Leibniz
Bioactive
Compounds

Abstract Book

Leibniz Conference on Bioactive Compounds

May 24-25. 2023

IPB Leibniz Institute of Plant Biochemistry

It is a great pleasure…

to welcome you to the Leibniz Conference on Bioactive Compounds. The actual situation allows us to meet again on-site: scientists from various disciplines present and discuss their latest research related to the topics of drug discovery, (non-)medical applications of bioactive compounds, method development, novel targets and biotechnology. We hope you enjoy the program and we thank all for their contributions to this conference!

The organizing committee

Prof. Ludger A. Wessjohann (IPB)and Dr. Anna Rusznyak (IPB)

And the speakers of the alliance

Prof. Ludger A. Wessjohann (IPB), Dr. Pierre Stallforth (HKI), and Dr. Dirk Janasek (ISAS)

LEIBNIZ RESEARCH NETWORK BIOACTIVE COMPOUNDS

Involving 16 institutions, the Leibniz Research Network Bioactive Compounds bundles the Leibniz Association's broadly-based research on molecules with biological effects.

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Conference Program

Wednesday, May 24, 2023	
12:00	**Registration**
12:30	**Welcome addresses** **Jörg Overmann** (Scientific Director, Leibniz Institute DSMZ, Braunschweig)
Session 1	**NATURAL PRODUCTS FROM MICROBIAL PRODUCERS** **Chair: Yvonne Mast** (Leibniz Institute DSMZ, Braunschweig)
12:45	**PLENARY TALK: Natural Product An□bio□cs: Past, Present, Future** **Mohammad R. Seyedsayamdost** Princeton University, USA
13:40	**Judith Boldt - Bursts in biosynthetic gene cluster transcription are accompanied by surges of natural compound production in the myxobacterium *Sorangium* sp.** Leibniz Institute DSMZ, Braunschweig
14:00	**Peter Sullivan - MyxoTech – a commercial vehicle to expand the potential pharmaceutical use of the myxobacterial specialized metabolome** Helmholtz Institute for Infection Research Saarland (HIPS), Germany
14:20	**Jethro Hemmann – Investigation of RiPPs originating from two-domain precursors** Leibniz-Hans Knöll Institute, Jena
15:00	**Poster session & Coffee break**
Session 2	**YOUNG RESEARCHER'S SESSION ON NATURAL PRODUCTS** **Chair: Ulrich Nübel** (Leibniz Institute DSMZ, Braunschweig)
16:30	**Dustin Joshua Vollmann - Heterologous production of non-ribosomal peptide indigoidine in *Myxococcus xanthus* (to be confirmed)** TU Dortmund University, Dortmund
16:45	**Laura Stock - Clickable Microcystins as payloads for Antibody-Drug Conjugates** Martin-Luther University Halle-Wittenberg, Halle
17:00	**Alina Zimmermann - Genome sequence-based screening for novel phosphonate producers** Leibniz Institute DSMZ, Braunschweig
17:15	**Esteban Charria Giron - Discovery of new anti-infectives in the Sordariales** Helmholtz Centre for Infection Research (HZI), Braunschweig
17:30	**Mohamad Saoud - Metabolic Profiling can predict Complex Mode of Action for Cytotoxic Drugs** Leibniz Institute of Plant Biochemistry, Halle
17:45	**Melanie Hanser – Elucidating antifungal phytochemicals from wild herbaceous plants** Leibniz Institute of Vegetable and Ornamental Crops, Großbeeren

Wednesday, May 24, 2023	
Session 3	**AWARD CEREMONY** **Chair: Pierre Stallforth** (Leibniz-Hans Knöll Institute, Jena)
18:00	**Leibniz Research Award 2023** **Mohammad R. Seyedsayamdost** Princeton University
18:15	**Leibniz Drug of the Year 2023** **Florian Kloß et al.** Leibniz-Hans Knöll Institute, Jena
18:45	**Dinner**
Thursday, May 25, 2023	
Session 4	**BIOACTIVE COMPOUNDS AND THEIR EFFECTS** **Chair: Ludger Wessjohann** (Leibniz Institute of Plant Biochemistry, Halle)/ **Dirk Janasek** (Leibniz-Institut für Analytische Wissenschaften, Dortmund)
09:00	**PLENARY TALK: Development of preventive vaccines in Latin America – the GLACIER project** Daniel Garcia Rivera University of Havana, Cuba
09:50	**Mohamed Nagia - Novel terpenoids by terpene synthase-mediated biotransformation of non-natural prenyl diphosphates** Leibniz Institute of Plant Biochemistry, Halle
10:10	**Franziska Hanschen - Glucosinolates in *Brassica* vegetables: Deciphering the mechanisms for the formation of bioactive products** Leibniz Institute of Vegetable and Ornamental Crops, Großbeeren
10:30	**Coffee break**
11:00	**Maik Behrens - The influence of temporal effects on human taste perception** Leibniz Institute for Food Systems Biology, Technical University of Munich
11:20	**Clara Correia-Melo - Microbial natural products and community survival - a role for metabolite exchange interactions** Leibniz Institute on Aging, Fritz Lipmann Institute, Jena
11:40	**AWARD CEREMONY POSTER PRIZE 2023/CLOSING REMARKS** **Chair: Ludger Wessjohann** (Leibniz Institute of Plant Biochemistry, Halle)
12:00	**Lunch**
13:15	**Member Assembly** X1.01 room HZI Forum, Helmholtz Centre for Infection Research, Inhoffenstraße 7, 38124 Braunschweig
13:15	**Guided tour DSMZ (participants)** Inhoffenstraße 7B 38124 Braunschweig
16:00	**Guided tour DSMZ (LRN assembly members)** Inhoffenstraße 7B 38124 Braunschweig

ORAL PRESENTATIONS

Natural product antbiotics: past, present, future

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Microbial natural products have served as a dominant source of antibiotics and comprise some of our most celebrated cures. Until the turn of the century, they were identified via tedious 'grind-and-find' approaches, increasingly leading to the re-isolation of old compounds. More recently, the availability of microbial genome sequences has ushered in a renaissance in natural product research and significantly impacted their discovery. In this talk, I will present new methodologies that my group has developed to locate otherwise hidden or 'cryptic' natural products, notably antibiotics, from diverse bacteria and to explore their therapeutic utility, mechanism of action, and ecological relevance. Our results provide deeper insights into microbial metabolism with implications for drug discovery and antibiotic research.

