Synthetic Biology Research Centre Newsletter

University of Nottingham

Issue 7 November 2018

SBRC Centre Manager Update

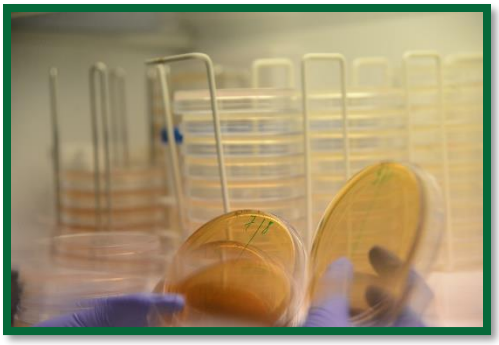
It is not until you stand back from everything and take in the 'landscape' that you appreciate how much the SBRC has achieved. The Research Council reviewers of SBRC-Nottingham commented that there was much to celebrate and that the aerobic and anaerobic gas fermentation facilities were the 'best academic facility they had seen globally'. Not only does the SBRC have cutting-edge specialist facilities for microbial synthetic biology, but already it has published 91 academic papers. By the time the 5-year funded programme for the centre is complete, it will have trained over 90 PhD students in aspects of synthetic biology and cross-discipline research, contributing significantly to the UK's Industrial Strategy by creating a specialist and highly interdisciplinary workforce.

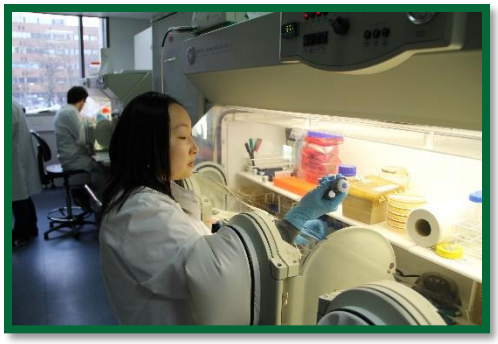
There is now a critical mass in applied microbial synthetic biology at Nottingham: advanced genome engineering tools have been developed, enabling even the most untransformable of microbial chassis to be transformed, and a deeper understanding of metabolic engineering informed by in silico modelling is helping to shape tailored industrial chassis. Lab-scale fermentation systems are fully functional, enabling growth and productivity to be assessed on-line in continuous and batch cultures.

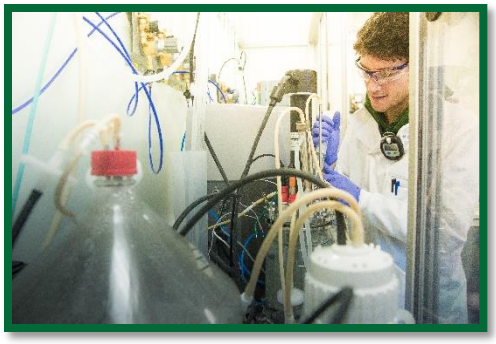
Responsible Innovation has been physically fully embedded within the SBRC by creating a dedicated social science hub with researchers working closely with colleagues at the Manchester and Edinburgh SBRCs. There is a strong commitment to Outreach activity which has seen innovative ideas being developed to engage with the public, including educational games, an interactive virtual reality lab, a popular YouTube video series and high profile presence at national events such as New Scientist Live.

We are increasingly interacting with companies and are part of their journey towards sustainable products for the bioeconomy.

Dr Alan Burbidge, SBRC Centre Manager
alan.burbidge@nottingham.ac.uk







Responsible Research and Innovation Update

Carmen McLeod (SBRC social science lead) and Brigitte Nerlich (SBRC Emeritus Professor social science advisor) have recently completed the editing a collection of articles for *Life Sciences Society & Policy* called: 'Synthetic biology: How the use of metaphors impacts on science, policy and responsible research'. This collection presents an interdisciplinary and international discussion of the impact that metaphors can have on science, policy and public interests in the context of synthetic biology. It also includes background on the current RRI agenda and consideration of the increasing pressure on scientists to demonstrate 'responsibility'.

