



RESEARCH CONFERENCES

ESF-EMBO Symposium

Synthetic Biology of Antibiotic Production

Hotel Eden Roc, Sant Feliu de Guixols (Costa Brava) • Spain
2-7 October 2011

Chair: Eriko Takano, *Microbial Physiology, University of Groningen, NL*

Co-Chairs: Roel Bovenberg, *DSM Biotechnology Center, Delft, NL and Centre for Synthetic Biology, University of Groningen, NL*; Rainer Breitling, *Groningen Bioinformatics Centre, University of Groningen, NL and Institute of Molecular, Cell & Systems Biology, University of Glasgow, UK*

www.esf.org/conferences/11360

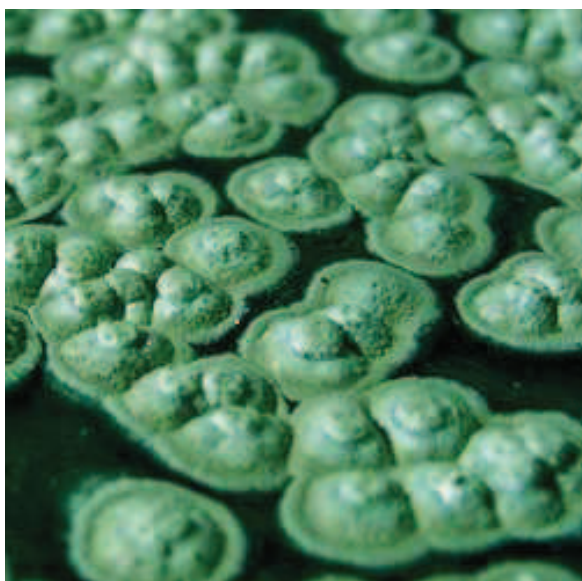
With support from:



Generalitat de Catalunya
Departament d'Innovació,
Universitats i Empresa
Comissionat per a Universitats
i Recerca

**DSM – the Life Sciences and
Materials Sciences Company**

HIGHLIGHTS and SCIENTIFIC REPORT



Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

Synthetic biology is considered as the major future trend for biotechnology: our newly increased ability to sequence and (most importantly) synthesize entire genomes enables a new engineering-style approach to manipulating biological systems. At the moment, much of the potential of Synthetic Biology is realized only at the level of proof-of-principle studies and general plans, but some areas of microbiology are already now ready for exploring synthetic biology concepts at the applied level. The field of secondary metabolism, especially the discovery and production of bioactive compounds, including antibiotics, is particularly well positioned for such a strategy. Biosynthetic pathways for secondary metabolites are modular at multiple levels, and therefore are a natural target for re-engineering and the synthetic creation of additional chemical diversity.

This conference focused on providing a setting for synthetic biologist and the fungal/actinomycete natural products community to come together, to exchange ideas and to form collaborations. This aim was more than achieved, with talks and posters from established group leaders, as well as the young scientists who will lead the future of Synthetic Biology. All 53 talks from the keynote and invited speakers, as well as the short talks selected from the submitted abstracts, were of excellent quality. In some cases the talks included unpublished and hot-off-the-bench data and inspired all participants to have very lively discussions.

The scope of the presentations was very wide, as intended in this interdisciplinary meeting, but a few common topics emerged repeatedly:

1. Understanding the evolution of the “genomic treasure troves” of secondary metabolites will stimulate engineering approaches towards further increases of the accessible chemical diversity.
2. The ecology of antibiotics and their role in development and species-species interactions can inform the search for new bioactive compounds from novel environmental niches.
3. Large-scale genetic engineering of the huge genomic clusters responsible for the biosynthesis of natural products is becoming a realistic possibility, based on major technical advances, as illustrated by a diverse set of applications presented at the meeting.
4. Similar advances in bioinformatics are needed to support successful engineering of secondary metabolism.