Bursts in biosynthetic gene cluster transcription are accompanied by surges of natural compound production in the myxobacterium *Sorangium* sp.

Judith Boldt[1,2*], Laima Lukoševičiūtė[1], Chengzhang Fu[3], Matthias Steglich[1**], Boyke Bunk[1], Vera Junker[1], Aileen Gollasch[4], Birte Trunkwalter[4], Kathrin I. Mohr[4], Michael Beckstette[5], Joachim Wink[4], Jörg Overmann[1,2,6], Rolf Müller[2,3], Ulrich Nübel[1,2,6]

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A better understanding of the genetic regulation of the biosynthesis of microbial compounds could accelerate the discovery of new biologically active molecules and facilitate their production. To this end, we have investigated the time course of genome-wide transcription in the myxobacterium *Sorangium* sp. So ce836 in relation to its production of natural compounds. Time-resolved RNA sequencing revealed that core biosynthesis genes from 48 biosynthetic gene clusters (BGCs; 92% of all BGCs encoded in the genome) were actively transcribed at specific time points in a batch culture. The majority (80%) of polyketide synthase and non-ribosomal peptide synthetase genes displayed distinct peaks of transcription during exponential bacterial growth. Strikingly, these bursts in BGC transcriptional activity were associated with surges in the net production rates of known natural compounds, indicating that their biosynthesis was critially regulated at the transcriptional level. In contrast, BGC read counts from single time points had limited predictive value about biosynthetic activity, since transcription levels varied >100-fold among BGCs with detected natural products. Taken together, our time-course data provide unique insights into the dynamics of natural compound biosynthesis and its regulation in a wild-type myxobacterium, challenging the commonly cited notion of preferential BGC expression under nutrient-limited conditions. The close association observed between BGC transcription and compound production warrants additional efforts to develop genetic engineering tools for boosting compound yields from myxobacterial producer strains.

MyxoTech – a commercial vehicle to expand the potential pharmaceutical use of the myxobacterial specialized metabolome

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The Helmholtz Center for Infection Research (HZI) and Leibniz Institute – German Collection of Microorganisms and Cell Cultures (DSMZ) house a unique collection of bacteria that exist on the fringe of microbial dark matter. These myxobacteria are established producers of pharmaceutically relevant natural products, such as epothilone B, the precursor to ixabepilone, approved by the US FDA to treat breast cancer. There are currently several compound families, including the chlorotonils and cystobactamids, from this group of organisms being advanced as anti-infective leads.

While anti-infective work at HZI has been a highly fruitful endeavor, myxobacterial specialized metabolites need to be evaluated in other indications to fulfill their true therapeutic value. With this conviction, researchers at the HZI and the Helmholtz Institute for Pharmaceutical Research Science (HIPS) are spinning out a new company called MyxoTech. The company will serve as a preclinical contract research organization to pharmaceutical companies focused on disease areas other than anti-infectives. MyxoTech will offer access to its myxobacterial specialized metabolite library and provide downstream natural products drug discovery services.

The company will build a strain library from selected copies of strains from the HZI/HIPS/DSMZ myxobacterial collection. This collection's diversity exists nowhere else in the world and, thus, produces chemistry exclusive to the collection. With this in mind, MyxoTech will offer a library of unique chemical diversity to pharmaceutical drug discovery companies only available through MyxoTech. To ensure this diversity, a phylogenetic assessment is ongoing to maximize diversity of strains included in the MyxoTech library.

Our company will offer three work packages to our pharmaceutical industry clients. In the first package, clients will have access to the specialized metabolite library to screen in their proprietary biological assays. In the second package, MyxoTech will identify and elucidate the active components identified from the initial screening. In the third package, MyxoTech will improve production yield of the active component sufficient for more advanced preclinical evaluation via application of genetic engineering and culture manipulation strategies.

With MyxoTech, we are committed to maximizing the potential societal value of HZI's world-class myxobacterial library.

Investigation of RiPPs originating from two-domain precursors

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Ribosomally synthesized and post-translationally modified peptides (RiPPs) are a diverse class of secondary metabolites with a wide range of bioactivities. They all share a ribosomal origin, as the peptide sequence is encoded in a so-called precursor gene. Often, precursor peptides are short and lack clear structural features. As an exception, the family of the "nitrile hydratase leader peptides" (NHLP) are characterized by unusually long leader sequences that show similarity to the enzyme nitrile hydratase. In certain species of the order Burkholderiales, these NHLP precursors further appear as tandem genes, i.e. two copies of the precursor are present in a row. Intriguingly, in a few strains, these genes are fused into a single two-domain precursor, resulting in a ~270 amino acid precursor protein. Notably, the gene clusters lack peptidases or export systems and commonly observed protease cleavage motifs are not present in the precursor. The function of the two leader domains as well as the nature of the resulting RiPP(s) are thus currently unclear.
Here, we investigated these so-far uncharacterized RiPP clusters to identify the produced metabolite(s), characterize the biosynthetic enzymes, and explore the role of the two leader domains in the precursors. We selected *Acidovorax oryzae*, which harbors a single two-domain precursor, and *Burkholderia thailandensis*, which encodes two separate NHLP precursors as tandem genes, to study both types of gene clusters. We heterologously expressed the gene clusters in *Escherichia coli* and analyzed the precursor protein for the appearance of post-translational modifications using LC-MS. The activity of a cyclodehydratase and a methyltransferase present in the gene cluster could successfully be reconstituted and the resulting modifications were localized at the C-terminus. In case of the tandem NHLP precursors, the two proteins co-eluted as a dimer and only the C-terminus of the second precursor was modified, suggesting that only one core peptide is present. Size-exclusion chromatography surprisingly revealed that the precursor proteins further assembled into multimeric complexes of ~160 kDa. We then crystallized the post-translationally modified precursors and determined their structures using X-ray crystallography. In case of the tandem precursors, the structure revealed a symmetric assembly of six precursor dimers. Such multimeric complexes are unexpected for a RiPP precursor and we are currently investigating the function and activity of these structures.

