Introduction to the Special Issue “Bioinformatic tools and approaches for Synthetic Biology of natural products”

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Microorganisms are the major source for the identification of novel bioactive natural products, which may serve as future lead molecules for drug development to treat infectious and other diseases. However, the research efforts to find such molecules have been hampered by high re-discovery rates of known biomolecules and a lack of new innovative screening technologies resulting in reduced screening efforts by large parts of the pharmaceutical industry. With recent advances in whole-genome sequencing technologies, mass spectrometry, cheminformatics and Synthetic Biology, new technologies are now available that could become game-changers in the field. All these technologies require strong computational efforts to analyze and mine the large datasets, and/or design and optimize new pathways for Synthetic Biology applications.

This Special Issue of Synthetic and Systems Biotechnology tries to cover these developments by including eight reviews and research papers on the "state-of-the-art bioinformatic tools and approaches for Synthetic Biology of natural products". They focus on reviewing the most recent approaches and strategies to identify and analyze secondary metabolite biosynthetic gene clusters with dedicated software programs and databases, providing new publicly accessible web services for gene cluster identification and CRISPR-design for Synthetic Biology applications. In addition, some articles demonstrate the application of such approaches to identify and study secondary metabolite biosynthetic pathways and biochemical reactions in the producers.

The review by Weber and Kim[1] summarizes the current approaches implemented in a variety of bioinformatics software programs to identify, analyze and engineer secondary metabolite biosynthetic pathways and their producers. The article contains a comprehensive collection of available tools and databases, and also introduces the "Secondary Metabolite Bioinformatics Portal" at http://www.secondarymetabolites.org, a community-driven online catalog of bioinformatics software and databases related to natural products/secondary metabolites research.

While the majority of bioinformatics approaches that are currently implemented use a "gene to metabolite"-approach, Khater et al. introduce a new method that allows the correlation of existing polyketide or non-ribosomal peptide structures to their biosynthetic pathways[2] complementing the currently available tools.

In the review by Pupin and colleagues,[3] the latest features of the NORINE database, which currently is the largest curated collection of bioactive non-ribosomally synthesized peptides, are introduced and use-cases are demonstrated.

While most genome mining approaches for secondary metabolite biosynthetic gene clusters currently aim at identifying genes encoding core biosynthetic enzymes like polyketide synthases or non-ribosomal peptide synthetases, the review by Liu[4] demonstrates that cytochrome P450 can also be valuable targets to mine for secondary metabolite biosynthetic pathways and to identify enzymes for the tailoring of the metabolites.

In addition to the complexity of the various biosynthetic gene clusters and their encoded pathways, growth conditions and the interaction with other organisms in the environment also play crucial roles for bioproduction. In the article of Jia et al., the current knowledge on synthetic microbial consortia and their influence on physiology are reviewed.[5]

Metabolic engineering and Synthetic Biology approaches in natural product/secondary metabolite producing microorganisms are often hampered by low efficiency or complete lack of genetic tools. The discovery of CRISPR/Cas9-based engineering technologies and their applications[6] will likely revolutionize the field by providing highly efficient tools also for "difficult" organisms. In their article, Blin et al. present the web-based tool "CRISPy-web", which provides an easy way to design sgRNAs (single guide RNA), which are prerequisites for most CRISPR/Cas9 applications based on user-provided genome sequence data.[7]

Meanwhile, the new web-based software "FunGeneClusterS" can be used to identify fungal secondary metabolite biosynthetic gene clusters by integrating genomics and transcriptomics data.[8] The manuscript of Vesth et al. not only describes a highly improved

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algorithm, but also a web-based interface that now makes the method easily available to the scientific community.

Johnston et al. make use of state-of-the-art bioinformatics approaches to investigate the biosynthetic potential of the genus *Legionella*. Using a combination of bioinformatics assessment and analytical techniques, they were able to identify a new PKS-derived surfactant legionellol, demonstrating that this genus can also be a source for novel natural products.[9]

I hope that the readers of this Special Issue will find the articles, tools and methods interesting and inspiring to their own research.

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