

CeBiTec – Quarterly

Spring 2023



- ▶ Schmidt-Schippers lab identifies new component of retrograde signalling under oxygen deficiency in *Arabidopsis*
- ▶ CeBiTec member Johanna Nelkner qualified for the German FameLab final
- ▶ CeBiTec member Karl-Josef Dietz elected as president of the International Union of Biological Sciences
- ▶ Marie Skłodowska-Curie fellowship (MSCA) for microalgae biotech work at the CeBiTec
- ▶ Metagenomic identification of *Thaumarchaeota* in European arable soils
- ▶ Schönhut group develops capsule network to predict the prevalence of complex diseases from genetic profiles
- ▶ CeBiTec group “Genome data Science” led by A. Schönhut finds new way of correcting errors in long reads using pan-genome graphs
- ▶ 9th Assembly of CeBiTec Advisory Board
- ▶ Comprehensive School from Neuss visits the teutolab-biotechnologie for 3 days

Schmidt-Schippers lab identifies new component of retrograde signalling under oxygen deficiency in *Arabidopsis*

Under climate change, weather extremes are occurring at an increased rate, including flooding, which poses a major threat to crop survival. Crop yield is significantly reduced worldwide due to waterlogging and flooding. As a characteristic, flooding leads to oxygen deficiency (hypoxia) and thus strongly affects oxygen-dependent ATP production in the mitochondrion. Communication from the mitochondrion to the nucleus is therefore essential in order to activate genes enabling fast plant adaptation to hypoxia stress. In collaboration

with researchers from IPK Gatersleben, Kiel University, RWTH Aachen University and VIB Ghent, we discovered a novel molecular mechanism in the model plant *Arabidopsis thaliana* that is crucial for mitochondrial retrograde signaling under oxygen constraints. Specifically, the involved transcription factor ANAC013 is anchored to the endoplasmic reticulum (ER) via its C-terminal transmembrane domain (TMD). At the very onset of hypoxic conditions, ANAC013 is proteolytically cleaved near its TMD, whereupon the soluble part of ANAC013 translocates to the nucleus (Fig 1). Pharmacological blockage of mitochondrial function similarly leads to ANAC013 release from the ER. We further demonstrated in our

[PNAS publication](#) that ANAC013 is important for Arabidopsis tolerance to oxygen deprivation and that the transcription factor binds directly to the promoters of important tolerance genes.

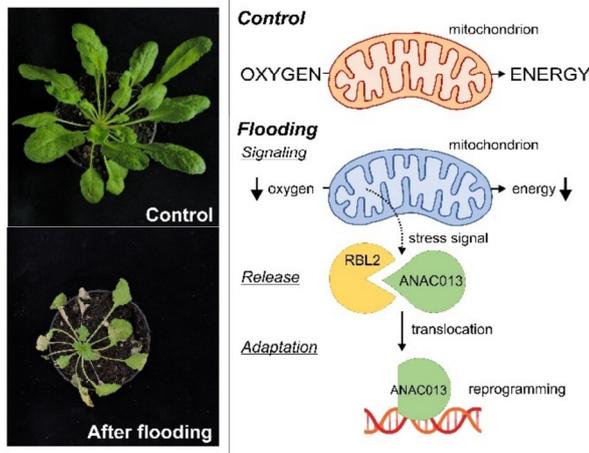


Figure 1 | Release of ANAC013 under hypoxia is catalyzed by the protease RBL2. Free ANAC013 protein translocates to the nucleus to activate hypoxia core genes essential for adaptation to oxygen constraints. The ANAC013-RBL2 module is crucial for mitochondrion-to-nucleus communication under stress.

Mechanistically, proteolytic processing of ANAC013 is catalyzed by RHOMBOID-LIKE 2, a member of the intramembrane protease family (Fig. 1).

RBLs are present not only in plants but also in animal systems and yeast, among others. We demonstrated for the first time the function of an RBL protease in plant stress signaling.

Both naturally occurring hypoxia and artificially induced mitochondrial dysfunction require the activity of RBL2 for ANAC013 to be released from the ER. Since NAC factors as well as RBLs are conserved in all major crops, the discovery of the ANAC013-RBL2 module is an important step toward potential strategies to

improve crop resilience to future flooding events as part of climate change.

