European Marine Biological Research Infrastructure Cluster Workshop
Treasures from the deep
5th March 2019

Venue: Scotland House, Rond-Point Schuman 6, B-1040 Brussels, Belgium see:
https://www.eventbrite.co.uk/e/treasures-from-the-deep-tickets-53903061508

EMBRIC showcases European research in "Mining for Valuable Bioactive and Enzymes from Marine Algae and Bacteria". This workshop welcomes a range of experts from academia and industry to discuss steps to unlock the vast potential for this research to positively impact health, society and the economy. A poster exhibition will run during the whole workshop and a prize will be awarded to the best posters.

11.45 Doors open

12.00-13.00 Lunch and posters

13.05-13.15 Opening remarks Professor Melody Clark (British Antarctic Survey, UK)

13.15-14.00 Plenary Professor Carmen Cuevas Marchante (Pharmamar, Spain)

14.00-14.50 Presentations

Professor Mark Brönstrup (Helmholtz Centre for Infection Research, Braunschweig, Germany) -Drug discovery from marine bacteria

Olafur Fridjonsson, Matis (Iceland)- Mining enzymes

14.50-15.20 Coffee and posters Prize for the best poster

15.20-16.10 Presentations

Professor Nadine Ziemert (University of Tübingen, Germany)- Applying Genome Mining to Marine Microbes

Dr Mariella Ferrante (SZN, Naples) - The Beauty and Bioactives of Marine Algae

16.10-17.00 Plenary Professor Marcell Jaspars (Aberdeen, UK) - The Marine Biodiscovery Pipeline: Challenges and Opportunities

17.00-18.00 Round table and discussions: chaired by Melody Clark and Marcel Jaspars

18.00 Reception and poster awards

Awarded by Clare Moody (MEP) and Baroness Mobarik (MEP)

Sponsors

List of Posters

P01: Benthic Cyanobacteria from mangrove ecosystems as producers of bioactive compounds: when biodiversity meets chemistry; Marie-Lise Bourguet-Kondracki

P02: INMARE: Industrial Applications of Marine Enzymes; The INMARE Consortium Nathalie Tonné

P03: NGS methods to unlock environmental and extreme microecosystems; Alan Buddie and Giovanni Cafa

P04: Bacterial Co-culture: Exploring Microbial Interactions for the Production of Specialised Metabolites; Fleurdeliz Maglangitab, Rainer Ebela, Hai Denga

P05: ProBone – New tools for prospecting the marine bone-degrading microbiome for novel enzymes; Erik Borchert

P06: Discovering and enhancing bioactives in marine diatoms; Francesco Manfellotto

P07: Biocatalytic access to halogenated molecules; Danai S Gkotsi, Jagwinder Dhaliwal, Duncan RM Smith, Matthew McLachlan, Rebecca JM Goss

P08: Combined Genomic and Metabolomic Approaches to Antibiotic Discovery; Emily Abraham, Yunpeng Wang, Jinlian Zhao, Rebecca J.M. Goss

P09: Combining Synthetic Biology and Synthetic Chemistry to Dial in to New to Nature Peptidic Natural Products *in vitro* and *in vivo;* Christopher Cartmell, Sunil V. Sharma, Tong Xiaoxue, Cristina Pubill-Ulldemolins, Emma Bogosyan, Emma J. Rackham, Enrico Morelli, Michael Corr & Rebecca J. M. Goss

P10: Photoprotection of the Potent Polyene Antibiotic Marinomycin; Christopher Bailey, Joseph Zarins-Tutt, Matthias Agbo, Alberto Diego Taboada, Maoluo Gan, Emily Abraham, Refaat Hamed, Grahame Mackenzie, Andrew Evans and Rebecca Goss

P11: Discovering, elucidating and exploiting biosynthesis; Scarlet Ferrinho, Jack Connolly, Rebecca JM Goss.

P12: Isolation, Structure Elucidation, and Synthesis of Albopeptides; Qing Fang, Rainer Ebel, Hai Deng

Exhibit 1 Xanthella

Exhibit 2 Jellagen

Sponsors

Poster abstracts

P01: Benthic Cyanobacteria from mangrove ecosystems as producers of bioactive compounds: when biodiversity meets chemistry

Sébastien DUPERRON 1,4, Sylvain DURAND1, Benjamin MARIE1, Charlotte DUVAL1, Cécile BERNARD1, Olivier GROS2, Claire GOLLETY3, Marc TROUSSELLIER3, Arlette LONGEON1,

Marie-Lise BOURGUET-KONDRACKI1

1 UMR 7245 MCAM, Muséum national d'Histoire Naturelle, Paris, France

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3 UMR 9190 MARBEC et CUFR de Mayotte, France

4 Institut Universitaire de France, Paris, France

In view of the diversity of secondary metabolites they produce, Cyanobacteria have emerged as a target group of interest in the search for new types of bioactive compounds.

