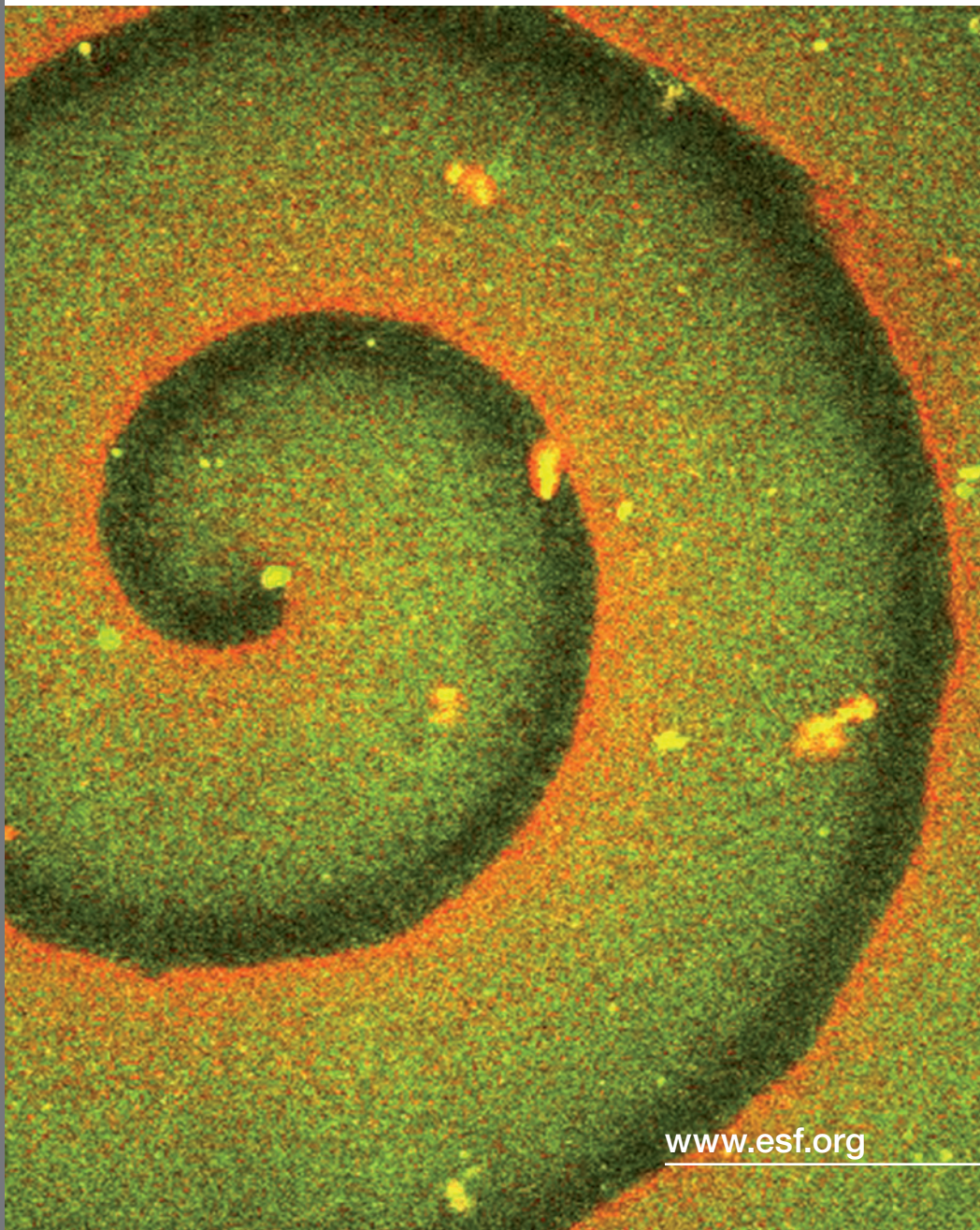
EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

EuroSYNBIO
Synthetic Biology: Engineering Complex Biological Systems



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Synthetic Biology: Engineering Complex Biological Systems (EuroSYNBIO)

