct consequences on other organisms interacting with the plant.

1. Schweiger R, Baier M, Persicke M, Müller C (2014). High specificity in plant leaf metabolic responses to arbuscular mycorrhiza. Nature Communications. DOI: 10.1038/ncomms4886

The B2 flowering time locus of beet encodes a zinc finger transcription factor

The biennial crop sugar beet stores sucrose in a thickened taproot and is the only crop cultivated for sugar production in Europe. Stem elongation (bolting) and flowering results in decreasing root yield. Consequently, full bolting and flowering time control are major breeding aims. For sugar beet breeding substantial knowledge of the involved genes and pathways as well as their interactions is of crucial importance. Scientists from the Kiel university in cooperation with the CeBiTec have cloned a new flowering time regulator (*B2*) which acts epistatically to the recently identified bolting gene *B*. The results indicate that *B2* acts in conjunction with *B* upstream of floral integrator genes to induce bolting and flowering. Mutations in each of the two genes resulted in a loss of competence to flower prior the exposure to cold temperatures over winter. These findings shed new light on the flowering time regulation in a biennial crop species, and offer the perspective that a combination of the mutations in each of both genes could result in a hybrid which lost the competence to bolt even after winter.

1. Dally N, Xiao K, Holtgräwe D, Jung C (2014). The B2 flowering time locus of beet encodes a zinc finger transcription factor. PNAS, published ahead of print June 25, 2014, doi:10.1073/pnas.1404829111

Parallel development of tools and techniques for transcriptome sequencing

During the last years sequencing technologies took a large leap ahead. The so called Next Generation Sequencing (NGS) technologies allow sequencing not only DNA in a high throughput fashion, but indirectly also RNA molecules by using a detour over cDNA [1]. This approach, called RNA-Sequencing (RNA-Seq), offers new insights into the biological processes inside an organism. In contrast to the classical DNA-Array technologies RNA-Seq offers not only the information if a gene is expressed in a given sample, it also provides fine-grained information about the level of expression.

However, RNA-Seq also creates new challenges for bioinformatics. The amount of created data is huge compared to Sanger sequencing and array technologies. When differentially expressed genes are searched for, algorithms are needed to identify those genes in a pool of thousands of others that do not show a different level of gene expression between conditions. Tools like baySeq [2] and DESeq [3] address this problem. In the first place, the sequence read data from an RNA-Seq run must be mapped onto a reference genome or at least a transcriptome assembly. For prokaryotic data various short read mapper, for example SARUMAN [4] or Bowtie [5], have been introduced in the last years. For eukaryotic data the problem of mapping short reads from an RNA-Seq experiment back to a reference genome has one more level of complexity: genes in eukaryotic organisms display an intron exon structure. Various split read mappers, like for example Tophat [6], exist but there is still room for improvement.

To handle the large amount of data created during RNA-Seq experiments, a novel tool, called ReadXplorer [7], has been developed during the past three years by scientists from the Gießen University (group Goesmann) and the CeBiTec (groups Weisshaar, Kalinowski). ReadXplorer is a platform-independent Java application running on all major operating systems (Windows, Mac and Linux). It enables visual exploration of mapped sequencing reads from different experiments in relation to a reference genome in various synchronized data viewers and offers automatic analysis functions for these data sets from within the software – minimizing manual effort of the researcher. The software is freely available at http://www.readxplorer.org

ReadXplorer was developed in parallel with the RNAseq techniques on the model bacterium *Corynebacterium glutamicum*, showing the bilateral synergy between genome research and bioinformatics, a speciality of the CeBiTec.

RNAseq now delivers a genome-wide transcriptome of an organism with single-base resolution and the possibility for quantification of transcription with an almost unlimited dynamic range. The methods developed comprise RNAseq

in different forms. A "whole transcriptome", comprising mRNA enrichment, cDNA generation and paired-end sequencing. This data is then used for the identification of operons (read-pairs in different coding regions) and for quantification. In a special procedure, the native 5'-ends of transcripts are enriched and later sequenced only from their 5'-ends. This method delivers a maximum resolution with respect to (true) transcript starts and allows the high-throughput identification of promoters. A special approach has to be taken for small RNA, since these RNA species were quantitatively lost during column-based RNA purification. This small RNA approach involves the classical phenol-chloroform purification of RNA.

All these methods were developed at the example of *C. glutamicum* first and led to 'milestone publications' (in the words of a reviewer) on the total transcriptome [8] and the small RNA transcriptome [9] of this industrially important bacterium. The techniques developed have also been applied to a number of other microorganisms, leading to several more publications.