The benthic species, in particular in tropical zones, that may form dense biofilms on various types of substrates are particularly interesting in this regard. However, they are little known compared to pelagic species. Therefore, in the framework of a French CNRS research initiative (X-Life CABMAN 2018) aiming to explore benthic Cyanobacteria, a consortium of research groups of the MNHN initiated a sampling program in mangrove ecosystems from Guadeloupe and Mayotte.

Field works led to collection of dozens of cyanobacterial strains, which added to the MNHN collection of Cyanobacteria. Their taxonomic identification and their bioactivities against different human and environmental bacterial strains are currently under way. The first results will be presented and discussed.

This approach hand-in-hand combines the exploration of biodiversity of new benthic cyanobacteria of mangroves with the search for new antimicrobial molecules.

P02: INMARE: Industrial Applications of Marine Enzymes

The INMARE Consortium Nathalie Tonné
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The Ocean is not the first place to spring to mind when thinking of the industrial enzyme market. However, a group of researchers in Europe, inspired by the microbial diversity of our Ocean, set out to tap its hidden depths for novel enzymes with industrial potential. As their four-year journey comes to an end, their explorations in remote habitats, combined with their pioneering technological developments have advanced the state-of-the art in the industrial enzyme sector. Proof of their success is demonstrated by the fact that they have already delivered the most extensive, curated collection of enzymes worldwide, some of which are already performing better than current commercial products.

The Ocean's microbial diversity remains largely undersampled and poorly understood, although it biotechnological potential has been long recognised. At a time when natural resources are limiting and a growing population places ever-increasing demands on limiting natural resources, biotechnological processes provide a cleaner and more sustainable alternative to energy-depleting and waste-producing industrial processes. Enzymes, nature's catalysts, are the key to this. We need more industrially relevant enzymes, and we need them now.

INMARE work has shown how to find these enzymes and how to find them fast. Through targeted sampling of remote biodiversity hotspots, developing state-of-the-art in vitro and in vivo screening and platforms, constructing novel sequence analysis pipelines and bioinformatics tools and much more, INMARE has streamlined the enzyme biodiscovery pipeline.

INMARE is an exemplar of how European collaboration fast-tracks innovations in industrially relevant research and development. Its innovations can and will reduce the laborious industrial enzyme screening and optimization steps, leading to more industrially relevant enzymes from marine origins.

P03: NGS methods to unlock environmental and extreme microecosystems

Alan Buddie and Giovanni Cafa, CABI, Bakeham Lane, Egham Surrey UK; Email: a.buddie@cabi.org

Water associated environments are difficult to characterise by traditional culture-based methods, leading to under-reporting of microbial diversity. One increasingly useful solution is the application of Next Generation Sequencing (NGS) techniques. Knowledge of the microbial diversity in an ecosystem is the first step in understanding the function of the component taxa in a complex environment (such as that found in marine sediment). In the present study, we investigated three anoxic environments and focused on significant changes in bacterial abundance. One early aim of this approach is to attempt to correlate differences in the occurrence of taxa and/or functional groups across their distinct microecosystems.

This poster presents preliminary data from this study, describing the progress to date. In addition, we suggest the next steps for future work that could be applied to the search for novel and existing bioactive molecules. This approach would enhance cross disciplinary marine investigations and enable the development of bioactive compounds for biotechnological applications.

DNA was extracted from cell pellets of each of three anoxic water environments, and subjected to PCR-based, 16S rRNA next generation sequencing (NGS) on an Illumina MiSeq. The estuarine sediment, pond sediment and fuel-associated water samples generated 732K, 1.1million and 1.28 million reads, respectively, of which roughly 65% in each case passed the quality filters. Satisfactory sequences were screened against the Illumina curated database in order to classify the organisms present.

