Imperial College London

SYNTHETIC BIOLOGY – ENGINEERING BIOLOGY AT **IMPERIAL COLLEGE LONDON**

HISTORY

Professor Richard Kitney: Co-Director of the Centre for Synthetic Biology and Innovation

Professor Paul Freemont: Co-Director of the Centre for Synthetic Biology and Innovation

Preliminary research in synthetic biology started at Imperial College London in 2004. In 2005 Professors Richard Kitney and Paul Freemont were awarded an internal grant by Imperial to establish a laboratory for synthetic biology research.

In addition to Kitney and Freemont, this comprised a handful of PhD students - plus the part-time assistance of Kirsten Jensen as the laboratory manager. The work of the laboratory, with limited funds, grew steadily until 2008. It was during this year that the Research Councils launched a call for synthetic biology as part of the programme for Science and Innovation Centres aimed at building academic capacity. Imperial's application was successful and in the spring of 2009 the EPSRC Centre for Synthetic Biology and Innovation (CSynBI) was established. CSynBI's strategy is one of applying engineering to biology by way of systematic design. This involves the application of the engineering principles of modularity, standardisation and characterisation - via the development of platform technology - to a range of applications.

CSynBI's capacity has continued to build and expand and it now comprises 10 PIs and around another 60 researchers - consisting of Postdoctoral Fellows and PhD students - from the Life Sciences, Engineering and the Natural Sciences departments. They were supported by the Science and Innovation Award and subsequently by a range of other grants made possible by the existence of CSynBI. Within Imperial there are around another 40 scientists and engineers working on projects associated with CSynBI demonstrating its collaborative reach. In addition, Professor Nik Rose and collegues from the Department of Social Science, Health and Medicine, at King's College London study the responsible innovation issues (i.e. societal, ethical and environmental considerations) relating to synthetic biology.

The Centre's collaborative reach is now international and it has strong links with the United States, including Stanford University and UC Berkeley - as well as being a key member of European grants.

It has significant ongoing collaboration with NTU and NUS in Singapore.

Many international observers now consider CSynBI to be one of the leading international centres for research in synthetic biology, indeed its international influence is considerable. CSynBI has been proud to welcome international delegations from countries such as France, China and Singapore (including the Singaporean Economic Development Board) and assist them in their synthetic biology policy development.

Members of the Centre (principally Professors Kitney and Freemont) have been heavily involved in the development of synthetic biology strategy for the UK.

EPSRC
Engineering and Physical Sciences Research Council

In 2008 Professor Kitney chaired a Royal Academy of Engineering inquiry into synthetic biology, which was published in May 2009.

Professor Freemont was also a key member of the inquiry. The report of the inquiry has been, and remains, influential in the development of synthetic biology strategy in many countries. In the autumn of 2011 the Rt Hon David Willetts MP, the then Minister of State for Universities and Research, organised a roundtable discussion at the UK Government's Department of Business Innovation and Skills to which both Kitney and Freemont were invited. One of the results of the roundtable discussion was the establishment of a working group to develop a roadmap for synthetic biology for the UK – this was published in July 2012. Both Kitney and Freemont made significant contributions to both the development of the strategy and the writing of the Roadmap. Again, this document has been influential internationally.

Also in 2011, CSynBI organised a two-day workshop at Imperial College for the groups involved in synthetic biology at the Universities of Cambridge, Edinburgh, Newcastle and Kings College London. The aim was to broaden activities to encompass the additional strengths of these universities in the area of synthetic biology. The plan was to establish a consortium of research activity.

Because the workshop was held in the Flowers Building at Imperial, the consortium was called the Flowers Consortium and was established by a written agreement between the groups. In the spring of 2012 the Flowers Consortium was awarded a significant grant by EPSRC for the specific purpose of developing platform technology (sometimes called foundational technology) for synthetic biology.