Reference:

Emese Eysholdt-Derzsó, Tilo Renziehausen, Stephanie Frings, Stephanie Frohn, Kira von Bongartz, Clara P Igisch, Justina Mann, Lisa Häger, Julia Macholl, David Leisse, Niels Hoffmann, Katharina Winkels, Pia Wanner, Jonas De Backer, Xiaopeng Luo, Margret Sauter, Inge De Clercq, Joost T van Dongen, Jos H M Schippers, Romy R Schmidt-Schippers (2023) Endoplasmic reticulum-bound ANAC013 factor is cleaved by RHOMBOID-LIKE 2 during the initial response to hypoxia in *Arabidopsis thaliana*. *Proc. Natl. Acad. Sci. U S A.*; 120(11):e2221308120. [doi: 10.1073/pnas.2221308120](https://doi.org/10.1073/pnas.2221308120)

(R. Schmidt-Schippers and co-workers)

CeBiTec member Johanna Nelkner qualified for the German FameLab final



Figure 2 | J. Nelkner during her stage performance in the Tor 6 theatre.

On March 10th eight young researchers competed in the FameLab preliminary round in Bielefeld for two tickets to the final of the FameLab Germany science competition. In the

FameLab science competition, young researchers face the challenge of explaining a scientific topic in an entertaining and engaging way in just 180 seconds. It was an inspiring evening in front of around 300 spectators at the Tor 6 theatre: Johanna Nelkner, member of the CeBiTec research group “Genome Research of Industrial Microorganisms”, won over the jury with her performance of her poetic yet easily digestible presentation "[Bifido's journey - with charm through the gut](#)", and will compete as the second-place winner at the FameLab Germany final on 25 May in the Rudolf Oetker Hall.

Bielefeld strongly represented

As in previous years, the participants on the FameLab stage succeeded in explaining complex research topics in a factually correct, entertaining and engaging way for a lay audience - and in just three minutes! With three of the eight participants that Bielefeld University and Bielefeld University of Applied Sciences were able to send into the race, the science location of Bielefeld was once again the real winner of the evening.

FameLab takes place worldwide, this year for the 13th time. Since 2022 Bielefeld Marketing has been the national partner responsible for FameLab Germany. More information and the latest news about [FameLab Germany](#) are also available online.

(J. Nelkner)

CeBiTec member Karl-Josef Dietz elected as president of the International Union of Biological Sciences



[The International Union of Biological Sciences \(IUBS\)](#)

represents biosciences in their entirety at the international stage and links national interests with transnational policy making and networking. The general assembly (GA) is the main governance body and convened in Tokyo early in March 2023. The GA elected the new Executive Committee for the upcoming triennium (2023-2026).



Karl-Josef Dietz, professor for biochemistry and physiology of plants at the faculty

of biology and founding member of the CeBiTec, was elected president of IUBS.

Founded as early as 1919 IUBS promotes the biological sciences and biological understanding worldwide as amplifier for its national and societal members. The main missions are

- fostering bioscience by stimulating research, providing a platform for exchange and coordination of biological information,
- support of education, young researchers and career building,
- biologist networking by catalyzing international cooperation and exchange with other science unions, councils and organizations, and
- bioscience diplomacy by informing decision makers and the public.

Current activities concern open science and open data policy, guidelines in the domains of bio-nomenclature and biodiversity, public health, agriculture and global sustainability. Since its inception in 1919, IUBS has undertaken a leading role particularly in the Convention of Biodiversity (CBD), Climate Change Education and Open Biodiversity and Health Big Data (BDHD). IUBS has aligned itself with the changing world of the 21st century by close cooperation with other science and social science unions in addressing the challenges posed by global warming, deforestation, increased population and livestock, rapid urbanization, invasive species and new epidemics. The major contributions of IUBS both in the field of science and leadership include broadening international scope for the scientists on relevant issues in close cooperation with its national and societal members.

(K.-J. Dietz)

Marie Skłodowska-Curie fellowship (MSCA) for microalgae biotech work at the CeBiTec



Foto: Universität Bielefeld

Dr. Magdalena Miklaszewska has received a **Marie Skłodowska-Curie grant (MSCA)** for postdocs from the European Commission. The scientist from the University of Vienna will work from September 2024 to August 2026 at the CeBiTec in the research field of microalgae biotechnology with Professor Dr. Olaf Kruse.