The eight articles and thematic series editorial can be accessed via the links below:

1. CRISPR as agent: a metaphor that rhetorically inhibits the prospects for responsible research Author: Leah Ceccarelli
2. How to do things with metaphors: engineering life as hodgepodge Authors: Matthew Kearnes, Declan Kuch and Angus Johnston
3. Creating life and the media: translations and echoes Authors: manuel Pocar and Juli Peretó
4. Evolutionary tinkering vs. rational engineering in the times of synthetic biology Author: Víctor de Lorenzo
5. Who are the users of synthetic DNA? Using metaphors to activate microorganisms at the center of synthetic biology Author: Erika Amethyst Szymanski
6. Synthetic biology in the German press: how implications of metaphors shape representations of morality and responsibility Author: Martin Döring
7. Machine metaphors and ethics in synthetic biology Author: Joachim Boldt
8. Scientific iconoclasm and active imagination: synthetic cells as techno-scientific mandalas Author: Hub Zwart
9. Synthetic biology, metaphors and responsibility (Editorial) Authors: Carmen McLeod and Brigitte Nerlich

Other News

Building a low carbon future: £11m to fund Industrial Biotechnology and Bioenergy Networks announced

BBSRC, with the support of EPSRC, have committed £11 million to fund 6 unique collaborative Networks in Industrial Biotechnology and Bioenergy (BBSRC NIBB) to support, encourage, and facilitate this essential work. From seaweed to metals, these multidisciplinary networks will drive new ideas to harness the potential of biological resources for producing and processing materials, biopharmaceuticals, chemicals and energy. In 2014, BBSRC funded 13 Networks in Industrial Biotechnology and Bioenergy (BBSRC NIBB). Based on the outstanding achievements of these Networks, in 2018, BBSRC Executive agreed to support a second phase of networking activities in Industrial Biotechnology and Bioenergy.

The second phase of the BBSRC NIBB will continue to build capacity and capability in the UK supporting research and translation in biologically based manufacturing, with the aim of continuing to foster collaboration between academic researchers and business at all levels, in order to find new approaches though excellent research to tackle research challenges and help deliver key benefits in industrial biotechnology and bioenergy.

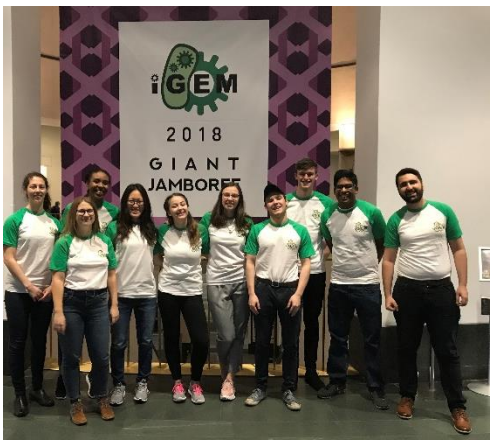
Director of the University of Nottingham's BBSRC/EPSRC Synthetic Biology Research Centre, Professor Nigel Minton, has been awarded Carbon Recycling: Converting waste derived GHG into chemicals, fuels and animal feed (CCnet) a continuation of the C1net (Chemicals from C1 Gas) NIBB. 'Two of the greatest challenges facing society are the future sustainable production of chemicals, fuels and protein for animal feed, while at the same time reducing GHG emissions. One of the few, readily available UK feedstocks are single carbon gases, generated either as side products of existing industrial processes or through the deliberate processing of biomass wastes and residues. They are available in high volumes and at low cost UK-wide. Autotrophic or phototrophic microbial chassis able to utilise these resources can be engineered to synthesise a broad array of requisite molecules in scalable biological processes. The Network will focus on the development of the requisite engineered chassis and the required scalable processes. It will expand the scope of C1net, which focussed specifically on gas fermentation, to include closed, photosynthetic processes reliant on waste CO2. The Network will be underpinned by sustainable exploitation of AD-derived biogas (CO2 and CH4) as a feedstock for C1 chassis process development.' Professor Nigel Minton, Director of the University of Nottingham's BBSRC/EPSRC Synthetic Biology Research Centre,

The networks will run from 2019 to 2024, will provide flexible funding for Proof of Concept projects, and are open to new members through-out their lifetime.

iGEM team win GOLD

The concept of a new bacteria-eating virus designed to fight the modern-day superbug *Clostridium difficile,* has been developed by a team of University of Nottingham students in a global competition. The 'bacteriophage' was devised by the team as part of their synthetic biology project that recently won a prestigious Gold Medal at the International Genetically Engineered Machine (iGEM) competition in Boston, USA.