In addition to the conference talks, there were 47 posters presented, and each poster author gave a 1-minute talk on their work (without slides). This was a widely approved highlight of the whole conference, which led to many enthusiastic interactions during the subsequent poster sessions.

The SGM young speaker prize was awarded to Daniel Scharf, PhD student, Leibniz Institute for Natural Product Research and Infection Biology e.V., Jena, Germany for his talk entitled: ***Gliotoxin pathway reconstruction as a prerequisite for pathway engineering***. The Nature Reviews Microbiology poster prize was awarded by Andrew Jermy (senior editor) to Eva-Maria Niehaus, PhD student, Westfälische Wilhelms-Universität Münster, Germany for her poster with the title: ***Molecular and chemical characterisation of secondary metabolite gene clusters in Fusarium fujikuro: the fusarin gene cluster***. The EMBO Reports poster prize was awarded to Tina Strobel, PhD student, Albert-Ludwigs-University, Freiburg im Breisgau, Germany for her poster with the title: ***Identification of a highly flexible glycosyltransferase from Saccharothrix espanaensis***.

X I hereby authorize ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

Scientific Report

Executive Summary

(2 pages max)

Synthetic Biology is at a critical phase in its development: it has finally reached the point where it can move from proof-of-principle studies to real-world applications. Secondary metabolite biosynthesis, especially the discovery and production of antibiotics, is a particularly relevant target area for such applications of synthetic biology.

This meeting showed how far we have proceeded in the last couple of years, both in our understanding of secondary metabolite biosynthesis and in our tools for large-scale genetic manipulation. The meeting proved to be a perfect opportunity for bringing the two communities, synthetic biology and natural products, together and stimulate increased interaction. This meeting even inspired collaborations within the natural products community, the fungal and *Actinomyces* community. It also identified important bottlenecks in the current synthetic biology pipeline and important limitations of our biological understanding of the relevant biosynthetic pathways and their regulation, which will benefit from the joint attention of both groups of experts.

The active participation of numerous participants from industry reflected a (re-)growing interest in natural products in the light of the recent advances of synthetic biology approaches in the field. Again the meeting encouraged interactions between companies and academics which will certainly be advantageous to the Synthetic Biology of Antibiotic Production.

Scientific Content of the Conference

(1 page min.)

- Summary of the conference sessions focusing on the scientific highlights
- Assessment of the results and their potential impact on future research or applications

The conference was broadly divided into four topical sessions: two sessions with a strong emphasis on synthetic biology concepts and tools on the first and last day flanked two sessions on the main natural producers of antibiotics and other bioactive natural products on the second and third day.

The following summary can only highlight a few representative examples from a very rich scientific program.

In the very first talk of the meeting, **Roy Kishony** (Harvard University, US) provided the evolutionary context for the rest of the meeting in his inspiring presentation on “The ecology of antibiotics”, using experimental and computational modeling strategies to explain the natural evolution of antibiotics resistance, answering the intriguing question, why haven’t all bacteria become resistant yet? **Christina Smolke** (Stanford, US) presented a large collection of tools for the control of gene expression in yeast, mostly based on RNA and its secondary structure, and showed how to use these switches to control antibiotic production in yeast. In the most unusual presentation of the meeting, **Markus Schmidt** (Biofaction and IDC, AT) discussed “Biosafety and Public Dialogue in Synthetic Biology”, raising awareness of an important but often neglected issue by showing examples of public engagement through animation, films and art. **Karsten Temme** (UCSF/MIT, US) discussed a particularly advanced example of re-engineering a complex biological

system, the nitrogen fixation cluster of *Klebsiella oxytoca*, by replacing the entire natural regulatory machinery of this very large and fragile gene cluster by synthetic elements. **Arnold Dreissen** (University of Groningen, NL) reported on the engineering of *Penicillium chrysogenum* (which produces penicillin) by the investigation of the antibiotic transporters. He also reported the biosynthesis pathway of a novel NRPS. **Todd Peterson** (Life Technologies, US) gave a peek-preview of some of the technologies for large-scale DNA manipulation currently in the pipeline. **Jörg Stelling** (ETH, CH) provided a systems-biologist's perspective on synthetic biology, discussing to which extent can we come up with a biological design that really works, in the face of lack of knowledge, sloppiness, stochasticity and limited insulation, by exploiting general design principles.