Magdalena Miklaszewska examines wax esters (WE). Wax esters are neutral lipids of great industrial importance, used as ingredients in lubricants, drugs and cosmetics. There is a great need for an alternative bio-based production of WE from renewable resources, as the current large-scale production of waxes is based on chemical processes using mainly petroleum-derived raw materials and generating hazardous waste. The main goal of this



project is the establishment of a more sustainable production chain in microalgae with the help of genetic engineering and its further improvement by optimizing the culture conditions. The cultures of the WE-producing transgenic microalgae will be scaled up to check their productivity and WE yield for industrial application. "The results of this project will make a valuable contribution to the future development of new strategies for a sustainable "green" WE production from CO₂ and sunlight," says Professor Dr. Kruse.

(O. Kruse)

Metagenomic identification of *Thaumarchaeota* in European arable soils

PhD student Johanna Nelkner from the CeBiTec working group "Genome Research of Industrial Microorganisms" has published the article "[Abundance, Classification and Genetic Potential of *Thaumarchaeota* in Metagenomes of European Agricultural Soils: a Meta-Analysis](#)" in

the renowned journal "Environmental Microbiome". The techniques underlying the article concern the high-throughput sequencing of microbial community DNA from arable soils and the bioinformatic analysis of the sequence data obtained. CeBiTec is well equipped for these analyses as it hosts the Technology Platforms Genomics running state-of-the-art sequencing devices and Bioinformatics enabling large-scale computational analyses.

The just published article follows up on experiments that J. Nelkner already successfully carried out in 2019. In those experiments, metagenomically assembled genomes (MAGs) were obtained from soil metagenome sequence data. To generate MAG genomes, sequence contigs were assembled from metagenomic sequence reads and then bundled to MAGs using a binning procedure. The reconstructed MAG genomes represent dominant microbial species of the analyzed microbial community. Of interest is that these MAGs also enable characterization of microbial species that have not yet been isolated and therefore have not been studied physiologically. In 2019, J. Nelkner specifically focused on the analysis of microbial communities from arable soil samples from the Bernburg area (Magdeburger Börde, Saxony-Anhalt). After metagenome sequencing, she was able to obtain MAG genomes that characterized both bacterial and archaeal representatives as dominant species of the microbial community of the arable soil samples. The identified archaeal MAGs were assigned to the phylum *Thaumarchaeota*.

Previously, an Austrian group isolated a representative of *Thaumarchaeota*, namely *Nitrososphaera viennensis*. The genome of this isolate is highly similar to a MAG described by J. Nelkner that was also classified to belong to the genus *Nitrososphaera*.

After analyzing the microbial community from Bernburg arable soil, J. Nelkner pursued the question of whether related microbial communities are present in other European arable soils. For this purpose, she used metagenome sequence datasets of microbial communities from arable soils that had already been generated by other groups and whose sequencing results were available in public databases to conduct a meta-study.



Figure 3 | Location of European arable soils analysed.

After intensive searches, she was finally able to identify 19 data sets for in-depth bioinformatic analysis. These data sets provided the basis for a bioinformatic meta-analysis, the result of which is described in the article just published in the journal "Environmental Microbiome". The meta-analysis carried out shows that often,

despite a limited sequencing depth, the generation of MAG genomes was possible. MAG genomes of both bacterial and archaeal representatives could again be reconstructed. Among the archaeal MAGs, *Thaumarchaeota* again play a decisive role. From their genome sequence information it can be predicted that the corresponding species are capable of carbon dioxide (CO₂) fixation and ammonia oxidation and therefore are considered to represent soil beneficial microorganisms. With the work published in "Environmental Microbiome", J. Nelkner has followed the recommendation to re-analyze existing life science data sets with improved bioinformatics programs and optimized computer infrastructure to enable more reliable comparability of obtained results and to achieve deeper insights into metagenome datasets. Her results impressively confirmed this strategy and exemplify the quality of the computer infrastructure installed at CeBiTec.