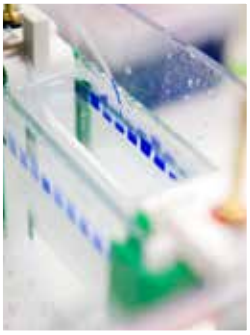
This project has been running for two and a half years and last summer underwent a full review by its international advisory board - which comprises leading synthetic biologists from the United States and Europe. As a result of the strength of the research within the Flowers Consortium, CSynBI was invited to become a member of SynBERC. There will be a Flowers Consortium session at the 2015 SynBERC meeting, in Berkeley, USA.

SYNTHETIC BIOLOGY HUB

encompassing:

- CSynBI
- The Flowers Consortium
- SynbiCITE
- The Foundry
- Frontiers Engineering

Synthetic biology at Imperial College London continues to grow and CSynBI is now a leading centre of excellence with a network of research teams and innovation and knowledge centres. CSynBI is proud of the scale of its activities, which range from education to world-leading research to industrial applications. It influences strategy and spearheads engineering in synthetic biology. It is leading the way in automating the production of interchangeable genetic elements. Development of these elements is critical if we are to scale up synthetic biology processes such that we can make a real impact in the big challenges facing society.



CSynBI

Centre for Synthetic Biology and Innovation

CSYNBI

The Centre for Synthetic Biology and Innovation (CSynBI) is the academic arm of the Hub, which is led by Professors Richard Kitney and Paul Freemont. It specialises in the research and development of foundational tools for synthetic biology and the use of these tools in new applications to solve problems for example in industry and healthcare. CSynBI is committed to responsible research and innovation (RRI) and is therefore comprised of scientists and engineers at Imperial College London and societal and ethical issue researchers from the Department of Social Science, Health and Medicine at King's College London.

The scientific research goals of CSynBI are to establish an engineering framework for the design and optimisation of new biological parts, devices and systems, and, in tandem, to apply synthetic biology to develop a wide range of novel biotechnologies. Led by Professor Nik Rose from Kings College London, CSynBI is also addressing issues of public engagement and trust, as well as engaging with the central concerns of policy and regulation in this novel and rapidly developing area.

A programme of research, training, development and dissemination has, through upstream involvement from the very outset of CSynBI, enhanced capabilities to understand the ways that developments in synthetic biology impact and shape the world around us, and continues to facilitate the development of informed dialogue and an appropriate regulatory and policy regime. CSynBI also works with key social scientists from the University of Edinburgh on responsible research and innovation.

Academics in CSynBI were the first to design and implement synthetic biology courses in the UK (and possibly in Europe). Consequently, researchers at CSynBI play a large role in teaching synthetic biology at Imperial College through undergraduate and postgraduate courses. Synthetic Biology is a technical option for year 3 BEng and MEng undergraduate students following both the Electrical and Mechanical pathways of the Biomedical Engineering programmes. It is also available to students working towards a BSc in Biochemistry or Biology. At the postgraduate level CSynBI is proud to offer an MRes in Systems and Synthetic Biology and many PhD opportunities.

www.imperial.ac.uk/syntheticbiology

PRINCIPLE INVESTIGATORS IN THE CENTRE

Professor Richard Kitney,
Co-Director: BioLogic, biosensors, modelling

Professor Paul Freemont,
Co-Director: Biosensors, part characterisation

Professor Nik Rose,
Kings College London: Ethical, legal and societal issues

Dr Tom Ellis:
DNA assembly, gene networks and modules

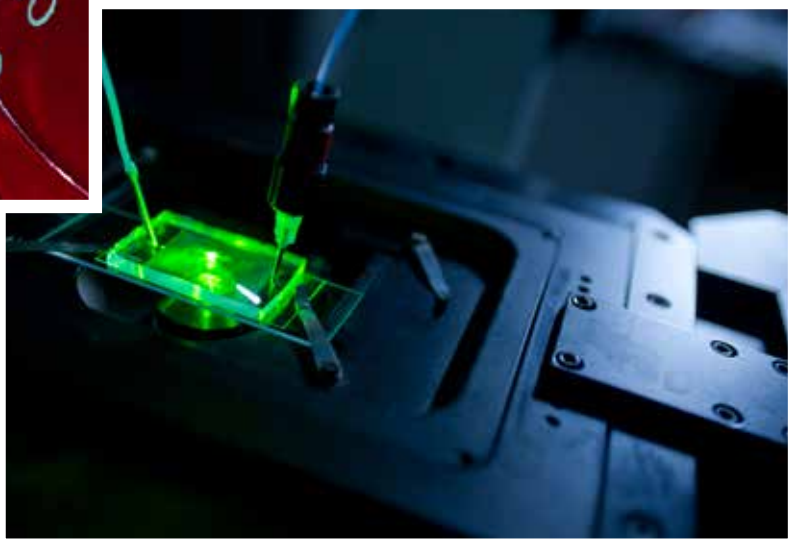
Dr Geoff Baldwin:
Directed protein evolution

