SCIENTIFIC ABSTRACTS

Synthetic Biology Panel

Investigating the biosynthesis of tambjamines and prodiginines: bacterial alkaloid natural products

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The prodiginines and tambjamines comprise a large family of microbially produced bioactive alkaloids. They are characterized by a common bipyrrole and subclassified as prodiginines when they contain a third pyrrole or tambjamines with an alkyl amine instead. Despite isolation of a sizeable number of tambjamine molecules from natural sources, only a very small number of these molecules have been correlated with a producing microbe and a biosynthetic gene cluster, thereby limiting our understanding of the biosynthesis of the tambjamine subclass. In this presentation, the genome-guided isolation of several tambjamines will be discussed alongside our work to investigate several enzymatic steps in the later stages of prodiginine and tambjamine production.

SynBio and Marine Biotech: serving the servant

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Synthetic Biology (SynBio) is an emerging field of science and engineering that uses synthetic processes to design, alter, and create biological components. Distinctively, in SynBio, the engineering principles of "decoupling", "standardization", and "hierarchy" are applied to Biology. The ultimate goal is to tweak biological parts and systems to perform novel and/or unnatural tasks. In this talk, a couple of examples will be given to illustrate how SynBio can serve Marine Biotechnology to generate knowledge, promote greener approaches to otherwise polluting chemical processes, and foster solutions to address key societal challenges.

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Biocatalysis Panel

Microbial Biosynthetic Pathways – a treasure trove of novel enzymes and bioactive molecules

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Bacterial natural products continue to serve as one of the main sources of innovative chemical structures with diverse biological activities. Nature has evolved streamlined multi-step enzymatic processes to efficiently assemble these functional small molecules, which are often characterized by their complex molecular architectures. Chemical synthesis of many of these structurally intriguing small molecules, by contrast, remains challenging, even with the current advanced synthetic repertoire available to modern organic chemistry. The functional characterization and biocatalytic application of natural product biosynthetic enzymes has huge potential to complement the current chemical toolbox for complex molecule (bio-)synthesis.

We are particularly interested in elucidating unusual natural strategies yielding (poly-)cyclic natural products and in applying the underlying biosynthetic concepts to manipulate structurally complex natural product scaffolds. Within this talk our most recent work on the exploitation of natural core and tailoring biosynthetic enzymes for bioactive molecule synthesis will be presented. This includes strategies for their application by heterologous full pathway expression and manipulation in vivo, as well as their use as recombinant biocatalysts in chemo-enzymatic synthesis in vitro. The presentation will focus on regio- and stereoselective Red/OX manipulations as well as unusual C,C-bond forming transformations.

Biocatalytic strategies to unravel features of Fischerazol biosynthesis

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The Fischerazoles are lipopeptide natural products discovered from the cyanobacterium Fischerella sp. PCC 9431. These fatty-acid derived compounds are characterized by several unusual structural features, such as a pendant allyl alcohol moiety and a gem-dichlorovinylidene aliphatic chain terminus. We aim to recreate key steps of fatty acid modification in vitro, to understand the mechanism of fatty acid chain branching and establish a platform for targeted biocatalytic modification of fatty acids by using recombinant Fischerazol biosynthesis proteins. In this talk, several aspects of this projects are highlighted: artificial protein fusions to help track protein expression and increase solubility, surrogate redox partners for the P450 enzyme FshL, and peptide-based fatty acid conversion and MS analysis.

Bioinformatics Panel

Natural product biosynthesis off the beaten path: Machine learning-guided discovery of non-canonical natural products

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Over the last four decades, more than 50% of approved drugs have either been natural products or have at least drawn inspiration from them. Traditionally, natural products were discovered through bioactivity-guided fractionation. Since the low hanging fruits have been picked, the traditional workflow results in the frequent rediscovery of already known natural products.