Initial results have shown major differences in microbial diversity among fuel-associated water, pond and estuarine sediments. Of these, the most significant change was within Deltaproteobacteria, specifically at large proportion of *Desulfomicrobium norvegicum* present in the estuarine sediment sample. No traces of this species were found in fuel-associated water or in the pond sediment sample. The next step for this study will be the application of whole genome sequencing for the full characterisation of key taxa.

Significant changes in the relative distribution of microorganisms present in extreme environments may be used to highlight the function(s) of these microbes in broader marine environments, by exploiting their metabolism and, thereby, to increase ecosystem functioning.

P04: Bacterial Co-culture: Exploring Microbial Interactions for the Production of Specialised Metabolites

Fleurdeliz Maglangit[ab], Rainer Ebel[a], Hai Deng[a]

[a] University of Aberdeen, Aberdeen, Scotland, UK

[b] University of the Philippines Cebu, Lahug, Cebu City, Philippines

Interactions among microorganisms are fundamental to microbial ecosystem dynamics [1]. Bacteria live in communities and they depend on other organisms to grow and reproduce. This can be best illustrated by the so-called - “great plate count anomaly”, [2] which claims that only 1% of the known organisms can be readily cultivated on its own using standard laboratory methods. In this study, we cultured two interacting bacterial species, *Streptomyces sp.* MA37 and *Pseudomonas sp.* that are physically separated by a semi-permeable membrane yet allows exchange of nutrients, and dissolved or colloidal chemical signals. Results showed that many metabolites were absent in the monocultures were co-culture specific, hence microbial interactions elicit the production of these natural products[3]. Using bioactivity-guided screening, we were able to target the metabolites for isolation. The active extract was fractionated using SPE followed by semi-prep reversed-phase C18 HPLC, and the structure was elucidated by NMR spectroscopic techniques and LCMS analysis. Herein, we report the characterization of an indolocarbazole alkaloid. Neither bacteria produced this compound when cultured alone. Co-culture approach paves the way for increasing the chemical diversity of microbes when grown *in vitro*.

References:

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2 S. R. Vartoukian, R. M. Palmer and W. G. Wade, *FEMS Microbiol. Lett.*, 2010, **309**, 1–7.

3 A. Milshteyn, J. S. Schneider and S. F. Brady, *Chem. Biol.*, 2014, **21**, 1211–1223.

P05: ProBone – New tools for prospecting the marine bone-degrading microbiome for novel enzymes

Erik Borchert[1], Manuel Ferrer[2], Antonio García-Moyano[3], Sandra Alonso[2], Sergio Sánchez-Carrillo[2], Thomas D. Dahlgren[3], Ramona Suharoschi[4], Gro Elin Kjæreng Bjerga[3] and Ute Hentschel[1]

[1]GEOMAR, Helmholtz Centre for Ocean Research, Kiel, Germany
[2]CSIC, Institute of Catalysis, Madrid, Spain
[3]NORCE, Norwegian Research Centre, Bergen, Norway (Coordinator of ProBone)
[4]University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania

Driven by industrial demands, the ProBone project focuses on streamlining discovery of valuable bone hydrolytic enzymes, by selectively prospecting the unique genes and proteins of the non-cultivable marine bone-degrading microbiome. Despite its resilience, bones are degraded by free-living bacteria as well as symbiotic microorganisms associated to bone-thriving invertebrates in the marine environment. This bone-degrading microbiome is, however, largely unexplored for its biotechnological potential. ProBone aims at delivering an innovative toolbox based on omics technologies and synthetic biology methods, to expedite discovery of active bone-degrading enzymes, and to accelerate the transition from discovery to end-user applications. We applied state of the art metagenomic sequencing to various type of samples (biofilms, *Osedax mucofloris*, *Vigtorniella* sp., *Ophryotrocha* sp, *Capitella* sp.) collected from artificially deployed cow, swine and turkey bones for several months in Byfjorden outside Bergen, Norway, to assess the biotechnological potential of associated and perhaps symbiotic bacterial communities. The metagenomes were screened via hidden Markov model (HMM) profiling for a range of industrially relevant enzymes supposedly involved in bone degradation including, but not limited to collagenases, cholesterol oxidases, galactosaminidases, glucosaminidases, mannosidases, sialidases, glucuronidases and fucosidases. The obtained sequences were phylogenetically analyzed in respect to their relatedness to known enzymes to assess the novelty of the sampled resource and its potential application for biotechnological processes. A large amount of novel sequences, exceeding 50 Gbp of raw sequence data, was identified in the bone thriving communities, yielding more than 15.000 enzyme sequences of interest. Within this data pool a lot of novel enzyme domain architectures have been observed for the different classes of investigated enzymes, suggesting a treasure throve for potential novel functioning and modes of action. The most promising enzyme candidates will be heterologously expressed in different host systems and their capabilities to degrade recalcitrant bone material will be assessed using innovative screening methods.