Heterologous production of non-ribosomal peptide indigoidine in *Myxococcus xanthus*

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Indigoidine is an antimicrobial and antioxidant natural product which is used as natural blue dye in food and textile industry. Potentially, it is even useful in bio-electronics as semiconductor [1] making it a highly interesting molecule for industrial applications. The indigoidine molecule was first described in *Vogesella indigofera*, but is widely distributed in many other genera, such as *Dickeya*, *Streptomyces* or *Corynebacterium* [2]. This dimeric non-ribosomal peptide (NRP) is generated by a single-module non-ribosomal peptide synthetase (NRPS) that generates the monomer by cyclizing the precursor amino acid L-glutamine. It has been proposed that two monomers spontaneously and oxidatively dimerize to indigoidine. By now, two homologous NRPSs, namely blue pigment synthetase A (BpsA) and IndC, are known to be responsible for the monomer synthesis [3]. *Myxococcus xanthus* is a gram negative *δ*-proteobacterium that is well known for its motility and cooperative behaviour. Additionally, it is a native producer of a variety of secondary metabolites including NRPs, polyketides or hybrids thereof [4]. Due to its biosynthetic proficiency, it is now also gaining attention as host for the heterologous production of bioactive natural products. In this work, the *bpsA* gene from *Streptomyces lavendulae* was successfully expressed in *M. xanthus* to produce the NRP indigoidine. An endogenous PPTase of *M. xanthus* was found to be sufficient to activate the NRPS from its *apo*- to its functional *holo*-form. Furthermore, the impact of various fermentation parameters on the production and stability of the pigment was investigated.

References:

[1] Yumusak C, Prochazkova AJ, Apaydin DH, Seelajaroen H, Sariciftci NS, Weiter M, Krajcovic J, Qin Y, Zhang W, Zhan J, Kovalenko A: Indigoidine – Biosynthesized organic semiconductor. *Dyes and Pigments* 2019, 171:107768.
[2] Santos MCD, Bicas JL: Natural blue pigments and bikaverin. *Microbiol Res* 2021, 244:126653.
[3] Pang B, Chen Y, Gan F, Yan C, Jin L, Gin JW, Petzold CJ, Keasling JD: Investigation of Indigoidine Synthetase Reveals a Conserved Active-Site Base Residue of Nonribosomal Peptide Synthetase Oxidases. *J Am Chem Soc* 2020, 142:10931–5.
[4] Sester A, Korp J, Nett M: Secondary Metabolism of Predatory Bacteria. In *The Ecology of Predation at the Microscale*. Edited by Jurkevitch E, Mitchell RJ. Springer International Publishing; 2020:127–53.

Clickable microcystins as payloads for antibody-drug conjugates

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Microcystins (MCs) are nonribosomal cyclic heptapeptides produced by freshwater cyanobacteria like *Microcystis* and *Planktothrix*. Microcystins are well studied cyanotoxins, and known for their inhibition of the eukaryotic serine/threonine protein phosphatases 1 and 2a with IC_{50} values in the pico- to nanomolar concentration range [1]. Unlike many other cytotoxic agents that enter cell by passive diffusion, MCs are dependent on an active uptake via organic anion transporting polypeptides (OATP) 1B1 and 1B3, which are expressed especially by liver cells [2]. The transportability strongly depends on the structure of the MCs and can dramatically differ by the exchange of one single amino acid in the core structure [3].

Because of the high potency, the yet unexploited mode-of-action of MCs, the unlikely resistance development, and the prospect of lower side effects compared to known payloads of antibody-drug conjugates (ADCs), we strive to develop MC derivatives with optimized properties that can be used as cytotoxic payloads for ADCs. Here, we present the semi-synthesis of MC analogues bearing different properties and their *in vitro* characterization. Easily derivatizable, "clickable" MCs were produced in distinct *Microcystis* sp. strains by precursor-directed biosynthesis [4], followed by extraction of biomass and isolation of these unnatural MCs by flash chromatography and HPLC. The obtained MCs were modified with a library of small molecules with different properties (e.g., charge, lipophilicity, size) using copper-catalyzed cycloaddition ("click chemistry"). The structures of the synthesized MC derivatives were confirmed by $HRMS^2$. To study structure-activity as well as structure-transportability relationships of the compounds, both cell viability studies as well as phosphatase inhibition assays have been performed.

References:

[1] MacKintosh, C. et al.: *FEBS Lett.* **1990**, 264(2) :187-192.

[2] Hagenbuch, B., Gui, C.: *Xenobioatica* **2008**, 38(7-8): 778-801.

[3] Niedermeyer, T.H.J. et al.; *PLoS ONE* **2014**, 9(3): e91476.

[4] Moschny, J. et al., *J. Nat. Prod.* **2020**, 83(6): 1960-1970.

Genome sequence-based screening novel phosphonate producers

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Phosphonates are a unique class of natural products with diverse chemical structures and bioactivities. Numerous phosphonate natural compounds found their way into the market as for example the herbicide bialaphos, the antimalarial agent fosmidomycin or the antibiotic fosfomycin. An initial biosynthetic reaction step catalysed by the enzyme phosphoenolpyruvate phosphomutase (PepM) forms the characteristic C-P bond, in the isomerisation of phosphoenolpyruvate (PEP) to phosphonopyruvate (PnPy) [1]. Due to the conservation of the PepM enzymatic reaction in the vast majority of phosphonate producers, the respective biosynthetic gene *pepM* is well suited to be used as a molecular marker to screen for potential phosphonate producer strains.

In our study, we screened the DSMZ *Actinomycetales* strain collection for novel phosphonate producers. The DSMZ strain collection harbours > 4.000 actinomycetes, many of which have already been genome-sequenced. A bioinformatic analysis of ~600 genome sequences resulted in 49 strains containing a *pepM* gene and thus a potential phosphonate biosynthetic gene cluster (BGC). Out of these, 17 showed antimicrobial activity against the phosphonate-sensitive *E. coli* strain WM6242 [2]. Phylogenetic analysis of the PepM amino acid sequences revealed a BGC-specific cladding. Cluster networking analysis were performed in order to prioritize strains with unique clusters for further analysis. Two strains, *Kitasatospora* sp. DSM 114396 and *Streptomyces iranensis* DSM 41954, have been prioritized for further analysis regarding genetic engineering and phosphonate compound identification which will be discussed in more detail.

References:

[1] Metcalf, W. W. & van der Donk, W. A., *Annu Rev Biochem* **78**, 65–94 (2009).

[2] Eliot, A. C. *et al.*, *Chem Biol* **15**, 765–770 (2008).