The second day illuminated a wide range of fungal model systems for secondary metabolite production. **Nancy Keller** (University of Wisconsin, US) used case studies from a range of different *Aspergillus* species to illustrate the power of developmental biology in unlocking the treasure chest of fungal secondary metabolites. **Axel Brakhage** (HKI, DE) demonstrated the activation of silent gene clusters by the overexpression of pathway-specific regulatory factors, an important strategy for awakening the biosynthetic potential of gene clusters identified by genome sequencing. **Gerhard Braus** (University of Goettingen, DE) illustrated the complex regulatory elements in *Aspergillus nidulans*, and how each regulators are controlled by different environmental signals and also can effect each other. **Daniel Scharf** (HKI, DE), the speaker prize winner who is currently a PhD student, reported on his project on the elucidation of the gliotoxin biosynthesis pathway.

The third day of the meeting was dedicated to exploring the diversity of actinomycete secondary metabolism. The scene was, however, set by two talks that focused on non-actinomycete bacteria with particularly diverse secondary metabolomes: **Jörn Piel** (University of Bonn, DE), who presented the astonishing chemical richness of secondary metabolites produced by animal-associated filamentous bacteria, mostly symbionts of marine sponges; and **Rolf Müller** (Saarland University, DE) gave a broad-ranging overview of the engineering of biosynthetic pathways mostly in myxobacteria, and also illustrated the power of improve bioanalytical strategies for identifying novel secondary metabolites by comparative metabolomics. Returning to the evolutionary theme of the first day, **Peter Leadlay** (Cambridge University, UK) emphasized that successful natural products have been shaped and preserved by natural selection, but that the natural repertoire represents only a limited sampling to the entire available chemical space. He then illustrated how synthetic biology approaches, in particular the modular engineering of polyketide synthases, can be used to extend the range of accessible chemical diversity. Several synthetic approaches were presented: **Anna Eliasson Lantz** (Technical University of Denmark, DK) spoke of the construction of a promoter library while **Justin Nodwell** (McMaster University, CA) presented his small molecule library and its potential physiological impact of *Streptomyces*. **Hiroyasu Onaka** presented the engineering of NRPS using goadsporin as a proof of concept; **Wolfgang Wohlleben** (University of Tuebingen, DE) spoke of redirecting flux for balhimycin production and of building modules libraries of NRPSs.

On the final day, **Luis Serrano** (CRG, ES) started the session by a systems-biology overview of our current ability to create a comprehensive quantitative picture of a microbial systems (specifically *M. pneumoniae*), including the quantitation of protein and transcript levels, but also of translation rates, protein half-lives and protein-protein and protein-DNA interactions, using a combination of technologies, ranging from next generation sequencing to electron microscopy tomography. **Haruo Ikeda** (Kitasato University, JP) illustrated how large-scale engineering can