P06: Discovering and enhancing bioactives in marine diatoms

Francesco Manfellotto[1], Monia Teresa Russo[1], Camilla Borgonuovo[1], Clementina Sansone[1], Christophe Brunet[1], Angela Falciatore[2], Adrianna Ianora[1] and Maria Immacolata Ferrante[1].
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[2] Laboratory of Computational and Quantitative Biology (LCQB), Institut de Biologie Paris-Seine (IBPS), 4, Place Jussieu, 75005 Paris, FRANCE

Diatoms are a major group of microalgae found in the oceans, waterways and soils of the world. They are unicellular photosynthetic eukaryotes with an estimated 100,000 species in ocean and fresh water.
Because they naturally produce various beneficial substances for human health, food and feed, such as polyunsaturated fatty acids, vitamins, antioxidants, enzymes, polysaccharides and carotenoids, diatoms represent a potential source for commercial and industrial applications.
Our research focuses on planktonic species, for which we have developed several resources, including genomes, transcriptomes and tools for functional genomics approaches. Within EMBRIC, we analysed metabolomics profiles of different marine diatom species and ecotypes to discover new natural products with potential beneficial effects. We optimized different algal cultivation conditions in order to enhance the physiologic production of bioactive substances and maximize product yield. In addition, we focused on carotenoid and xanthophylls, known for their anti-oxidant activity, anti-metabolic syndrome activities (anti-obesity, anti-diabetes) and beauty-enhancing activities (skin-enhancing, skin-lightening, anti-acne). In order to increase carotenoid synthesis in the marine diatom *Phaeodactylum tricornutum*, we exploited genetic engineering techniques to overexpress the genes involved in the carotenoid biosynthesis pathway obtaining transgenic lines with enhanced carotenoid content.

P07: Biocatalytic access to halogenated molecules

Danai S Gkotsi, Jagwinder Dhaliwal, Duncan RM Smith, Matthew McLachlan, Rebecca JM Goss
School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK

Selective halogenation of a drug or an agrochemical can have a dramatic influence on bioactivity and bioavailability [1-2]. It can also offer an orthogonal chemical handle, which can be used for further diversification through cross-coupling chemistry [3-5]. The Goss group have an active interest in identifying and developing novel halogenases with broad substrate specificity isolated from various sources including metagenomic samples or from even more challenging uncurated genomic data deposited in public databases [6]. In addition to halogenases we have developed and optimised a simple one-pot gram scale production of halotryptophans by harnessing the enzyme tryptophan synthase, in a purification free, crude lysate biotransformation [7]. Here the discovery, characterisation and utilisation of series of new broad substrate specificity halogenases is described.