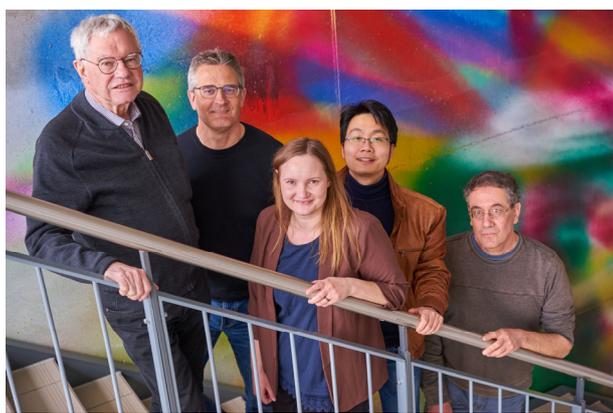


Figure 4 | Team of authors behind the publication. From left to right. Prof. Dr. A. Pühler, Prof. Dr. A. Sczyrba, J. Nelkner, Dr. Liren Huang and Dr. A. Schlüter.

Several CeBiTec members have contributed substantially to the present publication. J. Nelkner, of course, did the main work in the

context of her PhD project. Liren Huang was responsible for bioinformatics issues. A. Schlüter took over the role of corresponding author. A. Sczyrba and A. Pühler were both involved in the supervision of the work performed.

Reference:

Nelkner, J., Huang, L., Lin, T.W. *et al.* Abundance, classification and genetic potential of *Thaumarchaeota* in metagenomes of European agricultural soils: a meta-analysis. *Environmental Microbiome* 18, 26 (2023). <https://environmentalmicrobiome.biomedcentral.com/articles/10.1186/s40793-023-00479-9#citeas>

(A. Pühler)

Schönhut group develops capsule network to predict the prevalence of complex diseases from genetic profiles

Although known to have a genetic background, various diseases, such as amyotrophic lateral sclerosis (ALS), Alzheimer's (AD) or Parkinson's disease (PD) are often by far not yet sufficiently understood: large amounts of genetic factors have not yet been exposed as such. The reason is the high level of complexity that governs the patterns of interactions that establish the disease risks. Therefore, associating genetic factors with disease related phenomena escapes discovery when using standard approaches, such as commonly employed in genome-wide association studies (GWAS).

Disentangling the associations requires novel ways of thinking. Non-linear approaches to connecting disease related quantities with the genetic profiles of patients appear to be a

must. CeBiTec member Prof. Dr. A. Schönhuth and his research group have developed “DiseaseCapsule” to predict the prevalence of genetically involved diseases from individual genetic profiles. DiseaseCapsule implements capsule networks as a non-linear model to map genetic factors to clinically relevant phenotypes. Capsule networks were originally suggested in 2017/2018 as an improvement over standard neural network models. Their advantages are enhanced interpretation of results, sustainable use of training data, which greatly limits the size of the required patient cohorts, beyond just considerably improved accuracy in prediction.

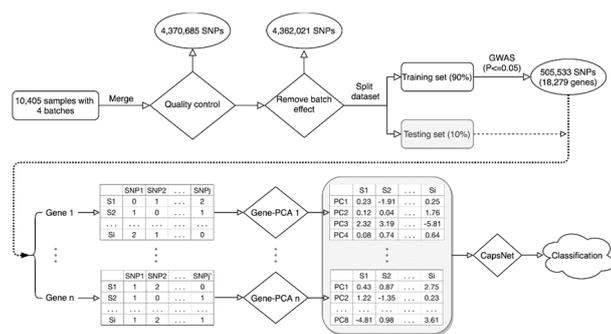


Figure 5 | Workflow of DiseaseCapsule: “CapsNet” implements a capsule network.

In experiments, we demonstrate that DiseaseCapsule can predict the prevalence of ALS at an accuracy of approximately 87%. Thanks to the non-linearity of the model and the opportunities in terms of enhanced interpretation that capsule networks provide, we also expose 922 genes as being crucially involved in the classification process in a collaborative manner. Last but not least, we also reveal 644 genes as interacting in non-additive ways to establish the disease, the great majority of which had not been exposed as disease-related in the

literature before.

Reference:

X. Luo, X. Kang, A. Schönhuth: “Predicting the prevalence of complex genetic diseases from individual genotype profiles using capsule networks”. *Nature Machine Intelligence* 5, 114-125, 2023.