improve even established hosts for secondary metabolite production, showing how mega-deletion mutants can achieve improved industrial potential. **Kristala Jones Prather** (MIT, US) demonstrated the versatility of new computational algorithms for biosynthetic pathway design in an example of increasing the productivity for a specific small molecule of industrial interest in a heterologous host. **Michael Fischbach** (UCSF, US) presented a wide-ranging perspective on the discovery and characterization of secondary metabolites based on genome sequences, emphasizing the broad (and largely unexplored) phylogenetic distribution of secondary metabolite biosynthetic gene clusters, many of which encode for biosynthetic machineries that are larger than a ribosome and must have immense evolutionary benefits for their carrier organisms if they show such persistent evolutionary conservation. **Marnix Medema** (University of Groningen, NL) presented some of the bioinformatics tools that underlie such genome-based discovery of secondary metabolites. **Wayne Mitchell** (Experimental Therapeutics Centre, SG) placed synthetic biology in the industrial context, exploring the financial constraints on natural product discovery and the potential of synthetic biology and related technologies to overcome these serious limitations, to provide the necessary secondary-metabolite-based drugs that are necessary in the view of increased resistance observed in many pathogens world-wide. **Beatrix Suess** (Frankfurt University, DE) presented the engineering of the riboswitches which respond to tetracycline and neomycin. In the final presentation of the meeting, **Chris Voigt** (MIT, US) challenged the natural product community to be more daring and ambitious in their adoption of synthetic biology concepts and technologies, illustrating the potential of large-scale engineering of biology by several examples from his group that had succeeded in completely refactoring complex biological systems, ranging from nitrogen fixation and light harvesting, to protein secretion systems. He not only presented the necessary computational design tools and experimental components for such an enterprise, but also highlighted the various pitfalls along the way, stressing that natural products like antibiotics are of “nice intermediate complexity” to allow a successful application of synthetic biology.

Forward Look

(1 page min.)

- *Assessment of the results*
- *Contribution to the future direction of the field – identification of issues in the 5-10 years & timeframe*
- *Identification of emerging topics*

At the end of the conference, participants were asked (1) to reflect on the take-home message from the meeting, (2) to identify challenges and needs of the field, (3) to predict its medium- to long-term future, and (4) to recommend actions by ESF and other stakeholders that would stimulate the research even further.

All participants were asked to provide written comments on each of these four aspects, followed by a general discussion of each point by the audience. In total, 72 written contributions were collected, 26 from PhD students, 11 from postdoctoral researchers, 25 from academic PIs and 10 from industry participants. The spectrum of views was naturally very diverse, but a few important common themes emerged.

Concerning the take home message, there were two recurring views, best reflected in two comments from PhD students: **“Synthetic biology is really just starting”** and **“We won’t be running out of work any time soon”** – there is general enthusiasm about the potential of synthetic biology (**“Synthetic biology ideas will continue to rejuvenate natural products research in industrial and academic groups”**), but also a strong realization that it will be challenging to fully exploit this potential in the rather traditional field of natural products/antibiotics

research (“**Uptake of synthetic biology approaches by the natural product community is very limited at present**”). The importance of interdisciplinary conferences bridging the two communities is widely acknowledged, and participants in general expressed their excitement about the learning opportunities offered by bringing together industry, synthetic biologists and natural products researchers (“**I have learned an immense amount at this meeting – one of the most valuable conferences I have attended in many years**”).

A number of important needs and challenges in the field were repeatedly identified. They included “**cooperation and communication between biologist, bioinformatics and chemists**” (or similar permutations of researchers from various academic and industrial backgrounds like organic and analytical chemists), a “**reduction in the cost of DNA sequencing and assembly**” and “**support for interdisciplinary work**”, as “**natural product chemists and synthetic biologists should work together**”. There was also mention of the need for efficient production systems. The oral discussion further stressed the need for interdisciplinary training for a new generation of students to facilitate such research across traditional boundaries.

Participants were overall very reluctant to express their view on the future development of the field, reflecting the enormous rapidity of progress that makes viable predictions very hard, even on a 5- to 10-year scale. There is, however, cautious optimism that some major advances will have been made to overcome the challenges identified above: In 5–10 years “**optimized “general” expression hosts are available**”, “**there will be synthetic biosynthesis pathways both for natural and (hopefully) unnatural products**”, “**new natural products will be obtained from heterologously expressed gene clusters**” and, perhaps most importantly, “**DNA assembly and synthesis will be cheap and easy**”. The oral discussion emphasized that sequence information will be very plentiful, but the interpretation of this information will be limiting (due to lack of biological data, computational infrastructure, and bioinformatics tools), and the time scale of taking new compounds to industrial usability would remain another important limitation (“producing 10,000 new compounds would still be impossible”).