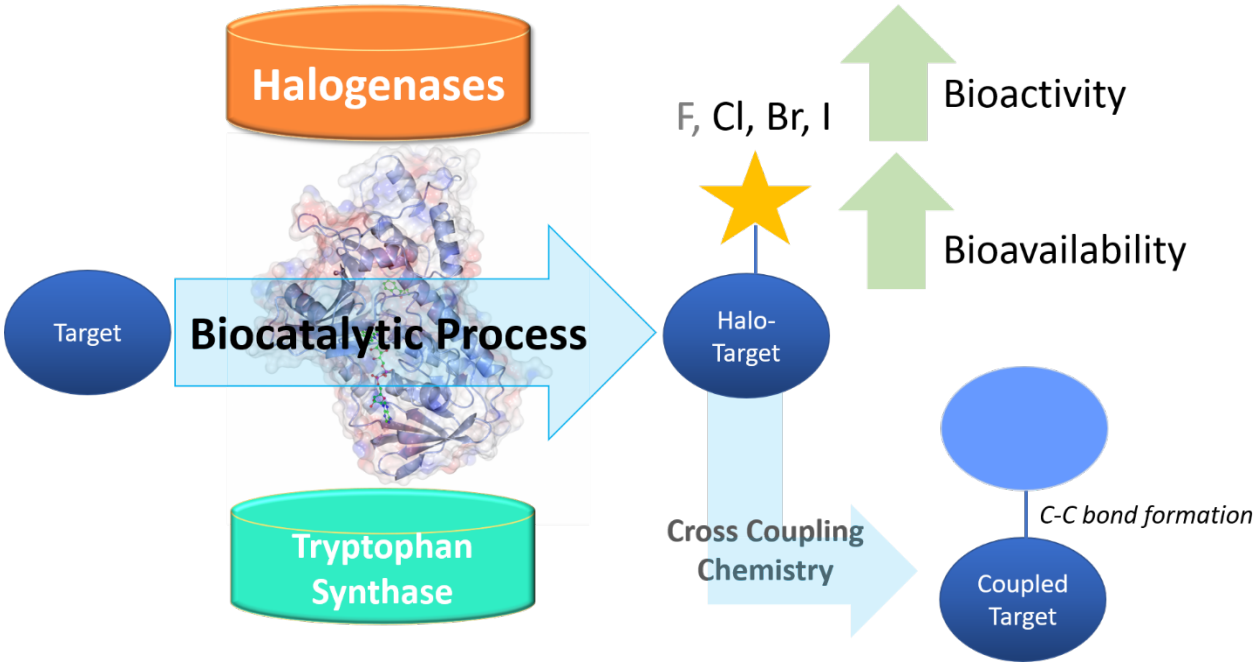

Figure 1 Biocatalytic access to halogenated compounds using halogenases and tryptophan synthase. In addition to the dramatic changes that halogens can have on the bioactivity and the bioavailability of the target molecule, they can also be utilised for further diversification through cross coupling chemistry.

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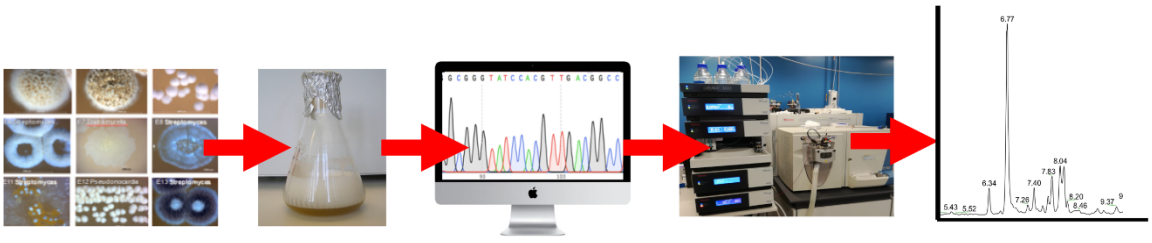
P08: Combined Genomic and Metabolomic Approaches to Antibiotic Discovery

Emily Abraham, Yunpeng Wang, Jinlian Zhao, Rebecca J.M. Goss*
School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK

Natural products provide an unparalleled starting point for drug discovery, with over 60% of anticancer agents and over 70% of antibiotics entering clinical trials in the last three decades being based on such compounds.[1] The majority of such compounds have been derived from microbial sources. However, as the same highly potent compound can be produced by many different microbes, there is always a risk of rediscovering the same antibiotic using a traditional bacterial screening approach.

Recently however, advances in genome sequencing has revealed that only a small proportion of microbial biosynthetic capability has been tapped and excitingly there are many more natural products waiting to be discovered.[2,3,4]

We are employing a state of the art approach for antibiotic discovery where we are using a combination of genomics and metabolomics to identify novel antibiotics. We are reading the genomes of a series of actinomycete bacteria to identify signature genes for natural products such as hybrid non-ribosomal peptide synthetases, polyketide synthases, terpenoids and lantibiotics. We can then target and clone biosynthetic gene clusters that are very different from known gene clusters, and therefore likely to produce novel antibiotics, for heterologous expression. By identifying and discounting previously known and isolated compounds from further analysis, we can focus efforts on pursuing the compounds that are likely to show the highest novelty. A major challenge to this work is that cloning biosynthetic gene clusters can be difficult; we are therefore exploring different cloning methods including using cosmid libraries, BAC libraries and Gibson Assembly.