To circumvent the rediscovery problem in the post genomics era, a new discipline, termed genome mining, was introduced into natural product research. Genome mining is an in-silico natural product discovery strategy. Several generations of highly sophisticated genome mining pipelines have been developed to identify natural product biosynthetic gene clusters in bacterial genome sequences. State-of-the-art genome mining pipelines largely rely on hard-coded biosynthetic rules for the identification of natural product biosynthetic blueprints. These biosynthetic rules have been deciphered over the past three decades and are specific to each individual natural product class. While these pipelines have successfully been used to map the biosynthetic space of well-studied natural product classes, they tend to overlook pathways that deviate from these seemingly universal biosynthetic principles or belong to very heterogenic natural product classes such as the ribosomally synthesized and posttranslationally modified peptides (RiPPs) that can be subdivided into more than 40 families.

We have developed a machine learning-based genome mining algorithm to systematically chart the biosynthetic space of the atropopeptides, a new RiPP family that is characterized by peptides with an intricate 3-dimensional shape. Using our AtropoFinder algorithm we have characterized several atropopeptide gene clusters and deepened our biosynthetic understanding of the RiPP family. The insights obtained from this machine learning-based approached were subsequently leveraged to develop a machine learning-algorithm for the systematic identification of novel RiPP families that elude recognition by current genome mining algorithms. Preliminary investigations indicate that this hypothesis-driven approach extends beyond RiPPs and holds promise for the discovery of a wide range of non-canonical biosynthetic pathways.

Cyanobacterial biofilms biosynthetic gene cluster diversity using genome-resolved metagenomics

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Cyanobacteria are recognized as one of the bacterial phyla richest in natural products (NPs). Recent (meta)genomic studies have shown that Cyanobacteria genomes encompass a large diversity of biosynthetic gene clusters (BGCs) which are not associated with known NPs, highlighting the small fraction of currently known cyanobacterial metabolites. This knowledge gap occurs in part due to the difficulty to grow many Cyanobacteria in large-scale in the laboratory and the difficulty to collect large amounts of biomass directly from the environment in non-tropical

regions, which would be necessary to obtain biomass for the discovery and isolation of sufficient amounts of NPs for structural characterization. An alternative route to NP discovery involves capture and expression of BGCs in a heterologous host. In this study, a metagenomics approach was employed to study the diversity of BGCs from 20 cyanobacteria-enriched environmental samples, collected from marine, freshwater, soil and hot spring environments. In total, 97 cyanobacterial metagenome-assembled genomes belonging mainly to Oscillatoriales, Pseudoanabaenales and Chroococcidiopsidales orders, were recovered. Anti-SMASH analysis allowed for the identification of over 1600 BGCs, the majority of which shared less than 30 % of similarity to known BGCs. Several promising BGCs were selected for heterologous expression, and we are currently attempting the expression of two new microviridin BGCs using the DiPaC-SLIC method.

Bioprocesses Panel

Hypes, Hopes, and the way forward for Microalgal Biotechnology

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The urge for food security and sustainability has advanced the field of microalgal biotechnology. Microalgae are microorganisms able to grow using (sun)light, fertilizers, sugars, CO2, and seawater. They have high potential as a feedstock for food, feed, energy, and chemicals. Microalgae grow faster and have higher areal productivity than plant crops, without competing for agricultural land, and with 100% efficiency uptake of fertilizers. In comparison with bacterial, fungal, and yeast single-cell protein production, based on hydrogen or sugar, microalgae show higher land use efficiency. New insights are given into the potential of microalgae replacing soy protein, fish oil, and palm oil, and being used as cell factories in modern industrial biotechnology to produce designer feed, recombinant proteins, biopharmaceuticals, and vaccines.

Cyanobacteria: The green gold of bioprocess

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This conference presentation explores the promising field of cyanobacteria bioprocessing under the theme "Cyanobacteria: The Green Gold of Bioprocess", exploring the potential of cyanobacteria as nature's green factories for high-value-added products. The session will cover the optimization of cyanobacterial cultivation, showcasing practical results achieved within our research group. Cyanobacteria, with their remarkable photosynthetic capabilities, offer a sustainable platform for producing a spectrum of valuable compounds, from biofuels to pharmaceuticals. Also, we will discuss hurdles and future opportunities in harnessing cyanobacteria's potential for a greener, more sustainable bioprocessing industry.

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