<https://www.nature.com/articles/s42256-022-00604-2>

(A. Schönhuth)

CeBiTec group “Genome data Science” led by A. Schönhuth finds new way of correcting errors in long reads using pan-genome graphs

Third generation sequencing (TGS) such as Pacific Biosciences (PacBio) or Oxford Nanopore Technologies (ONT) has been emerging rapidly over the last few years. However, elevated error rates affecting the sequencing reads put their tremendous advantages in terms of read length into question. This explains why error correction is a canonical first step in long-read sequencing data analysis.

Error correction standard practice is to make use of sequence templates with which one compares the erroneous reads. Based on the alignment of the reads with the template, one identifies errors in the reads and corrects them. However, the inability of *sequence* templates to capture ambiguities that affect the reads—note that each position in a sequence is unique—introduces biases during the correction process. As a consequence, correction prevents the identification of alleles that are

characteristic of genome copies appearing at relatively low frequency in the mix of genome copies that one deals with. The technical effect is referred to as “overcorrection”: rather than leaving these characteristic variants untouched, the sequential template dictates to overrule them.

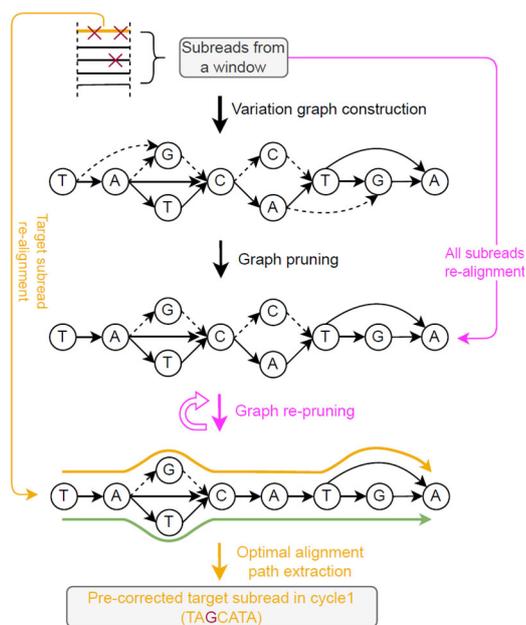


Figure 6 | Pan-genome graph-based error correction procedure.

We have developed VeChat as a method that addresses this issue. As a novelty, VeChat does not make use of sequential, but of *pan-genome graph-based* templates. Unlike one-dimensional genome sequence, pan-genome graphs capture the great majority of ambiguities that can affect the genome copies in a sequencing sample of greater complexity. As a consequence, VeChat does not “overcorrect”, but can distinguish between true low-frequency variants on the one hand and errors on the other hand. Most relevant application scenarios are mixed sequencing samples, such as viral quasispecies or metagenomes and

genomes of ploidy greater than one. The application of VeChat yields error rates that are substantially improved over those of state-of-the-art approaches when dealing with genomes of elevated ploidy or with metagenomes in particular. In summary, VeChat appears to establish the first approach to not overcorrect in these relevant sequencing scenarios.

Reference:

X. Luo, X. Kang, A. Schönhuth, “VeChat: Correcting errors in long reads using variation graphs”. Nature Communications 13, 6657, 2022.
<https://doi.org/10.1038/s41467-022-34381-8>

(A. Schönhuth)

9th Assembly of CeBiTec Advisory Board

From the 13th to 14th of February 2023, the 9th assembly of the CeBiTec Advisory Board (Figure X) was held to discuss the CeBiTec`s future strategy besides evaluating recent achievements and defining future tasks.

The first day of the meeting started with opening remarks by Prof. Dr. Angelika Epple (Prorector for Research and International Affairs) and Prof. Dr. Olaf Kruse (Scientific Director of CeBiTec).

The Scientific Director then reported about the current state of the CeBiTec, comprising aspects such as publication output or funding acquisition and forecasted challenges ahead, such as the need to shape the generational change within the group of CeBiTec PIs, while

connecting this task to the requirement for an increased female share. Furthermore, he addressed tasks contained in the previous report of the Advisory Board and how they were fulfilled.



Figure 7 | The CeBiTec Advisory Board.