Discovery of new anti-infectives in the Sordariales

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The order Sordariales (Ascomycota, Fungi) represent one of the largest and most diverse taxonomic groups within the class Sordariomycetes, and contains soil-borne, lignicolous, herbicolous, and coprophilous species. Sordarialean fungi are also well-known as a reservoir of secondary metabolites with potential beneficial applications, even though the majority of the genera remain unexplored [1]. Recent studies using polyphasic approaches have provided the basis for a better understanding of the taxonomic placement of species from this order [2,3]. In order to translate this taxonomical diversity into the effective discovery of new anti-infectives we have integrated state of the art metabolomics tools as part of our current screening pipeline. Consequently, this has resulted in the discovery of more than 30 new natural products with diverse biological activities, which demonstrates the large diversity of biosynthetic pathways in these fungi [4,5]. We could expect that in the future the incorporation of different –OMICs techniques (genomics, proteomics, etc.) might further accelerate the identification of biologically active molecules that can be made available for our discovery program on anti-infective natural products.

References:

[1] Charria-Girón et al. (2022). Diversity of biologically active secondary metabolites in the ascomycete order Sordariales. Myc Prog.
[2] Marin-Felix Y. and Miller A. (2022). Corrections to recent changes in the taxonomy of the Sordariales. Myc Prog.
[3] Marin-Felix Y. et al (2020). Re-Evaluation of the Order Sordariales: Delimitation of Lasiosphaeriaceae s. str., and Introduction of the New Families Diplogelasinosporaceae, Naviculisporaceae, and Schizotheciaceae. Microorganisms.
[4] Charria-Girón E. et al. (2023). *Amesia hispanica* sp. nov., Producer of the Antifungal Class of Antibiotics Dactylfungins. J Fungi.
[5] Charria-Girón E. et al. (2023). Neochetracin, an unusual chetracin-type epithiodiketopiperazine produced by the fungus *Amesia atrobrunnea*. Submitted

Metabolic profiling can predict complex modes of action for cytotoxic drugs

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One bottleneck in the discovery of novel anti-cancer drugs is the identification of the molecular target(s) of a drug candidate in cancer cells. In view of this, metabolomics can be an excellent tool to mechanistically investigate the responses of cancer cells upon treatment with new drug candidates. Herewith, we describe the application of ion-pairing LC-MS/MS by using a multi-targeted, MRM-based approach to profile 180 metabolites of the central carbon and energy metabolism (CCEM) in prostate cancer cells (PC3). We developed an extraction protocol for adherent cells for the reproducible assessment of the abundance of CCEM metabolites including labile CoA esters, NADPH and ATP. Treating PC3 cells with a set of anti-cancer drugs with known modes of action (MOA), we obtained metabolic fingerprints, so called “metabotypes”. Strikingly, these training data supplied distinctive metabolic patterns specific to individual MOAs, which were evaluated by hierarchical clustering of different metabotypes and descriptive statistical analyses on their predictive power. Moreover, most metabolic fingerprints allowed for plausible interpretation of inhibitory drug effects in the CCEM. Applying machine learning to predict the MOA of highly cell-toxic, plant-derived and (semi)synthetic compounds, our model promises to be a valuable tool in the developmental pipeline of novel anti-cancer drug candidates.

Elucidating antifungal phytochemicals from wild herbaceous plants

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Wild plants play an important role in the ecosystem. Through their nectar and pollen supply, they attract pollinating insects. In addition, they can provide an alternative to insecticides by biocontrolling pests in flowering strips, thus securing or even increasing yields. Wild plants can have a phytosanitary effect and are widely used as food or medicinal products. So far, only a few wild plants have been studied in more detail with respect to their bioactive compounds.
In the InnoWild project, we are investigating seven wild plant species: wild thyme (*Thymus serpyllum*), rabbitfoot clover (*Trifolium arvense*), wild carrot (*Daucus carota*), burnet-saxifrage (*Pimpinella saxifraga*), meadow clary (*Salvia pratensis*), common evening primrose (*Oenothera biennis*) and mountain-parsley (*Peucedanum oreoselinum*), for which various effects have been observed (e.g., antimicrobial properties, phytosanitary effects).
In a bioactivity assay, the effects of ethanol and water soluble extracts of organs from wild plants (root, shoot) have been screened in vitro for their antimicrobial activity against the soilborne pathogen *Rhizoctonia solani* and the leaf pathogen *Xanthomonas campestris*. For this *R. solani* was grown on agar plates without nutrients and by spreading extracts on agar plates and then allowing the fungus to grow from the center. Mycelial growth was monitored for one week and evaluated in comparison to the solvent control.
For the bacterial assays, the bacteria were grown overnight in liquid cultures and adjusted to a specific OD. Subsequently, the extracts were added and the OD was measured at specific time points. The highest antimicrobial properties were detected for *P. saxifraga*, *P. oreoselinum*, *O. biennis* and *T. arvense*.
In order to identify the compounds responsible for the growth inhibition of the pathogens, extracts showing high antimicrobial activity were fractionated by solid phase extraction and the fractions were also tested against the pathogens.
With a growth inhibition of up to 66%, the 50% ethanolic fraction of the seeds of P. *saxifraga* was the most inhibitory fraction. Inhibiting fractions were again fractionated into subfractions. Subfractionation and its testing will eventually lead to the identification of the inhibiting pure substance.
Funding: This study and the InnoWild project is funded by the Federal Ministry of Education and Research (BMBF), through the Project Management Jülich, Grant No. FKZ 03WIR3012 A. The InnoWild project is part of the “Land-Innovation-Lausitz” Initiative, which is part of the WIR! Alliance (Wandel durch Innovation in der Region). F. S. Hanschen is funded by the Leibniz Association (Leibniz Junior Research Group OPTIGLUP; J16/2017).