Dr John Heap:
Development of foundational biological technologies

Dr Karen Polizzi:
Biosensors for bioprocessing

Dr Clare Marris,
Kings College London: Ethical, legal and societal issues

Dr Guy-Bart Stan:
Biomodelling analysis and control



FLOWERS

Imperial College London

UNIVERSITY OF CAMBRIDGE

THE UNIVERSITY of EDINBURGH

KING'S College LONDON

Newcastle University

THE FLOWERS CONSORTIUM

The Flowers Consortium is made up of representatives from the Universities of Cambridge, Newcastle, Edinburgh and Kings College London. Professor Nik Rose and Dr Clare Marris at Kings College London, and Drs Jane Calvert, Emma Frow and Professor Joyce Tait at the University of Edinburgh, specialise in researching the ethical and societal issues associated with synthetic biology as part of the Flowers Consortium's mission.

The fundamental aim of the Flowers Consortium is to create a prototype end-to-end synthetic biology systematic design platform that will be able to interface with a range of existing and emerging design technologies and deliver usable chassis/constructs that can be used in the design-build-test-learn cycle.

Now half way through, the Flowers Project has achieved a number of important goals.

- The community now has the ability to undertake multi-institutional research collaboration across the Flowers Consortium, enabling the cohesive development of platform technologies and the integration of tools and methodologies which will impact the ability to undertake systematic design.
- The definition and implementation of key emergent metrology concepts and standards (DICOM-SB and SBOL) and their integration into an enabling IT infrastructure (SynBIS) - built to enable efficient information exchange and extraction. This facilitates knowledge aggregation and consolidation.

www.synbiuk.org

SynbiCITE
SYNTHETIC BIOLOGY INNOVATION COMMERCIAL AND INDUSTRIAL TRANSLATION ENGINE

SYNBICITE

SynbiCITE is the UK's national centre for the commercialisation of synthetic biology. It is a resource of interacting partners from academia and business brought together to accelerate growth of high value manufacturing industries. It is part of the core activity of synthetic biology and is now becoming a major component in the industrial translation of the platform technology which is being developed by the Flowers Consortium. SynbiCITE currently comprises 19 academic institutions and 56 industrial partners and associated organisations, ranging from small spin out companies to large multinationals including GSK, Shell and Microsoft as well as the Northern Ireland, Scottish and Welsh Regional Governments, plus the Greater London Authority.

AIMS

SynbiCITE's aims are three-fold:

- To be a translation engine which translates university and industry based research in synthetic biology into industrial process and products
- To be an effective vehicle for the support of small to medium sized UK companies including start-ups in synthetic biology
- To actively engage in open dialogue with the public and other stakeholders focusing on the risks and benefits of synthetic biology technologies

To achieve this SynbiCITE offers a variety of programmes, services and expertise.

TRAINING AND SKILLS DEVELOPMENT

SynbiCITE offers innovation programmes and network training opportunities in business development, entrepreneurship and professional advancement.

Key training events include:

- Lean Launchpad: an eleven week programme which redefines the traditional business model and provides participants with a unique opportunity to iterate their product based on extensive customer consultation.
- LEAP: SynbiCITE supports and participates in LEAP, a programme designed to develop early career researchers who aspire to be leaders in synthetic biology.
- 3 Day MBA: SynbiCITE offers this intensive programme to train and teach participants how to build a synthetic biology start-up from scratch.