Synthetic biology unites multidisciplinary efforts directed at the design of complex biological systems to obtain useful novel properties and activities based on the exploitation of well-characterised, orthogonal and re-usable building blocks. It aims to adopt the design structures that are well established in classic engineering disciplines for biotechnology. Synthetic biology is predicated on the notion that successful design of a biological system from scratch is the ultimate proof of understanding, and concomitantly the most powerful way to advance biotechnological solutions to challenging global problems in bioenergy, biomedicine and bioremediation. Synthetic biology thus represents a radical change from the current practice of simplistic small-scale adaptation of poorly understood natural systems towards often incompatible goals. Synthetic biology requires advanced strategies for the design and implementation of autonomous parts or minimal functions, subsystems and finally complex systems into a suitable chassis. To realise this, synthetic biology has to address significant conceptual challenges in the design of complex systems, in particular those posed by orthogonality and evolution.

These experimental strategies have to be intimately supported by computational tools that employ computational interchange standards, ontologies and collaborative environments. They should help to mine the design-relevant data from literature and provide the required computational frameworks to address complex molecular and systems design tasks. In addition, we must advance the current synthetic laboratory infrastructure to a system-level scale through both novel bioengineering strategies and the adaptation of existing strategies through miniaturisation and parallelisation. A fundamental advance in synthetic capacity, encompassing *de novo* DNA synthesis, analysis and system assembly, will ultimately allow us to overcome significant current hurdles in biosystems design.

Finally, synthetic biology must be implemented in a broad societal context that will require explicit research into the ethical, legal, safety and security ramifications of these powerful new technologies.

With these ambitions in mind, five Collaborative Research Projects involving 25 research teams recently started within the framework of the EUROCORES Programme EuroSYNBIO.

List of funded Collaborative Research Projects (CRPs)

Encoded Synthesis, Replication and Evolution of Unnatural Nucleic Acid Therapeutics (SYNAPTA)

(DFG, EPSRC, FWO)

Information storage and propagation in biological systems is based on just two types of nucleic acids, DNA and RNA. We are building an artificial genetic system based on a third type of genetic material, 3NA, using orthogonal nucleic acid chemistry and evolved polymerases for the templated synthesis, replication and evolution of novel, sequence-defined nucleic acid polymers. Such a system will conclusively address questions such as the capacity of nucleic acid polymers other than DNA and RNA for information storage, heredity and evolution. Its application to the synthesis and evolution of nucleic acid therapeutics promises to address some of the systemic constraints inherent in DNA and RNA chemistry.

Project Leader:

Dr Philipp Holliger
MRC Laboratory of Molecular Biology, Cambridge, United Kingdom

Principal Investigators:

Professor Michael Famulok
University of Bonn, Germany

Professor Piet Herdewijn
Catholic University of Leuven, Belgium

Associate Partner:

Dr Valerie Pezo
Genoscope Evry, France

Synthetic Biology of Bacterial Cell Division (SynDiv)

(BBSRC, DFG, NWO)

This collaborative European project is aimed at the design of new biological, biophysical and nanotechnological strategies to discover how to manipulate and thereby investigate key steps in bacterial cell division in living bacteria, and to reconstitute these mechanisms in a minimal system based on liposomes. The final goals are twofold: first, better understanding of the relevance of topological constraints on cell division and proliferation and, second, design of an evolvable minimal cell system comprising the essential components for controlled encapsulation and replication of genetic material, using the key players of the bacterial cell division machinery (divisome). Our team is highly complementary, consisting of: 1) an expert in *E.coli* cell biology, particularly the chromosome organisation and segregation in the living cell (Sherratt, UK), 2) a biophysicist with a strong background of cell and membrane biophysics, employing giant vesicles as toolboxes for bottom-up biology (Schwille, DE), and 3) a nanotechnologist who developed new concepts for bacterial shape and growth control on micro- and nanofluidic structures (Dekker, NL). By bringing together this different expertise, we are convinced that we can build a powerful incubator for novel technology-driven synthetic biology on the basis of bacterial systems in Europe.