Development of preventive vaccines in Latin America – the GLACIER project

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GLACIER – German-Latin American Centre of Infection & Epidemiology Research & Training is a large network encompassing 18 higher education institutions, research institutes and public stakeholders from eight Latin American countries as well as eight higher education institutions from Germany. In close partnership with scientific institutions in Mexico, Cuba and Central America, the health centre follows a holistic "One Health" approach. Various disciplines – from virology to vaccine and drug research to social sciences – work together in close cooperation with national and international institutions involved in preventive health care and pandemic control. In total 35 partners in eight countries and five additional expert groups from Germany are involved in the centre. The GLACIER multidisciplinary consortium aims to strengthen the prevention and treatment of communicable diseases and the development of new vaccines and therapies. It also aims to improve crisis preparedness, response and post-crisis care. **GLACIER** is operated under the joint leadership of the the Institute of Virology at Charité – Universitätsmedizin Berlin and the Institute of Medical Immunology at Martin Luther University Halle-Wittenberg (MLU) in association with the Leibniz Institute of Plant Biochemistry (IPB). Central partner institutions in Central America are the region's leading universities, the University of Havana (UH) and the Independent National University of Mexico (UNAM), each of which will host central research and training laboratories. The international and transdisciplinary dimension of pandemic preparedness and response will also be strengthened by 35 partners in a total of 8 Central American countries and five additional expert groups from Germany. **GLACIER** aims to work towards strengthening capacities in the Latin American region by (i) serving as a think tank supporting a multidisciplinary network of institutions in 8 Central American countries, (ii) helping to build local research capacity, (iii) increasing the number of well-trained experts/scientists and trainers, and (iv) engaging regional and international policy makers, enabling information dissemination and faster regional crisis response.

URL: https://glacierproject.org

Novel terpenoids by terpene synthase-mediated biotransformation of non-natural prenyl diphosphates

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The primary components of flower scents and natural aromas are volatile mono- and sesquiterpenes. These terpenes are highly valued in various industries for their fragrance properties, including food additives, cosmetics, and cosmeceuticals. In addition to their commercial importance, they possess significant biological and pharmaceutical activities, such as attractants, repellents, toxins, and antibiotics. Terpenes are biosynthesized from prenyl diphosphates by terpene synthases (terpene cyclases). These enzymes convert these simple, linear, non-chiral substrates into complex multicyclic structures in an enantioselective manner.

In our study, we utilized two terpene cyclases, a limonene synthase from *Cannabis sativa* (CLS) and a 5-*epi*aristolochene synthase from *Nicotiana tabacum* (TEAS), as biocatalysts. These enzymes exhibited remarkable promiscuity towards non-natural prenyl diphosphates, resulting in the production of new terpenoids with oxa- and thia-heterocycles at their core, as well as terpenoids that were modified with alkynes. We determined the structures of five novel monoterpene-analogues and one known sesquiterpene-analogue. This demonstrates the potential of these two terpene synthases to produce novel structurally complex terpenoids from non-natural substrates. Docking studies indicated that the non-natural substrates underwent an on-off conversion.

Glucosinolates in *Brassica* vegetables: Deciphering the mechanisms for the formation of bioactive products

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Glucosinolates are sulfur rich plant secondary metabolites in *Brassica* vegetables such as cabbage or broccoli. They are precursors of bioactive and health-promoting isothiocyanates (ITCs). ITC are valued for their cancer preventing properties that are based on chemopreventive mechanisms [1].

Upon enzymatic hydrolysis by the enzyme myrosinase, glucosinolates in *Brassica* vegetables can form ITCs and in presence of specifier proteins also nitriles and epithionitriles [2]. Food processing conditions strongly affect the outcome of hydrolysis and the levels of ITC due to different mechanisms which will impact the health promoting value liked to these compounds. Here, the underlying mechanisms that affect ITC levels in *Brassica* vegetables will be discussed. For example, recently our group revealed that ITC can be quickly converted to amines by an enzyme-like mechanism in cabbage [3]. Thermal processing strongly affects these compounds and follow-up reaction products can be formed. For example, 3-alk(en)yl-4-hydroxythiazolidine-2-thiones can yield from ITC and thioglucose formed during boiling of cabbage. As, their formation does not contribute to health promoting effects related with *Brassica* consumption [4] and it should be target to maintain ITC levels.

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References:

[1] D. L. Palliyaguru, J.-M. Yuan, T. W. Kensler, J. W. Fahey, *Mol. Nutr. Food Res.* **2018**, *62*, 1700965.

[2] F. S. Hanschen, M. Schreiner, *Frontiers in Plant Science* **2017**, *8*, 1095.

[3] L. Andernach, K. Witzel, F. S. Hanschen, *Food Chem.* **2023**, *405*, 134907.

[4] H. Hoffmann, C. Ott, J. Raupbach, L. Andernach, M. Renz, T. Grune, F. S. Hanschen, *Frontiers in Nutrition* **2022**, *9:941286*.

The influence of temporal effects on human taste perception

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Human taste perception is crucial for the selection of healthy versus harmful food items. The reception of taste relevant molecules is facilitated by specialized receptors for the basic taste qualities sweet, sour, salty, umami (the savoury taste of L-glutamic acid), and bitter. As all taste receptors are expressed in sensory cells of the oral cavity, each compound capable to activate one of them should result in discriminable taste perception. However, this rather straightforward principle is frequently obscured by acute or temporal mixture effects as well as by the existence polymodal taste compounds.

Using functional heterologous expression assays of sweet and bitter taste receptors and psychophysical analyses of human volunteers, we recently observed the molecular basis for some of the temporal and mixture effects.

When comparing time-intensity curves observed for synthetic sweeteners in human probands with functional in vitro experiments for the same compounds, we found that for some sweeteners the receptor assay mimics temporal effects such as lingering and onset well, while for other sweeteners different mechanisms may be effective. Concerning bitter taste, we found that, in addition to previous observations on acute competitive mixture effects, also temporal effects exists. One such effect, which demonstrates a bitter taste-interaction between roasted coffee and chicory, as well as chicory-based surrogate coffee, will be discussed in detail.

In summary, our findings shed new light on human taste perception of complex food items.

Microbial natural products and community survival - a role for metabolite exchange interactions

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Metabolism is deeply intertwined with survival. While the molecular roles of intracellular metabolism have been investigated extensively, the metabolic communication between co-growing cells in tissues and communities remains poorly characterised. Here we identify a novel role of cooperative metabolite exchange between eukaryotic microbial cells in modulating the community survival. We observe cross-generational metabolic crosstalk, wherein young yeast cells export metabolites that are then imported by aged cells. We then show, in a synthetic community model that promotes metabolic cooperativity, that cell-cell metabolite exchange significantly increases the yeast chronological lifespan via a pro-survival exometabolome. Time-resolved multi-omic profiling and metabolic modelling revealed the specific role of long-lived methionine consumer cells. These are enriched during ageing and export protective metabolites, particularly glycerol, thus creating an environment that also promotes the longevity of all co-growing cells, including methionine producers. Our results establish metabolite exchange interactions as a determinant of cellular ageing and show that microbial communities modulate their survival and lifespan via a self-generated shared chemical space.