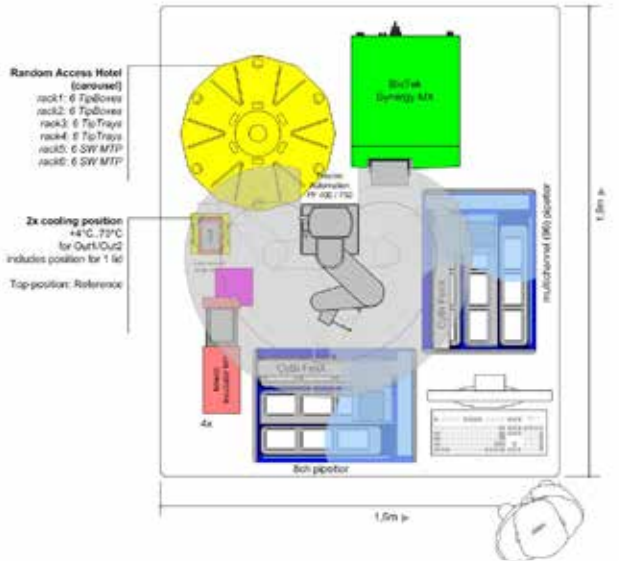
BUSINESS DEVELOPMENT

SynbiCITE supports and develops synthetic biology based businesses by offering funding, business incubation, business support services and specialist laboratory space and facilities.

SERVICES

SynbiCITE offers problem-solution brokerage and can link members in its network to specialists in synthetic biology to assist with specific projects.

www.synbicite.com



THE FOUNDRY

THE FOUNDRY

Designing, constructing and testing DNA is a crucial element in the systematic design of biological devices.

These devices are made from harmless cells, such as non-pathogenic yeast. Manmade yeast genes could then be used to create vaccines or even turn agricultural waste into biofuel.

Imperial recently received £3.5M (£4.5M total) to establish a 'DNA Synthesis and Construction Foundry'. Building interchangeable pieces of DNA, the building blocks of synthetic biology, is time consuming and expensive. CSynBI and SynbiCITE have designed a suite of automated platforms to perform gene assembly and verification of those assemblies. The platforms have a modular design supplying the flexibility to perform a range of different assembly protocols and cope with the development of new techniques. Modularity also allows the interchange of different robotic and analytical equipment, again to provide maximum flexibility. The resulting automation allows the high-throughput execution of all the most common gene/genomic assemblies and genomic editing protocols. Automation of synthetic biology techniques will greatly increase the robustness of the processes and reproducibility of data collected. The net result will be an increase in the size of the experimental space covered by the investigator, and greater quality of the data and models produced.

The strength of the modular design of the platform is its ubiquity and the range of analytical techniques it can apply to characterisation and verification.

Modularity also allows the exploitation of both conventional and acoustic liquid handling. The platforms have been specifically designed to allow the assembly and characterisation in multiple chassis, including *E.coli* and other bacterial stains, but also yeast and mammalian cells. A diverse range of cellular, biochemical and biophysical analytical tools capable of characterising DNA, RNA, protein and metabolite are integrated with the platform to provide a complete spectrum of qualitative and quantitative analyses. Also, to allow the Foundry to function efficiently, a Laboratory Information Management System (LIMS) has been developed. The ability to track the progress of various assets through the process and directly link the data acquired is of critical importance. The LIMS provides an audit trail for the synthesis, assembly and verification of the various components: DNA, parts, devices, circuits, modules and systems. In addition, the database and the ability to track the workflow enables more efficient scientific management of complex projects. The Foundry has an automated sample management store to provide a freezer storage system for secure sample management of plates and tubes.

The establishment of the DNA Synthesis and Construction Foundry complements SynbiCITE, which aims to bridge the gap between academia and industry to speed up developments in new synthetic biology technologies.

www.imperial.ac.uk/syntheticbiology/synbiohub/foundry

Frontiers Engineering
Scaling up synthetic biology

FRONTIERS ENGINEERING

In 2013, Imperial College London was awarded £5 million to investigate how to scale up synthetic biology.