Project Leader:

Professor Petra Schwille
University of Technology Dresden, Germany

Principal Investigators:

Professor Cees Dekker
Delft University of Technology, The Netherlands

Professor David Sherratt
University of Oxford, United Kingdom

A Synthetic Biology Approach for Engineering of Bacterial Methylotrophy (SynMet)

(DFG, NFR, NWO, SNF)

One-carbon (C1) compounds such as methane and methanol are attractive, non-food and low-cost carbon and energy sources for microbial bioprocesses, which can be utilised by specialised groups of microorganisms, the methylotrophs. Research efforts with different model strains revealed that methylotrophy consists of a set of discrete functional modules that are ultimately linked to a central metabolism. In the different phylogenetic groups of known methylotrophic bacteria, which include Proteobacteria and Gram-positive bacteria, alternative non-orthologous modules exist for C1 conversion. These ensure oxidation of the reduced C1 source to CO_2 for energy generation, and C1 assimilation with or without net CO_2 fixation for biomass formation. Formaldehyde is a key intermediate in bacterial C1 conversion; in consequence, the metabolism of this toxic compound must be very efficient and tightly regulated in order to avoid intracellular accumulation leading to cell death. By integrating genomic and experimental knowledge from different methylotrophic model organisms, e.g., *Bacillus methanolicus* and *Methylobacterium extorquens*, we will define – by means of *in silico* modelling – ideal combinations and minimal sets of modules, and design strategies for their synthetic assembly, transfer and coordinated expression in biotechnologically important bacterial hosts. It is anticipated that this approach will include generation of hybrid pathways involving the concerted action of heterologous genes and the hosts' natural genes. Physiological characterisation and omics approaches, including fluxomics, will be used to analyse and evaluate the genetically engineered cells with respect to the acquired methylotrophic properties. For further improvement this approach will be repeated iteratively to integrate and/or delete specific genes and operons. The generated knowledge will contribute to an increased understanding of bacterial methylotrophy and will facilitate transfer of methylotrophy to biotechnologically relevant bacteria as a new modular platform for methanol-based production of bulk chemicals.

Project Leader:

Dr Trygve Brautaset
SINTEF, Trondheim, Norway

Principal Investigators:

Professor Wim J. Quax
University of Groningen, The Netherlands

Professor Julia Vorholt
ETH Zürich, Switzerland

Professor Volker Wendisch
Bielefeld University, Germany

Associate Partner:

Professor Jean-Charles Portais
University of Toulouse, France

NANOCELL (NANOCELL)

(DFG, EPSRC, SNF)

The mission of NANOCELL is to engineer biomimetic molecular machineries of the cell as building blocks that can be robustly and flexibly assembled to nanocells with controllable functionality not found in nature. To approach this goal, we will take nature's cellular machineries apart and explore their potential to reconstitute them in new ways. The synthetic 'NANOCELL', resembling a molecular factory, is one strong vision that drives the project. In its first step NANOCELL will master the control of the following biomolecular machines developed by nature: (i) F1Fo-ATP synthases; (ii) ATP-driven nucleic acid translocating machines; (iii) ATP synthase-based propellers; (iv) proton-driven drug, solute and peptide transporters; and (v) spectrally-tuned light-driven proton pumps. Most of these machines have in common that either their structure and mechanism and/or their function have been characterised to unprecedented accuracy very recently, which provides the opportunity to move on now to this engineering approach. From a synthetic biology approach we will reconstitute these machines into stable synthetic vesicles. Proton gradients that power biomolecular machines will be generated by spectrally-tunable light-driven proton pumps such as bacterio- and proteorhodopsins. Short-term goals are to develop strategies to manipulate and engineer the individual biomolecular machines to be used as building blocks to establish a NANOCELL. Procedures for their reconstitution into synthetic vesicles building the frame of the future NANOCELL will be established. In the long term, we intend to use several of these engineered building blocks to create complex NANOCELLS. With this approach of establishing engineered building blocks we can functionalise NANOCELLS to generate, for example, a proton gradient that guides the uptake or release of drugs, peptides, DNA or solutes or to physically move the NANOCELL. Spectrally tuning proton gradients to synthesise ATP used for minimal metabolic processes within the NANOCELL is also being considered.