POSTER PRESENTATIONS

The Pathogen Repository at the Leibniz-Institute DSMZ - a reliable and lasting source for test isolates and reference strains

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The Pathogen Repository is part of the infrastructure “Bioresources, Biodata and Digital Health (TI BBD) of the German Center for Infection Research (DZIF) and is located at the Leibniz Institute DSMZ. The TI BBD is a DZIF-wide infrastructure providing biosamples and collections of pathogens and the corresponding information, databases, analysis tools and apps, as well as templates, samples or work instructions that are needed more than ever for translational infection research. Currently, the Pathogen Repository at the Leibniz Institute DSMZ comprises approximately 4,000 authenticated, clinically relevant microorganisms from >250 bacterial genera. This publicly accessible collection of isolates is growing continuously and ensures the availability of quality-controlled, standardized and well-documented microorganisms as well as the associated data for research projects. Specifically, the repository contains a variety of clinical isolates, including common pathogens (ESKAPE organisms, multiresistant strains) but also understudied human pathogens, e.g., of the genera *Myroides, Comamonas, Acinetobacter, Wohlfahrtiimonas* and *Roseomonas*. Another and increasingly important focus of the repository is the collection of microbiome strains from the gastrointestinal tract of humans, mice, pigs and chickens.

Tailored to the individual needs of DZIF researchers, various deposit options have been developed (public collection, closed collection with exclusive access, security deposit and backup storage). In order to support the selection of relevant strains by the depositors, a key strain concept has been developed, which contains relevant selection criteria (e.g. new pathogens, reference strains, strains of multicenter studies, important outbreak strains, microbiome strains).

Genomic Analysis of the freshwater fungus *Filosporella fistucella* (*Helotiales*) indicates potential for plant litter degradation in cold temperatures

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Freshwater fungi play an important role in the decomposition of organic matter of leaf-litter in rivers and streams. They also possess the necessary mechanisms to endure lower temperatures caused by habitat and weather variations. This includes the production of cold-active enzymes and antifreeze proteins. To better understand the physiological activities of freshwater fungi in their natural environment, different methods are being applied, and genome sequencing is one in the spotlight. In our study, we sequenced the first genome of the freshwater fungus *Filosporella fistucella* Marvanová and P.J. Fisher (45.7 Mbp) and compared the genome with the evolutionary close-related species *Tricladium varicosporioides* (Tubaki) P.R. Johnst. & Baschien (48.2 Mpb). The genomes were annotated using the carbohydrate-active enzymes database where we then filtered for leaf-litter degradation-related enzymes (cellulase, hemicellulase, laccase, pectinase, cutinase, amylase, xylanase, and xyloglucanase). Those enzymes were analysed for antifreeze properties using a machine-learning approach. We discovered that *Filosporella fistucella* has more enzymes to participate in the breakdown of sugar, leaf, and wood than *Tricladium varicosporioides* (855 and 719, respectively). *Filosporella fistucella* shows a larger set of enzymes capable to resist cold temperatures than *T. varicosporioides* (75 and 66 respectively). Our findings indicate that in comparison with *T. varicosporioides*, *F. fistucella* has a greater capacity for aquatic growth, adaptability to freshwater environments, and resistance to low temperatures.

Killifish Intervention Platform (KIP)

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Development of therapeutic drugs is critically dependent on the availability of reliable tools, allowing prognostic assessment of long-term health of humans and the impact of interventions thereupon. Classical vertebrate models, such as mice or zebrafish, have lifespans of several years, requiring extremely cost- and time-intensive long-lasting experimental protocols for research into ageing and health-span. Short-lived invertebrates are frequently used for this purpose. However, compared to vertebrates, invertebrates sometimes use completely different biological structures (such as body structure) or processes (such as immune responses). In addition, also *in vitro* systems of vertebrates cannot appropriately reflect the systemic response to compounds of different organs (and Microbiome) upon ageing and disease within a whole organism. Thus, many fundamental processes cannot be studied without the use of vertebrate animals.
Nothobranchius furzeri (killifish) is the shortest-lived vertebrate species that can be bred in captivity, with a mean lifespan of only 4-10 months. Killifish replicate many typical aspects of vertebrate biology and some of these spontaneous phenotypes resemble human diseases. We studied and analysed phenotypes of ageing and the associated dynamics of changes in proteome and transcriptome. Furthermore, we developed AI-based transcriptomic clocks that allow a precise prediction of age in fish and humans. These clocks could identify an anti-ageing effect or health improving effect of a compound when applied before and after a treatment on fin biopsies. This enables to perform pharmaceutical studies in a fraction of time in comparison to other species.
Our platform is particularly suitable for the characterization and quantification of therapeutic effects of bioactive compounds. Several routes of compound administration are established and we can assess the effects of a compound from organism to molecular level within a period of only 4 weeks or even shorter time (Baumgart et al., 2016; Kelmer Sacramento et al., 2020). Effects of interventions on lifespan are also measurable in less than a year (Valenzano et al., 2006; Terzibasi et al., 2009; Baumgart et al., 2016).
The killifish displays a particularly short lifespan. This offers the possibility of obtaining both quickly and cost-effectively new insights into the effects on ageing and health-span upon drug application.
We offer our expertise as killifish based intervention platform to create cohorts and derived tissues for follow-up analyses.