The participants very consistently identified recommendations for ESF and other funding agencies and governments to stimulate the progress of synthetic biology. These are most concisely captured in the comments of one academic PI: “**Meetings like this; funding of interdisciplinary projects**”. Many participants made concrete suggestions for repeating this meeting on a regular basis (every 2–3 years at most), and they shared the opinion that “**this meeting truly must be repeated**” / “**we need more conferences like this**”. Concerning the role of sustainable funding, participants emphasized that “**there is more support needed for high-risk projects**”, while also stressing the relevance of specific support to stimulate interactions between research disciplines and between industry and academia.

▪ Is there a need for a foresight-type initiative?

Yes. This was clearly identified by participants in their forward-looking suggestions to ESF: targeted initiatives to stimulate knowledge exchange across disciplines (synthetic biology vs. natural products) and a well-defined research and funding strategy were considered imperative requirements for progress in the field.

Business Meeting Outcomes

- Election of the Organising Committee of the next conference
- Identified Topics
- Next Steps

The success of the meeting has certainly raised the question whether a similar meeting should be held again. The unanimous opinion voiced by the participants (not only in person, but also on the anonymous feedback forms during the forward-look discussion) is: Yes. In addition to stimulating exchange of new ideas in this rapidly evolving field, a second meeting on Synthetic Biology of Antibiotic could also include speakers from other disciplines, including additional application-oriented participants from medicine and drug activity screening.

Atmosphere and Infrastructure

▪ *The reaction of the participants to the location and the organization, including networking, and any other relevant comments*

The meeting was composed of mostly young researchers and there was always a buzz of lively interactions at coffee breaks and during the meals, as well as during the long lunch breaks, where about 15-20 of the meeting participants would go swimming in the sea together. Due to the very pleasant atmosphere of the conference venue, there was plenty of interaction between participants from the different expertise groups and, most importantly, also between industry and academic groups. It was obvious that many new collaborations have been started as a result of this meeting.

The feedback from the participants was the best the organizers have ever experienced. Weeks after the meeting, the organizers still receive compliments on the organization, atmosphere, and the venue.

Some examples:

- “I just wanted to thank you for organizing such a good meeting last week – I really enjoyed it and have returned to work with lots of new ideas. I hope the meeting will be the catalysis for new grant income and collaborations in the future.” (Professor)
- “I wanted to take a moment to thank you and your co-chairs for organizing a truly exceptional meeting. I learned so much, made many new friends, and, I don't think I've attended a conference that flowed so flawlessly. Of course your mysterious ability to control the weather was an added blessing. It was really really good.” (Senior group leader)
- “I want to thank you again for organizing this fantastic conference at such a beautiful location.” (Junior group leader)
- “I would like to thank you for a great conference! The combination of natural products and synthetic biology researchers was unique and interesting, as well as the right combination of established and young scientists. I especially appreciated the extra attention and opportunity given to young researchers to present their work by both talks and posters. I greatly enjoyed the conference, the way everything was well organized and well thought through, and I learned so much this past week by interacting with such a diverse group of scientists. Thank you for giving me the opportunity to speak at the conference. It will be my pleasure to attend similar events in the future.” (PhD student)

Sensitive and Confidential Information

This report will be submitted to the relevant ESF Standing Committees for review.

In order to promote transparency, it is ESF policy to also publish the Scientific Reports on its website. Any confidential information (i.e. detailed descriptions of unpublished research, confidential discussions, private information) should therefore not be included in this report. Confidential issues can be addressed in the next page, which will not be published.



I hereby authorize ESF to publish the information contained in the above Scientific Report on the ESF Research Conferences Webpages. No sensitive or confidential information (see above) has been included in this report