C. difficile infection is the most common cause of antibiotic-associated diarrhoea in the western world and is a big problem in hospitals and healthcare facilities. The disease symptoms are caused by the release of two major toxins by the bacterium. Under normal circumstances, a healthy gut microbiome prevents the proliferation of *C. difficile*. However, when these good bacteria are obliterated by the use of broad-spectrum antibiotics, the bug proliferates and causes disease. One way to counter the expansion in numbers of toxin-producing *C. difficile* is to use competing strains that are not producing toxin as a probiotic.



The aim of the Nottingham iGEM team's project, called *Clostridium* dTox; it's not so *difficile* was to engineer a *C. difficile* bacteriophage (phage), to produce factors that would suppress toxin production. They demonstrated that the latest gene-editing techniques could be used to repress expression of both toxin genes (*tcdA* and *tcdB*) by targeting their mRNA. The ultimate goal

is a *C. difficile*-specific bacteriophage therapeutic which stops toxin production in those cells that are infected with the phage, converting them into health-promoting probiotics. Unlike antibiotics, phage cause no collateral damage to the native gut microbiome. The team was also nominated at iGEM for 'Best New Composite Part'. A composite part is a functional unit of DNA consisting of two or more basic parts assembled together. These must include all characterisation information and be added to the Registry.

Around 400 teams of more than 5,000 undergraduate and postgraduate students from 45 countries competed at iGEM. They were tasked with using the principles of synthetic biology, the 'Engineering of Biology', to design biological parts, devices or systems to address a real-world problem or to perform a novel, previously unseen function. The best 'parts' of every project are then submitted in the form of a 'BioBrick' to the iGEM BioBrick registry for use by others.

Director of the University of Nottingham's Synthetic Biology Research Centre, Professor Nigel Minton, said: "*This was a tremendous achievement considering the short time that the team had to design, build and test the parts needed for the innovative project they devised. We broke new ground for iGEM by engineering a strict anaerobic bacterium, rather than the more traditional chassis other teams focus on. This was made possible by the extensive skills and expertise available through the involvement of SBRC researchers who gave so much of their free time to supervise the team*."

The University's Gold-winning team members were; Lucy Allen, Hassan Al-ubeidi, Ruth Bentley, Sofya Berestova, Eun Cho, Lukas Hoen, Daniel Partridge, Varun Lobo, Fatima Taha and Nemira Zilinskaite. For the duration of their project they were embedded within BBSRC/EPSRC Synthetic Biology Research Centre (SBRC) at Nottingham, under the overall guidance of Nigel P Minton and Philippe Soucaille and under the close supervision of a dedicated multidisciplinary team comprising Louise Dynes, Daphne Groothuis, Dr Christopher Humphreys, Dr Carmen McLeod, Dr Michaella Whittle and Dr Craig Woods.

Computer Science undergraduate, Hassan Al-ubeidi, said: "*Taking part in iGEM has given me a holistic understanding of the synthetic biology process. Coming from a Computer Science background, I had no knowledge of the science prior to iGEM, but working alongside talented team-mates meant that I left with a much better understanding of our project. I feel that my communication skills have improved since starting iGEM, as it has allowed me to interact with students and experts from many disciplines*".

Ruth Bentley, who is studying for a Maths degree, said: "*iGEM was an exciting challenge. As the sole modeller for our team, I improved my ability to work independently to research and solve problems. I learnt how to communicate my work in a way such that those with less technical knowledge can understand. Attending the Jamboree and seeing other projects made me appreciate the power of synthetic biology to build a better world"*.

Human Practices and Public Engagement

The team devised a number of activities that explored how their creation, *Clostridium* dTox, could impact society. This included mining and carrying out a sentiment analysis of data from hundreds of social media comments on an online phage therapy video and exploring the current legislation surrounding phage therapy. They also researched what makes *C. difficile* such an important issue to society and how their project can help make a positive impact on communities by working towards the development of a novel therapy for its treatment. Finally, they held a discussion group with non-scientists, and interviewed five leading scientific experts in the field, including the UK Public Health England lead on *C.*

difficile infection, to understand how the team could make their project as effective as possible. Public engagement was an important focus for the team, which developed hands-on workshops to communicate the project in local schools, libraries, the media and to staff and students at the University.