Upper row. From left to right:

Dr. R. Apweiler (EMBL – European Bioinformatics Institute Cambridge); **Prof. Dr. B. Siebers** (University of Duisburg-Essen, Faculty of Chemistry, Molecular Enzyme Technology and Biochemistry); **Prof. Dr. S. Flitsch** (The Manchester Institute of Biotechnology)

Lower row. From left to right:

Prof. Dr. Dr. T. Lengauer (Max-Planck-Institut für Informatik, Research Group Computational Biology); **Dr. R. Kelle** (Evonik Nutrition & Care GmbH); **Prof. Dr. T. Erb** (Max Planck Institute for Terrestrial Microbiology)

The speakers of the two research areas “Large Scale Genomics and Big Data Bioinformatics” as well as “Metabolic Engineering of Unicellular Systems and Bioproduction”, Prof. Dr. Jens Stoye and Prof. Dr. Volker F. Wendisch, respect-

tively, reported on the state-of-the-art and further development of the research areas. Prof. Dr. Jörn Kalinowski informed the audience about the organization of a new perspectival research area “Molecular Medicine” with a special emphasis on research collaborations between the CeBiTec and research groups of the Medical Faculty. In regard to future research directions with the research areas and their interconnections, talks were given by Prof. Dr. Norbert Sewald, highlighting the continued activities of several CeBiTec PIs to establish biocatalysis research at Bielefeld University, and Prof. Dr. Jörn Kalinowski as well as Prof. Dr. Alexander Sczyrba, both addressing future topics in the field of “omics” and “bioinformatics”, respectively.

The final presentation of the day was given by Prof. Dr. Martin Egelhaaf, as the Rectorate Representative for Research Networking in Medicine, explaining the rectorate’s roadmap for the establishment of an university-wide, faculty-spanning core facility structure, which also includes the CeBiTec’s participation in building a core facility omics, based on its existing technology platform genomic. Day 1 then concluded with a lively discussion about the strategic measures to be taken in order to face the future challenges.

As in previous years, on the second day, PhD students of the CeBiTec groups presented their research to the Advisory Board in a poster session held in the foyer of the CeBiTec building.

Reflecting the impressions from the meeting, the Advisory Board’s Report recommended a catalogue of strategic measures to the recto-

rate, which should help tackling several future challenges. Importantly, this report concludes by saying, that despite of the challenges the CeBiTec has to face in the near future, the Advisory Board is deeply convinced about the enormous benefit that the CeBiTec represents for Bielefeld University, especially in reference to its high national and international reputation.

(Lutz Wobbe)

Comprehensive School from Neuss visits the teutolab-biotechnologie for 3 days

In the end of March, 13 students from the 11th grade with special interest in biology experimented in the *teutolab*-biotechnologie for 3 days to get to know the activities of biotechnologists. The study trip to Bielefeld was organized by the school to support the students' career orientation. They were accompanied by 2 teachers and stayed at the youth hostel in Bielefeld.



Figure 8 | Students discussing experimental result with the supervisor.

In the context of lactose intolerance, the participants first learned how to detect the enzymatic digestion of lactose by determining the glucose content after the addition of lactase. In the next step, the adolescents

themselves constructed a biosensor for detecting glucose. The following day, the participants carried out experiments on the enzyme kinetics of lactase. On the last day, the young people practiced scientific inquiry on the factors which can influence the activity of enzymes. They formulated their own questions and planned the experiments themselves. The three-day supply ended with a symposium in which the participants presented their experiments. For the first time, the young people also summarized their experiences as a post on [Instagram](#).



Figure 9 | Collage of photographs taken during the event.

The *teutolab*-biotechnologie has been active in this [social media platform](#) since short time. The out-of school student lab aims to get even more young people excited about biotechnology and to win participants for the [numerous opportunities](#) in the upcoming holidays.

(K. Röllke)

Impressum

Centrum für Biotechnologie
Universität Bielefeld
Dr. Lutz Wobbe
Universitätsstr. 27
33615 Bielefeld
Germany
info@cebitec.uni-bielefeld.de



Concept & Idea:
Dr. Stefan Weidner

Figures:
Fig. 1 © R. Schmidt-Schippers
Fig. 2 © Bielefeld Marketing GmbH
/ Thomas Starke
Figs. 3&4 © A. Pühler
Figs. 5&6 © A. Schönhut
Fig. 7 © CeBiTec
Figs. 8&9 © K. Röllke