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P09: Combining Synthetic Biology and Synthetic Chemistry to Dial in to New to Nature Peptidic Natural Products *in vitro* and *in vivo*

Christopher Cartmell, Sunil V. Sharma, Tong Xiaoxue, Cristina Pubill-Ulldemolins, Emma Bogosyan, Emma J. Rackham, Enrico Morelli, Michael Corr & Rebecca J. M. Goss

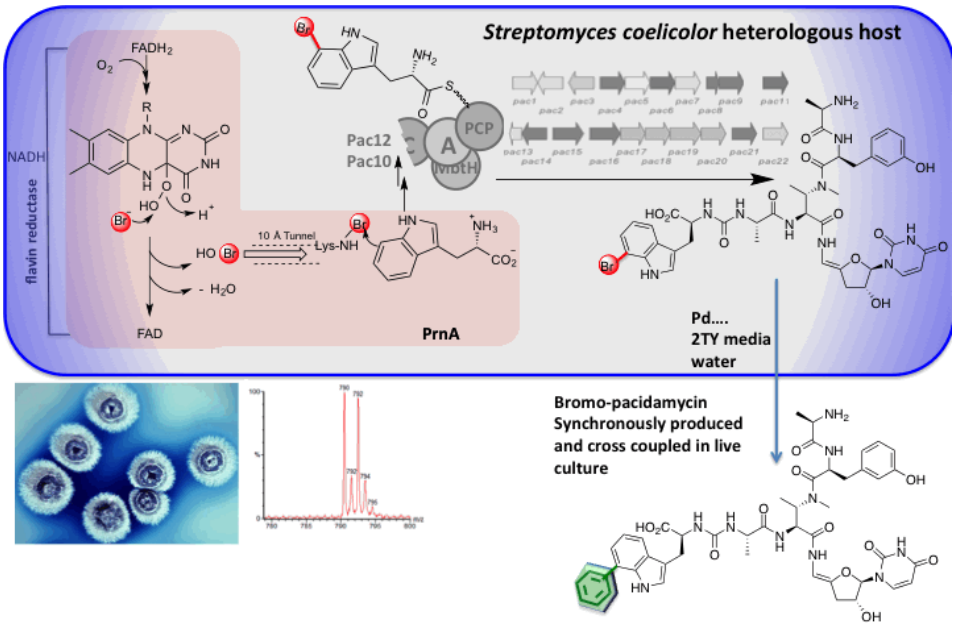
School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK

Peptidic natural products and peptide-polyketide hybrid natural products play a central role in medicine, key examples include daptomycin, a drug used to treat skin and skin structure infections[1] as well as vancomycin[2], a last resort antibiotic.

The GenoChemetic approach that we are developing affords access to diverse series of natural product analogues. One approach that we have been employing, within the GenoChemetics framework, is the utilization of halogenation and cross-coupling, in concert, to enable C-H activation.

This poster focuses on applying this strategy to the peptidic natural product pacidamycin[4].

GenoChemetics involves the introduction of a gene into the natural product generating host. This gene acts in concert with the existing biosynthetic pathway, installing a chemically orthogonal handle. By developing mild chemistries and compatible fermentation media we can selectively carry out chemical diversification in the presence of the living cultures. For example, we have constructed a bacterial host that can produce bromopacidamycin and have developed air and water tolerant Suzuki-Miyaura chemistry for its diversification *in vivo*. This exciting new approach draws flux through the system, enables labeling and tagging for tracking and purification and could potentially enable the production and testing of antibiotics in 1 step.



Scheme 1. Hyphenating synthetic biology and synthetic chemistry* in vivo *(Goss et al., Nat. Comm 2017)

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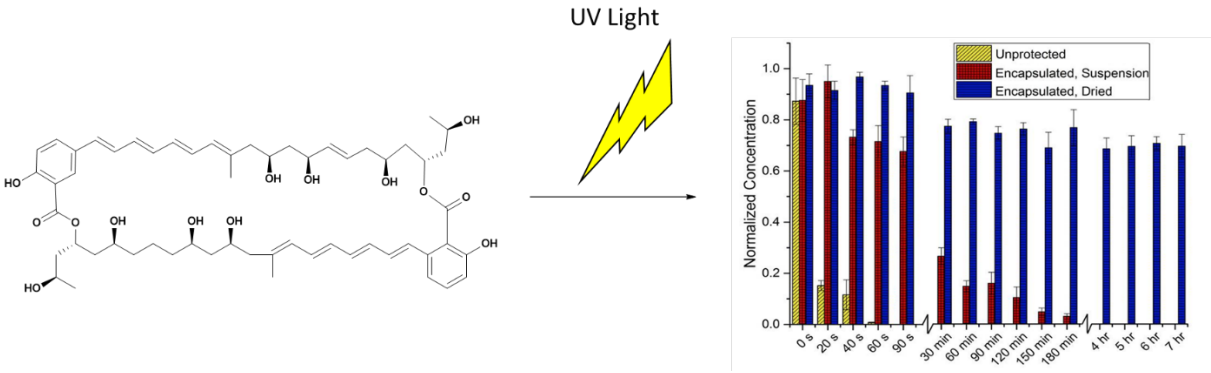
Sponsors