In order to realise the potential of synthetic biology in terms of revolutionising the way industry makes a host of consumer products from materials and energy to food and medicine, it is necessary to find ways of translating laboratory discoveries into operating industrial production processes. The challenge is to transition from existing factories into the factories of the future.

Today many consumer products are made from fossil resources using synthetic chemistry techniques. In the future it will be necessary to reduce dependence on petroleum products and move to renewable resources. At the same time, the advent of synthetic biology techniques for rapidly tailoring biological systems for manufacturing purposes will allow the transition away from synthetic chemistry to more environmentally friendly production mechanisms using non-pathogenic microorganisms. The synthetic biology Hub at Imperial College London is tackling the question of how to undergo this transition smoothly by working with industrial partners, GlaxoSmithKline, Lonza Biologics and Shell, on real-world applications in two consumer areas (therapeutics and chemicals manufacturing).

To develop these future biofactories, the Synthetic Biology Hub at Imperial is inventing new, generalised technologies to underpin the new manufacturing processes. It is producing new biologically based sensors in order to be able to monitor the production processes as they occur to ensure product quality (and allow intervention if necessary). The Hub is also researching new, more robust production cells that can tolerate the high levels of compounds they make and new microreactors and/or compartmentalisation strategies for using enzymes when whole cells are not required. Because the transition will not happen overnight, the Hub is developing intermediate production methods that combine biological and chemical catalysts. This requires solvents that are less toxic to proteins and cells and proteins that are engineered to be more robust in the presence of chemicals. In order to develop processes that are economical and efficient (minimal energy and water usage), the Hub is creating computer models to compare alternatives. The most promising processes will be implemented in the factories of SynbiCITE's industrial partners.

Two challenge areas have been selected in which to test the new technologies. The first is healthcare, specifically the manufacture of medicinal compounds and therapeutic proteins. These are already largely made using biological systems, but the existing processes are expensive and complicated. Also, in the future, it would be more efficient to make these medicines as and when they are needed (point-of-care manufacture). The Hub's goals are to make simpler, more cost effective, point-of-care manufacturing systems using a combination of the above mentioned platform technologies: enzyme microreactors, specialised cells, and biosensors.

The second target is to produce bulk chemicals without the need for petroleum inputs. To do this, manufacturing techniques are being adjusted for renewable inputs (such as biomass) and new processed are being developed that use biology and/or environmentally friendly chemistry to do the conversions.

Synthetic biology has never been attempted on such a large scale. The challenge is to adapt the current parts, devices, and systems to operate at the required level. The overall outcome will be novel, cost effective, energy efficient, and sustainable routes to therapeutics and chemicals.

www.imperial.ac.uk/syntheticbiology/synbiohub/frontiers

IGEM

iGEM is an extremely important annual international student competition in synthetic biology, attracting teams from the world's leading universities.

Since Imperial entered its first iGEM team in 2006, it has consistently entered talented teams with innovative projects ranging from water purification solutions, to drug delivery mechanisms, to soil erosion preventions.

Imperial is proud to have maintained its enviable position as the most successful UK, and probably international, university in the competition. This is despite the competition increasing in size from 32 teams in 2006 to 220 teams in 2014. In both 2006 and 2014 Imperial placed second overall and each year won a gold medal and a raft of prizes. In total Imperial has achieved 8 gold medals and 17 major prizes and now has more than 60 alumniGEM.

www.imperial.ac.uk/syntheticbiology/igem

www.igem.org

iGEM 2014 team with George Freeman MP, Parliamentary Under Secretary of State for Life Sciences

2006

Project I.coli
Position/medals awarded 2nd overall
Total number of teams in competition 32

Prizes awarded
Best documentation
Best measurement and part characterisation

2007

Project The Infector Detector
Position/medals awarded Gold
Total number of teams in competition 54

2008

Project Designer genes - Biofabricator subtilis
Position/medals awarded Gold
Total number of teams in competition 84

Prizes awarded
Best manufacturing project
Best natural new biobrick part

2009

Project The Encapsulator
Position/medals awarded Gold
Total number of teams in competition 112