What the Judges said

"*Great project, great wiki!! You just light up so many questions in my mind and actually this is the key of synthetic biology! Thank you so much for your effort and all hard work!"*

"*Super interesting idea to use temperate phages for this! …. You are clear on your achievements and reasoning throughout, which is super refreshing. Great effort!"*

"*Really terrific modelling efforts! I really liked how thoroughly your work was documented on your wiki; everything was very clear."*

"*Overall the project idea was very innovative, and you have great characterization on your parts. Good job!"*

"Very impressive! It is very inspiring that your project used phage therapy, RNA interference and the extended application of CRISPR/Cas technology."

"Amazing job, I hope that you continue this project."

Sponsors

Nottingham's iGEM team was generously supported by the University of Nottingham's Research Priority Area in Industrial Biotechnology, through grant funding from the Wellcome Trust, the Biotechnology and Biological Sciences Research Council (BBSRC) and the National Institute for Health Research (NIHR) via the Nottingham Digestive Diseases Centre, by generous cash donations from Don Whitley Scientific Ltd, LanzaTech and Seres Therapeutics and through in-kind support from Qiagen, Millipore Sigma, Promega, Eppendorf, New England Biolabs, LabFolder and Snapgene.

Collaborators

The team is also grateful for the support given by the following collaborators: Team Biomarvel Korea and the teams from Imperial College London and the University of Warwick.

Recent Publications

Alagesan, S., Hanko, E.K.R., Malys, N., Ehsaan, M., Winzer, K., Minton, N.P. Functional genetic elements for controlling gene expression in *Cupriavidus necator* H16. Applied and Environmental Microbiology, in press. DOI: 10.1128/AEM.00878-18

Alagesan S, Minton, NP and Malys N. ^{13}C-assisted metabolic flux analysis to investigate heterotrophic and mixotrophic metabolism in *Cupriavidus necator* H16. Metabolomics (2018); **14**(9): **DOI** https://doi.org/10.1007/s11306-017-1302-z .

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McLeod, C. Assuaging Fears of Monstrousness? UK and Swiss initiatives to 'open up' animal laboratory research. In, Nerlich, B., Smith, A., Hartley, S. and Ramen, S. (eds.) 'Here be Monsters': Science, Politics, and the Dilemmas of Openness. Manchester University Press, Manchester, Jan 2018. http://www.manchesteruniversitypress.co.uk/9781526106469/

McLeod, C. and Nerlich, B. (eds.) Thematic series - Synthetic biology: How the use of metaphors impacts on science, policy and responsible research. (2018)https://lsspjournal.springeropen.com/sbmi

Norman ROJ, Millat T, Winzer K, Minton N and Hodgman C. Progress towards platform chemical production using *Clostridium autoethanogenum Biochemical Society Transactions*. 2018; 46(3), 523-535

Norman ROJ, Millat T, Schatschneider S, Henstra AM, Annan FJ, Piatek P, Gilbert J, Hartmann HB, Poolman MG, Fell DA, Minton NP, Hodgman C Construction and analysis of a genome-scale metabolic model of *Clostridium autoethanogenum* with experimentally determined flux constraints, IET Eng. Biol. Under review.

Schatschneider S, Abdelrazig, S, Safo L, Henstra AM, Millat T, D-H, Winzer K, Minton N, Barrett DA. Quantitative isotope dilution high-resolution mass spectrometry analysis of multiple intracellular metabolites in *Clostridium autoethanogenum* using uniformly ^{13}C-labelled standards derived from *Spirulina*. *Analytical Chemistry.* 2018; 90(7), 4470-4477

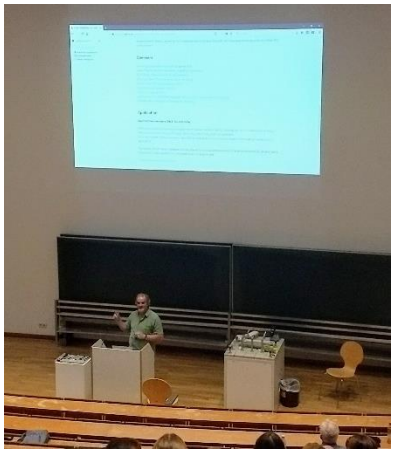
Conferences

CLOSTRIDIUM XV Conference

From 18 – 20 September, 2018 the Clostridium XV Conference was held in at the Technical University of Munich Campus in Freising, Germany.