P10: Photoprotection of the Potent Polyene Antibiotic Marinomycin

Christopher Bailey[1], Joseph Zarins-Tutt[1], Matthias Agbo[1], Alberto Diego Taboada[2], Maoluo Gan[1], Emily Abraham[1], Refaat Hamed[1], Grahame Mackenzie[2], Andrew Evans[3] and Rebecca Goss[1]
(1)University of St. Andrews, St Andrews, United Kingdom,
(2)Sporomex Ltd, Bridlington, United Kingdom,
(3)Queen's University, Kingston, ON, Canada

Bioactive polyenes are abundant in nature showing a broad range of chemical diversity and biological activities. Despite the promising bioactivity of many isolated polyenes, the inherent instability of polyene systems towards photoisomerization continues to deter their development towards potential lead drug candidates. Marinomycin is a particularly noteworthy, but photolabile, polyene antibiotic with excellent activity against MRSA and VRSA[1]. We envisaged that microencapsulating polyenes using a chemically inert, biocompatible, non-toxic natural polymers could be utilised to improve photostability and as a drug carrier. We have demonstrated a striking level of photoprotection (only 30% degradation after 7hrs UV irradiation) using a natural biopolymer. Our results show promise for the clinical development and administration of polyenes, such as marinomycin, that would otherwise be too unstable to consider. Additionally, a serendipitous discovery revealed that our biopolymer could be used to selectively extract culture broths containing marinomycin providing higher recovery than extraction with conventional XAD resins.



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P11: Discovering, elucidating and exploiting biosynthesis.

Scarlet Ferrinho, Jack Connolly, Rebecca JM Goss.
School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK

The Goss group's research includes a diverse array of projects within the field of **chemical biology** with **natural products** as the focus**.**
1. Biosynthetic Elucidation: We are particularly intrigued by medicinally relevant and biosynthetically exotic natural products, and in determining the chemistry, enzymology and genetic programming that underpins their assembly.
2. Harnessing Biosynthesis To Generate New to Nature Natural Products: Over 60% of anticancer agents and over 70% of antibiotics are based on natural products. The generation of analogues of these compounds is critical in order to probe the identity and nature of the targets, determine a compound's mechanism of action, explore structure activity relationships and develop designer compounds with improved activities and bioavailability. By blending together synthetic biology and synthetic chemistry we are able to expeditiously access analogues of structurally complex natural products which would otherwise be hard to access using synthesis alone. Our approaches to analogue generation include precursor-directed biosynthesis, mutasynthesis, semi-synthesis, total synthesis and a new approach that we have pioneered called **GenoChemetics**.
3. Natural Product Discovery: With a particular focus on finding new antibiotics with novel scaffolds and clinically unexploited modes of action – we employ state-of-the-art approaches and discovery is directed by combining genome reading, metabolomics and bioactivity assessment.
4. Discovering and developing enzymes for use in synthesis: A key interest within our group is the development of biotransformations that may be readily taken up by main-stream organic chemists who would normally be reluctant to employ enzymatic approaches. In complement to our biocatalyst discovery and development programmes we have developed a method of engineering biofilms of recombinant microorganisms in order to make robust biocatalysts of as potential components of flow chemistry.

P12: Isolation, Structure Elucidation, and Synthesis of Albopeptides

Qing Fang, Rainer Ebel, Hai Deng
The Marine Biology Centre, University of Aberdeen, UK

Natural product discovery through traditional methods is a time-consuming and a labour-intensive process, in which more often than not, has resulted in the repetitive isolation of known metabolites. In order to avoid this, a new approach using metabolomics [1] and molecular network analysis were incorporated in this study to target the isolation of albopeptides [2-3] . Following the OSMAC strategy, S. *albofaciens* was prioritised for fermentation out of the eleven Streptomyces strains collected from the NCIMB culture collection. From this strain, a novel tripeptide (Albopeptide) was isolated from the bioactive fraction. A synthesis scheme was employed to provide the Structure Activity Relationships (SAR) of different albopeptides[4] [5].

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