Prizes awarded
Finalist Best human practices advance
Best manufacturing

2010

Project Parasight
Position/medals awarded Gold
Total number of teams in competition 130

Prizes awarded
Finalist, Best human practices advance
Best wiki, iGEMers Prize

2011

Project Auxin
Position/medals awarded 2nd overall European Winner, Gold
Total number of teams in competition 165

Prizes awarded
World finalist, Best Poster, Grand prize winner (Europe), Best wiki (Europe), Safety commendation (Europe), iGEMers prize

2013

Project Plasticity
Position/medals awarded 3rd overall, Gold
Total number of teams in competition 215

Prizes awarded
Best manufacturing project
Best new engineered BioBrick part

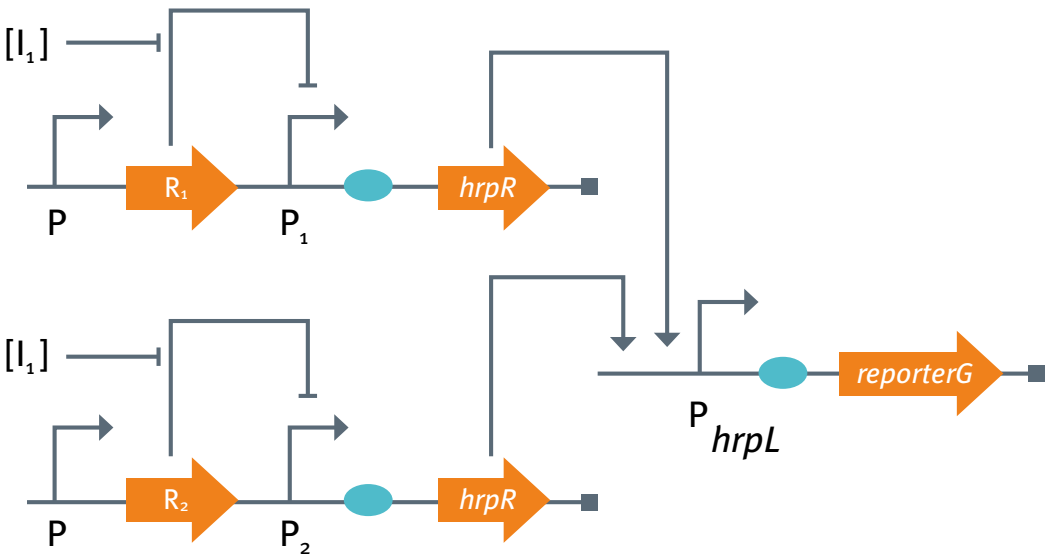
2014

Project Aqualose
Position/medals awarded 2nd overall, Gold
Total number of teams in competition 220

Prizes awarded
Best part collection
Best manufacturing project
Policy and Practices Commendation

RESEARCH CASE STUDIES

AND GATE CIRCUIT DESIGN



DEVELOPMENT OF IN VITRO BIOSENSORS FOR THE DETECTION OF INFECTIOUS BACTERIA

Cell-free synthetic biology has gained increased popularity in recent years as an alternative platform to live cells, enabling the study of biological systems in an environment of reduced complexity. We have developed biosensors in cell-free systems for the detection of pathogenic bacteria, with a focus on *Pseudomonas aeruginosa* – an opportunistic pathogen that can cause persistent infections in humans with compromised immune systems. It is a particular concern for cystic fibrosis patients, as it is able to colonise the lung and is resistant to antibiotic treatment.

To detect the presence of these bacteria, we utilised their natural cell-to-cell communication mechanism, known as quorum sensing (QS). Biosensors have been constructed using the native response elements of bacteria and coupled to a detectable output. This enables the detection of QS signalling molecules produced by bacteria, while its implementation in a cell-free platform provides improved biosafety when compared to whole-cell systems. After demonstrating that these biosensors are able to detect endogenous signalling molecules from cultured *P. aeruginosa*, we have now progressed to testing clinical samples from cystic fibrosis patients with *P.aeruginosa* infections. Ultimately the aim is to provide an improved detection method that can aid in the diagnosis and monitoring of bacterial infections.