INCATE: Supporting innovators to fight drug-resistant infections

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INCATE, the Incubator for Antibacterial Therapies in Europe is a unique not-for-profit organization that brings together translational and basic research, industry, experienced entrepreneurs and investors from across Europe to help meet the challenge of Antimicrobial Resistance (AMR). It was founded in 2021 by a partnership of four academic members: the Leibniz Institute for Natural Product Research and Infection Biology (HKI), the German Center for Infection research (DZIF), the Swiss National Centre of Competence in Research (NCCR) AntiResist and the University of Basel. Industry partner including Boehringer Ingelheim Venture Fund, SHIONOGI, Roche and MSD Germany provide non-dilutive funding, and importantly, insights on market demand and R&D advice. INCATE, together with partners, focus on supporting innovators to take their projects and ideas out of academia and research and develop them into investable ventures. We support by providing advice, access to our community and non-dilutive funding up to 250.000 € to accelerate the development of your innovation. We focus on the development of new treatments, diagnostics and interventions that help reduce the prevalence and impact of AMR.
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Antimicrobials discovery: targeted induction of streptomycetes specialised metabolism by heterologous expression of SARP transcriptional activators

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Streptomycetes are high-GC Gram-positive bacteria with an extraordinarily complex life cycle, and an equally extraordinary capacity for the production of specialised metabolites, many with important bioactivities useful in medicine.[1] Streptomycetes are our main source of antimicrobials, with almost two thirds of all antibiotics used in the clinic having originated from natural products isolated from streptomycetes.[2] Production of specialised metabolites is tightly regulated by a network of gene expression regulatory mechanisms, that hinder or even prevent the synthesis in the laboratory of most of the metabolites a strain is genetically capable of producing.[3] A type of transcriptional regulator is the Streptomyces Antibiotic Regulatory Protein (SARP). SARP encoding genes are often found within "biosynthetic gene clusters" (BGC, a continuous region of the genome where all genes required for the production of a particular specialised metabolite are located) to specifically regulate the expression of the pathway. SARPs are pathway-specific transcriptional activators that bind to specific motifs within the promoter sequence to induce the expression of the regulated genes, often the entire biosynthetic pathway.[4] PapR2 is a SARP that activates the biosynthesis of pristinamycin in *Streptomyces pristinaespiralis*. We have previously shown that heterologous expression of *papR2* is sufficient to induce the expression of silent BGCs in two unrelated *Streptomyces* strains, due to the presence of a SARP-binding motif in the promoter sequence that is similar enough to that recognised by PapR2.[5] We leverage on this genetics knowledge, our capacity to identify putative SARP genes and DNA-binding motifs by bioinformatic analysis, and to manipulate the genetics of streptomycetes, to activate the production of unknown bioactive natural products. Here we explain our current strategy and initial results, successes and failures, to obtain new antimicrobial natural products from streptomycetes. Our pipeline involves: 1) selection of genome-sequenced strains available at DSMZ collection; 2) blastP search for PapR2 homologs and selection of the most similar ones; 3) extraction of 150 kb of DNA sequence at each side of *papR2*-homolog (sufficient to include the entire putative BGC at either side) 4) search for the known PapR2-binding motif and selection of closest candidates; 5) Heterologous expression of *papR2* in these strains and assay for induced antimicrobial activity. With this strategy we have so far prioritised a dozen strains; we have mobilised different *papR2* overexpression constructs to eight strains; and we have found induced antimicrobial activity in four of them upon *papR2*-expression. We are currently focusing our efforts on identifying the molecules responsible for the antimicrobial activity, as well as expanding the target strains and improving the *papR2*-overexpression system.

References:
[1] Barka et al., 2016; *Microbiol. Mol. Biol. Rev*. 80:1
[2] Bérdy, 2012, *J. Antibiot*. 65:385.
[3] Bibb, 1996; *Microbiology* 142:1335. Baltz, 2017; *J Ind Microbiol Biotechnol* 44:573
[4] Wietzorrek and Bibb, 1997; *Mol Microbiol* 25:1181
[5] Krause et al., 2020; *Front. Microbiol*. 11:2020.00225

New plant-derived natural products for the treatment of chronic blood diseases

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Chronic blood diseases (CBD) are often associated with ageing and are a reason for increased dependency and premature mortality in older people. These diseases thus represent a relevant clinical and social challenge for our ageing society. The cause of such diseases, e.g., chronic myeloid leukemia (CML) or chronic myeloproliferative neoplasia (CMN), is the abnormal proliferation of blood progenitor cells. The pathological triggers are mostly mutations of proteins regulating the cell growth and cell differentiation. It was the aim of the presented project to identify and characterize new natural products (NPs) from plants (and fungi) addressing and inhibiting those CBD-associated molecular targets. The poster summarizes the natural products' *in silico* preselection from the Leibniz Institute of Plant Biochemistry's proprietary NPs library as well as the *in vitro* cell-based and biochemical screening and characterization of selected candidates by means of an example.

The DSMZ Actinomycetes Collection: A treasure trove for novel bioactive natural products

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The DSMZ *Actinomycetales* collection harbors more than 4.600 actinomycetes, many of which belong to the well-known potent antibiotic-producing genus of *Streptomyces*, as well as numerous strains of rare taxa. The collection encompasses taxonomically diverse type strains of validly named species and unique actinobacterial strains with agricultural, environmental and biotechnological interest. Two-thirds of all clinically relevant antibiotics, as well as many anticancer, antifungal or immunosuppressive agents are derived from Actinomycetes. Our research focuses on enhancing the diversity of the *Actinomycetales* taxon and highlighting their pharmaceutical and biotechnological potential based on taxogenomic and genome mining approaches. In an effort to discover novel bioactive compounds, the *Actinomycetales* collection has been screened for novel species on the premise that novel biology leads to novel chemical entities. We apply genome mining approaches to identify and prioritize interesting biosynthetic gene clusters and characterize them by genetic manipulation. With the help of genetic engineering techniques, we optimize production yields and manipulate chemical structures of natural compounds to improve compound characteristics. Special focus is laid on investigating regulatory circuits in antibiotic producers.

Novel antiviral concepts against SARS-CoV-2

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The COVID pandemic has started the world's quickest ever race for effective vaccines and specific antivirals. While some new vaccines became a huge success story, antivirals were lagging behind and ran into dead ends like Chloroquine did. Testing approved drugs against SARS-CoV-2 made absolute sense just as much as developing novel antiviral compounds and strategies in foresight of new virus variants and the next pandemic.
Here, I would like to summarize several highly collaborative projects leading to diverse antiviral drug candidates or concepts, including:

1. Antiviral Activity of Influenza A Virus Defective Interfering Particles against SARS-CoV-2 Replication In Vitro through Stimulation of Innate Immunity
2. Persicamidines – Unprecedented Sesquarterpenoids with Potent Antiviral Bioactivity against Coronaviruses
3. Foscarnet-Type Inorganic-Organic Hybrid Nanoparticles for Effective Antiviral Therapy
4. The short isoform of the host antiviral protein ZAP acts as an inhibitor of SARS-CoV-2 programmed ribosomal frameshifting

All of which involved screening and antiviral testing by me with the strong support of the VIRI research group of Prof Luka Cicin-Sain and the BSL3 lab led at the time by Dr Susanne Talay both at the Helmholtz Centre for Infection Research. Research groups of the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, the Helmholtz Institute for RNA-based Infection Research (HIRI) in Würzburg, the Karlsruhe Institute of Technology (KIT), the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken, and the TWINCORE - Center for Experimental and Clinical Infection Research in Hannover.
This overview intends to spark new ideas, interesting conversations, and new fruitful collaborations.