Project Leader:

Professor Daniel Müller
ETH Zürich, Switzerland

Principal Investigators:

Professor Richard Michael Berry
University of Oxford, United Kingdom

Professor Dimitros Fotiadis
University of Berne, Switzerland

Professor Helmut Grubmüller
Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

Dr Thomas Meier
Max Planck Institute of Biophysics, Frankfurt am Main, Germany

Professor Wolfgang Meier
University of Basel, Switzerland

Professor Sven Panke
ETH Zürich, Switzerland

Associate Partner:

Professor José Carrascosa
National Center of Biotechnology, CSIC, Madrid, Spain

Synthetic Biology to Obtain Novel Antibiotics and Optimised Production Systems (SYNMOD)

(BBSRC, DFG, FWF, NWO, SNF)

SYNMOD proposes to apply a comprehensive synthetic biology approach to the design and production of novel antibiotic molecules. First, evolutionarily pre-determined peptide modules are precisely defined and then re-combined for novel antibiotic functions. The modules are obtained from the group of lantibiotics, post-translationally modified peptide antibiotics. Next, we will assemble a context-insensitive post-translational machinery by exploiting promiscuous modification enzymes and enabling a fine-tuning of the composition of the modification pathway. This will be obtained by organising the pathway in a modular fashion and providing thoroughly characterised expression elements. This pathway will then be implemented in a novel production chassis of reduced complexity, specifically the Gram-positive *Staphylococcus carnosus* (2.56 Mg genome), and the resulting strain will be used to manufacture preparative quantities of a variety of novel lantibiotics. By consequently applying the principles of modularity and context-insensitivity on the various levels of the engineering process, we attempt to provide an antibiotic design and production system of unusual robustness and predictability. Using this project as a concrete example, we will analyse the potential impact of synthetic biology on the safety of biotechnological processes and its ethical implications for our society. These considerations will be shared with the public to institute a constructive dialogue about a potentially transformative novel technology.

Project Leader:

Professor Oscar Kuipers
University of Groningen, The Netherlands

Principal Investigators:

Professor Friedrich Götz
Eberhard Karls Universität Tübingen, Germany

Dr Markus R. Schmidt
Organisation for International Dialogue and Conflict Management, Vienna, Austria

Dr Nicolas Szita
University College London, United Kingdom

Professor Ralf Wagner
Regensburg University, Germany

Associate Partner:

Professor Sven Panke
ETH Zürich, Switzerland

The European Collaborative Research (EUROCORES) Scheme enables researchers in different European countries to develop collaboration and scientific synergy in areas where international scale and scope are required for top class science in a global context.
The scheme provides a flexible framework for national basic research funding and performing organisations to join forces in supporting forefront European research in and across all scientific areas. The national organisations support all aspects including scientific coordination, networking and research funding.

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THE FOLLOWING NATIONAL FUNDING ORGANISATIONS SUPPORT THE EUROCORES PROGRAMME EuroSYNBIO:

Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (FWF)
Austrian Science Fund, Austria

Fonds voor Wetenschappelijk Onderzoek – Vlaanderen (FWO)
Research Foundation Flanders, Belgium

Deutsche Forschungsgemeinschaft (DFG)
German Research Foundation, Germany

Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)
Netherlands Organisation for scientific Research, The Netherlands

Norges Forskningsråd (NFR)
Research Council of Norway, Norway

Schweizerischer Nationalfonds (SNF)
Swiss National Science Foundation, Switzerland

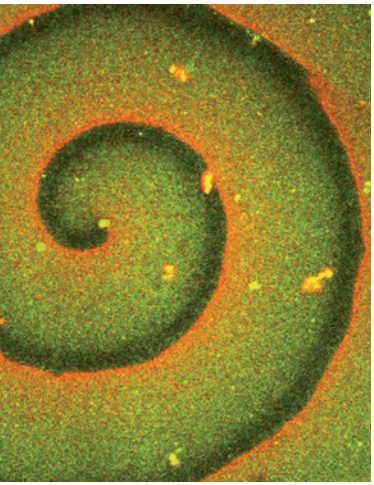
Biotechnology and Biological Sciences Research Council (BBSRC)
United Kingdom

Engineering and Physical Sciences Research Council (EPSRC)
United Kingdom

How can I participate in the EUROCORES Programme EuroSYNBIO?

The Scientific Committee of the Programme established a work programme for 2010-2013 to initiate and financially support conferences, workshops, summer schools, etc.
Information about these activities will be disseminated through the web pages:
http://www.esf.org/eurosynbio

If you are an Individual Project team member inside the EuroSYNBIO programme your participation in the networking and dissemination activities can be funded.



Patterns generated by the self-organisation of Min proteins *in vitro*
Source: Loose *et al.*, *Science* 2008

EuroSYNBIO

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