LOGIC GATES

Logic gates (e.g. AND, OR and NAND) are the basis of all electronic digital devices from mobile phones, to microprocessors, to computers. Similarly, the development of biologically based logic gates and logical devices has major potential in terms of information processing and control. We have designed and developed a range of modular, stable biological logic gates. The gates are conceptually similar to their electronic equivalents, but different in operation. They are designed to work in the biological domain, which means that, for example, their response times are very much longer – but compatible with the response times of biological systems. We have recently completed the design and testing of a more complex digital device called a half-adder. This comprises multiple gates that work stably in unison. Immediate areas of application are in advanced biosensors. In the longer term, there is the potential to development biologically-based devices for information processing and control, e.g. in the application of human-imposed intra-cellular control.

Sc2.0

CSynBI is leading the UK's contribution to the ground breaking Sc2.0 project to synthesise a new version of *Saccharomyces cerevisiae*. This project will result in the construction of a eukaryotic genome. This will be the first time that this has been achieved and once complete will provide synthetic biologists with a tool to make valuable products such as chemicals, vaccines or biofuels using synthetic genes and genomes.

TIMELINE

2006

- Imperial College Synthetic Biology Laboratory founded.
- First Imperial team enters the iGEM competition.

2007

- Research develops – research student numbers increase.

2008

- CSynBI offers a final year option in Synthetic Biology to undergraduates studying for a BSc in Biochemistry or Biology or a BEng or MEng in Biomedical Engineering, representing the first undergraduate synthetic biology programme in the UK.
- Professor Kitney chairs a Royal Academy of Engineering Inquiry into synthetic biology to define the term 'synthetic biology', review the state of the field and consider potential future developments and their likely technological, economic and societal impact.

2009

- Imperial College London and Kings College London launch CSynBI with just 4 Principle investigators and 6 students.
- CSynBI hosts its first panel debate: 'Creating the organisms that evolution forgot?'. Held at the London School of Economics the event was chaired by Quentin Cooper, presenter of the most listened to science series in the UK, The Material World on BBC Radio 4.

2010

- CSynBI hosts a two day workshop: 'Synthetic biology and open source: normative cultures of biology' at the London School of Economics.

2011

- Creation of the Flowers consortium; a collaboration between Imperial College London, University of Edinburgh, University of Cambridge, Newcastle University and Kings College London to develop foundational technologies.
- CSynBI holds a workshop on the historical, social and philosophical aspects of modelling and their implications for synthetic biology at the London School of Economics.
- Professors Kitney and Freemont are invited to join a working group to develop a Roadmap for Synthetic Biology for the UK.

2012

- Publication of the influential 'Roadmap for Synthetic Biology for the UK'.

2013

- Launch of SynbiCITE.
- Professor Freemont delivers the Royal Institution Lecture.
- CSynBI invited to join SynBERC, a major U.S. research programme to make biology safer and easier to engineer. The first organisation outside of the US to do so.
- CSynBI hosts a workshop on the containment and release of engineered micro-organisms at Kings College London.

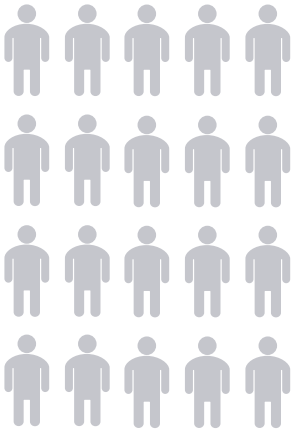
2014

- Professor Kitney delivers IET Kelvin Lecture.
- CSynBI hosts a workshop on synthetic biology and biosecurity at Kings College London.

2015

- CSynBI current population. 10 principle investigators, 60 other researchers, 20 associated groups/ centres at Imperial.
- Professor Kitney delivers Annual City and Guilds Fellowship Lecture.
- SynbiCITE brings Lean LaunchPad for Synthetic Biology to the UK for the first time.
- Imperial hosts SynBioBeta London 2015.
- Professor Freemont to deliver the Royal Society of Medicine Ellison-Cliffe Lecture 2015.