The DSMZ Phage Working Group:

Phage genomics & application - clinical phages & regulations

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It is the bacterial strain collection of the DSMZ itself that provides an essential basis for isolating, characterizing and investigating new phages at the DSMZ and for using them in our research projects. The growing bank contains over 1.200 phages for more than 150 species. Phages for the *ESKAPE* bacteria dominate the collection and are used in the externally funded projects: *Pseudomonas aeruginosa* in Phage4Cure, several prioritized species in PhagoFlow and *Enterococcus faecium* in EVREA-Phage. Other larger phage panels exist for *Achromobacter xylosoxidans* or *Stenotrophomonas maltophilia* and the DFG-funded SPP2330 Z project which is being worked on at the DSMZ also substantially feeds special phage collections from the project consortium into our bank. Major axes within the SPP2330 are isolation, deposit and provision of phages and hosts, phage characterization including morphology, genomes and establishing the novel database PhageDive.
One topic of the DSMZ phage bank is defined by medical needs: new phages can be searched for upon clinicians' requests. Phages were also isolated on rather rare patient isolates of different genera. For genomic phage authenticity confirmation in human investigational medicinal products (IMP), the DSMZ was granted certification of GMP compliance according to Sect. 64 para 3f, German Drug Law by the competent authority in 2022, representing a milestone for currently running and future medical phage projects. A special MTA excludes direct therapeutic application of DSMZ phages.
Accessioning external deposits towards broad biodiversity is an original task of a culture collection, including phages. However, the preconditions as laid down by the Nagoya Protocol created far-reaching international consequences. Being the first culture collection registered as "Nagoya compliant", the DSMZ takes care of all associated documentation of its bioresources. Like all other bioresources phages can be deposited with the DSMZ without costs.
Since 2017, the DSMZ got involved in human phage therapy projects e.g., in a clinical trial applying phages by inhalation (Phage4Cure, https://phage4cure.de, funding: BMBF) or following the "Belgian route" using magistral application (PhagoFlow, www.Phagoflow.de, funding: Federal Joint Committee). Our most recently started project envisages to compose a phage cocktail against VRE (vancomycin-resistant) *Enterococcus faecium* for later intestinal decolonization in immunocompromised patients (EVREA-Phage, https://www.dzif.de/de/projekt/evrea-phage, funding: DZIF).
Apart from phage application, other phage biology aspects also play an important role and are in current focus of our research, e.g., genomics and work on the taxonomic classification within the International Committee on Taxonomy of Viruses (ICTV), general phage diversity or aspects of phage-host interaction.

The Z-Project - bacteriophage repository, services and Phage*Dive* database

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Within the DFG priority programme SPP 2330 which focuses on “New concepts in prokaryotic virus-host interactions – from single cells to microbial communities”, the Z-project provides essential service functions and access to state-of-the-art methodologies for studying all relevant aspects of the biology of prokaryotic viruses and is in charge of the long-term conservation, quality control and distribution of the isolated bioresources and their data. At this stage, various collaborations have been set up with several SPP partners to characterize bacteriophages (lifestyle, lysis kinetics, adsorption kinetics, host range) with different techniques such as EM microscopy. Furthermore, the isolation of new phages is important to expand our knowledge on their diversity and mechanisms. In this perspective, several projects were created to isolate new phages. Another major project of Z-project is the development of Phage*Dive*, a dedicated database for bacteriophages and archeal viruses. The database aims to gather all available information on these viruses. Phage*Dive* provides fields for various experimental data (lifestyle, lysis kinetics, adsorption kinetics, host range, genomic data, etc.) and the available metadata (e.g., geographical origin, isolation source). Data are standardized employing controlled vocabulary and ontologies and integrated in a prototype. The next improvements will be the interlink with other resources such as culture collections and databases for example the Viral Host Range database (VHRdb) such as the development of a clickable graphical representation of phage genome and genes.

Novel molecule activating transsulfuration pathway: a promising treatment for oxidative stress and mitochondrial dysfunction

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In last two decades, transsulfuration pathway and endogenously produced hydrogen sulfide (H_2S) have emerged as critical players in combating oxidative stress, mitochondrial dysfunction and endoplasmic reticulum [1]. Interestingly, hydrogen sulfide (H_2S) donors showed potential to treat not only diseases linked to oxidative stress, but also to abolish viral infections in animal models [2].

We discovered a new small molecule with already known favourable pharmacokinetic and safety profile that activates the transsulfuration pathway and demonstrated increase in intracellular H2S level upon its administration. Furthermore, our molecule helped cells to maintain mitochondrial function under chronic treatment with tert-butyl peroxide.

In order to find optimal clinical indications for our molecule, we analyzed hundreds of publicly available genome-wide CRISPR/Cas9 screens. This analysis revealed that genes involved in the transsulfuration pathway are modulators of cellular sensitivity to various DNA damaging agents and to cellular hypoxia. Thus, activation of transsulfuration pathway by our molecule may not only alleviate adverse effects of oxidative stress, but also offer clinical benefits in a variety of pathological contexts, including genetic syndromes associated with DNA damage and mitochondrial dysfunction.

References:

[1] Murphy, B., Bhattacharya, R., & Mukherjee, P. (2019). Hydrogen sulfide signaling in mitochondria and disease. The FASEB Journal, 33(12), 13098.

[2] Ivanciuc, T., Sbrana, E., Ansar, M., Bazhanov, N., Szabo, C., Casola, A., & Garofalo, R. P. (2016). Hydrogen sulfide is an antiviral and antiinflammatory endogenous gasotransmitter in the airways. Role in respiratory syncytial virus infection. American journal of respiratory cell and molecular biology, 55(5), 684-696.