Whilst Clostridium species have achieved notoriety as human and animal pathogens, most members of this genus are entirely benign and many have distinctive features of interest for production of fuels and chemicals. Initiated in 1990 (Salisbury, UK), the Clostridium meetings have been held every two years, generally alternating between the USA and Europe. The 2016 meeting was held at Dartmouth College in Hanover, New Hampshire. These meetings have become the leading forum in the field, and owe their success to both to the quality of the science presented and the informal and welcoming atmosphere.

SBRC Director – Prof Nigel Minton, was invited to give a keynote at this year's conference, his talk was titled; "*Gene essentiality in Clostridia and other industrial chassis under different physiological conditions using Transposon Directed Insertion Sequencing (TraDIS)*".



SBRC Director Prof Nigel Minton giving a Keynote Talk

Several other members of the SBRC also gave talks at the conference including;

Dr Klaus Winzer (Nottingham, United Kingdom) CA_C0082 is an effector of Agr quorum sensing in *Clostridium acetobutylicum*

Dr Alexander Grosse-Honebrink (Nottingham, United Kingdom) Expression of a synthetic pathway in the whole cell biocatalyst *Clostridium saccharoperbutyl acetonicum* for production of chirally pure (R)-1,3-butanediol

Dr Thomas Millat (Nottingham, United Kingdom) hHw CO uptake, growth limitation and redox balance govern the metabolic activity in *Clostridium autoethanogenum*

PhD Student, Jonathan Humphreys (Nottingham, United Kingdom) Clostridial strain degeneration: new approaches to an old problem

View here for the full conference programme.

Synthetic Biology UK 2018

The annual Biochemical Society Synthetic Biology meeting was held in Bristol on 19th & 20th November. This year a schedule of social sciences and humanities themed satellite sessions was organised by members of the BrisSynBio Ethics and Responsible Research and Innovation (RRI) cross-cutting research theme group. Dr Carmen McLeod (Senior Research Fellow) and Dr Eleanor Hadley Kershaw (Research Fellow), who are members of the SBRC Interdisciplinary Responsible Research and Innovation Group (IRRIG), attended these sessions.

On the afternoon of 19th November, a 'UK synthetic biology research centres RRI component round table' provided an opportunity for social science and humanities scholars working on synthetic biology and RRI to share their work. This round table included presentations from, Prof. Julie Kent (UWE/BrisSynBio); Dr Robert Smith (University of Edinburgh); Prof. Philip Shapira (University of Manchester); Dr Carmen McLeod (University of Nottingham); Dr Sally Atkinson (University of Exeter); and Dr Ken Taylor (University of Newcastle). Following this, a panel was convened with contributions from scholars based in the UK and the Netherlands, including Dr Rob Meckin (University of Manchester); Prof. Joyce Tait (University of Manchester/Synthetic Biology Leadership Council); Mar Palmeros Parada (TU Delft); Dr Lotte Asveld (TU Delft); and Dr Achim Rosemann (University of Exeter). The final presentation of the day from philosopher Prof. Matthias Braun (MaxSynBio, Germany), provoked a lively discussion about definitions of artificial life.

On the second day of the conference another satellite session was held on 'Foundations and Futures of Responsible Innovation'. This workshop, convened by Dr Darian Meacham, Deputy Director for Responsible Research and Innovation at BrisSynBio, explored what philosophy can offer RRI, and how philosophy can be enriched by thinking about RRI in practice. It brought together a group of around 20 philosophers, sociologists, science and technology studies researchers, biologists, and public engagement practitioners from across the UK, Belgium, France, Germany, and the Netherlands. The session was organised into three thematic discussions. The first, led by philosopher Dr Robert Gianni (Sciences-Po) explored the history of the concept of 'responsibility', its links to 'freedom', and generating discussion on whether responsibility can be considered at a collective (as well as individual) level. The second, led by Prof. Matthias Braun (MaxSynBio)) focused on agency, considering the relational and contextually specific nature of responsibility, and the extent to and conditions under which 'bio-objects' (e.g. synthetic horsepox virus) can be considered to have agency. The third discussion was led by Viv Kuh, Mireia Bes, and Ellie Kent Hart (Centre for Public Engagement, University of Bristol), who described some of their public engagement work and its challenges. This prompted dynamic debate about the purposes, practices and responsibilities of engagement beyond the scientific community, engagement between disciplines, and engagement between scientists and public engagement practitioners.