1. Wang Z, Gerstein M, Snyder M (2009). RNA-Seq: a revolutionary tool for transcriptomics. Nature Reviews Genetics 10:57–63.
2. Hardcastle TJ, Kelly KA (2010). baySeq: empirical Bayesian methods for identifying differential expression in sequence count data. BMC Bioinformatics 11:422.
3. Anders S, Huber W (2010). Differential expression analysis for sequence count data. Genome Biology 11:R106.
4. Blom J, Jakobi T, Doppmeier D, Jaenicke S, Kalinowski J, Stoye J, Goesmann A (2011). Exact and complete short-read alignment to microbial genomes using Graphics Processing Unit programming. Bioinformatics 27:1351–1358.
5. Langmead B, Trapnell C, Pop M, Salzberg SL (2009). Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. Genome Biology 10:R25.
6. Trapnell C, Pachter L, Salzberg SL (2009). TopHat: discovering splice junctions with RNA-Seq. Bioinformatics. 25:1105–1111.
7. Hilker R, Stadermann KB, Doppmeier D, Kalinowski J, Stoye J, Straube J, Winnebald J, Goesmann A (2014). ReadXplorer – visualization and analysis of mapped sequences. Bioinformatics. 2014 Apr 30. pii: btu205. [Epub ahead of print].
8. Pfeifer-Sancar K, Mentz A, Rückert C, Kalinowski J (2014). Comprehensive analysis of the Corynebacterium glutamicum transcriptome using an improved RNAseq technique. BMC Genomics 14:888.
9. Mentz A, Neshat A, Pfeifer-Sancar K, Pühler A, Rückert C, Kalinowski J(3013). Comprehensive discovery and characterization of small RNAs in Corynebacterium glutamicum ATCC 13032. BMC Genomics 14:714.

3rd CeBiTec Students Academy Synthetic Biology/Biotechnology

The 3rd CeBiTec Students Academy Synthetic Biology/Biotechnology will be held at the CeBiTec from July 7 to 11, 2014. The Academy is designed for students one year before finishing their Abitur, the general qualification for university entrance. The Students Academy is jointly organized by the CeBiTec and the District Council Detmold. The main role of the District Council Detmold is to distribute the call for application to all relevant schools in the region Ostwestfalen-Lippe of Northrhine-Westfalia. Expenses associated with the course are covered by three sources. Main financial support is provided by the Familie-Osthushenrich-Stiftung (Gütersloh), which is a foundation dedicated to the support of gifted and talented pupils within Ostwestfalen-Lippe. Bielefeld University contributes to the course by organizing the lectures and the practical course programme. In addition, each student participant contributes to the Academy by a small fee. Admittance to the Students Academy is limited to 20 attendees. A total of 37 students applied for attendance of the 3rd CeBiTec Students Academy. Generally, applications were accepted if a combination of criteria was fulfilled. These included (i) superior grades, (ii) an excellent recommendation letter as well as (iii) a clear and concise motivation letter. According to these criteria, 20 applicants were chosen and invited to participate in the course. The 3rd CeBiTec Students Academy is jointly organized by Honorary Prof. Dr. Walter Arnold, Prof. Dr. Alfred Pühler, and Dr. Werner Selbitschka.

Miscellaneous

On June 21, 2014, the German-Japanese Society of Bielefeld (Deutsch-Japanische Gesellschaft Bielefeld e.V.) honoured Hironori Taniguchi with the Hajime Hoshi Award. Taniguchi born in Osaka and holding an M.A. in Life Science and a B.A. in Chemistry from Kyoto University, Japan, is a PhD student in the group of Prof. Dr. Voker F. Wendisch since summer 2013. The 1.000 Euro award is awarded to Japanese students of Bielefeld University, distinguished for their scientific achievements and their inter-cultural engagement.

Upcoming Events

- July 7–11, 2014 | CeBiTec building, Bielefeld University
  3rd CeBiTec-Schülerakademie
- August 25–27, 2014 | CeBiTec building, Bielefeld University
  CLIB Graduate Cluster Lab Course – Advanced Post-Genomics & Bioinformatics – Introduction to genome & transcriptome analysis
- September 21–24, 2014 | Center for interdisciplinary Research (ZiF), Bielefeld University
  ICRC 2014 – International CeBiTec Research Conference: Advances in Industrial Biotechnology – Prospects and challenges for the development of algal biotechnology
- September 28–October 1, 2014 | Bielefeld University
  GCB 2014 – German Conference on Bioinformatics
- March 23–25, 2015 | Center for interdisciplinary Research (ZiF), Bielefeld University
  10th CeBiTec Symposium – Bioinformatics for Biotechnology and Biomedicine

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