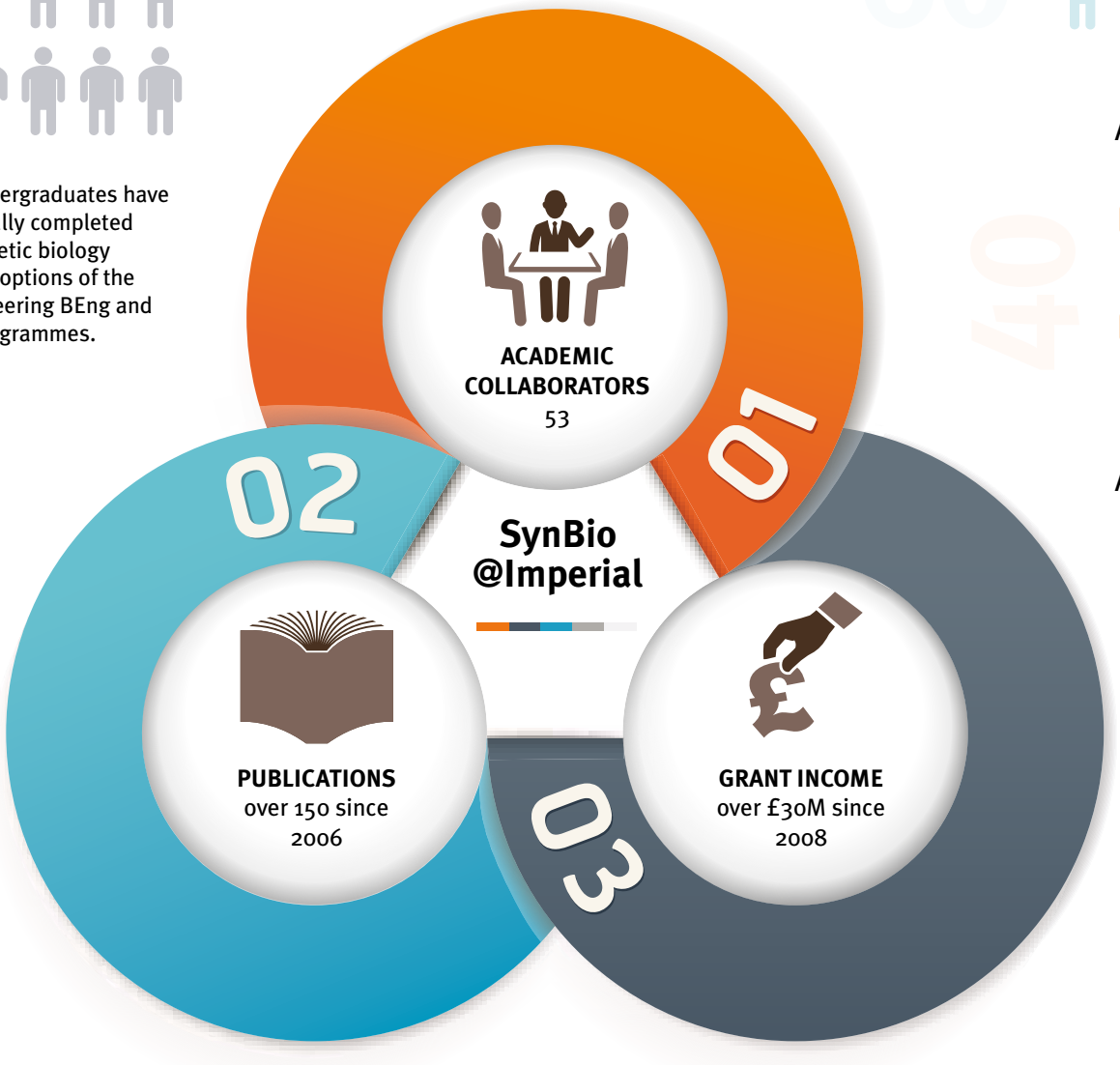
METRICS



200 undergraduates have successfully completed the synthetic biology technical options of the Bioengineering BEng and MEng programmes.

60
MRES ALUMNI

40
PHD ALUMNI



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