Concurrent with the second day social science satellite session, SBRC DTProg student, Nathan Dixon, presented a poster entitled, 'Prospective Life Cycle Assessment for the RRI of Synthetic Biology' in the main scientific conference venue. Nathan's poster was well-received, attracting the interest of a variety of delegates at the conference.

By Dr Carmen McLeod and Dr Eleanor Hadley Kershaw

New to the Team

Dr Eleanor Hadley Kershaw

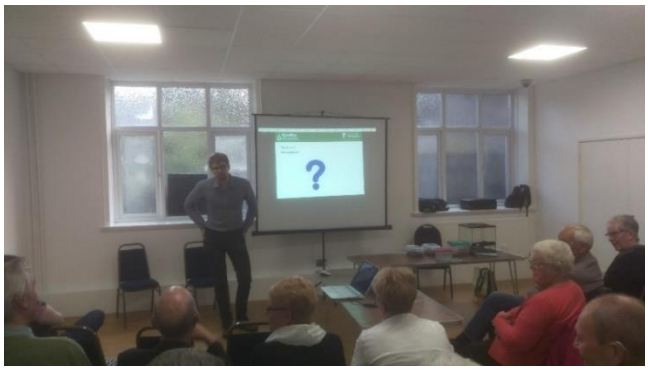
Dr Eleanor Hadley Kershaw is the social science Research Fellow on the Horizon 2020 funded ENGICOIN project: Engineered microbial factories for CO2 exploitation in an integrated waste treatment platform. She will be working with Dr Carmen McLeod in the SBRC's Interdisciplinary Responsible Research & Innovation Group. Eleanor completed her PhD in Science and Technology Studies at the Institute for Science and Society, University of Nottingham in January 2018. She has worked on a range of research projects exploring the relationship between science, technology and society in the context of grand challenges such as climate change and biodiversity loss, sustainability, and antimicrobial resistance. Between obtaining her BA in English (University of Cambridge, 2006) and commencing her PhD, Eleanor was a project manager, writer, and communications consultant in various international academic, NGO and research policy contexts, most recently at the International Social Science Council (Paris).

Outreach Activities

SBRC Talk at the University of the Third Age - U3A

On Friday 19th October 2018, SBRC PhD student - Francois Seys gave a 20 minute lay talk about his PhD and gene tool editing to a group of 25 people. A Q and A session followed the talk. François was asked many questions particularly on genes and genetics.

U3A stands for University for the 3rd Age, www.hucknallu3a.org.uk Members are retired who want to remain active and engaged in learning, members are usually 60+, but many do not have scientific backgrounds.



Francois Seys, SBRC PhD Student

3MT Competition

An 80,000 word PhD thesis would take 9 hours to present.

Your time limit..... 3 minutes! And that's the idea of the 3-Minutes Thesis, 3MT®, competition - an academic research communication competition developed by The University of Queensland (UQ), Australia.

The challenge was for PhD researchers to explain the complexity and relevance of their research to an intelligent but non-specialist audience in a concise and engaging way.

The competition at the University of Nottingham, UK, involved live presentations from 10 shortlisted finalists from various departments across the university at the Link'18 conference held at the East Midlands Conference Centre in May, 2018. Bunmi Omorotionmwan, PhD student at the SBRC, emerged as the winner. Her talk was on the sustainable production of biofuels like butanol from microorganisms and was entitled 'Better Fuel, More Savings'. She was also awarded the highest score in the Tri-Campus (UK, China and Malaysia) 3MT competition in October, 2018. View Bunmi's video here.

Bunmi says, '*It was definitely a great experience engaging in the 3MT this year. It has made me think about my research in a more generally relevant scope and made it easy for me to communicate my work to anyone anywhere!'*

Bunmi Omorotionmwan, SBRC PhD student