Synthetic Biology Leadership Council:

4th Meeting, Governance Subgroup: Minutes

14:30 – 17.00, Tuesday 10th March 2015.

Room C20, BIS Conference Centre, 1 Victoria Street, London. SW1H 0ET.

Attendees

Chair: Joyce Tait (JT), Innogen Institute, University of Edinburgh (SBLC)

Governance Sub-group:

Janet Bainbridge	SBLC
Linda Brooks	ThermoFisher
James Brown	KTN
Martin Cannell	DEFRA
Lionel Clarke (LC)	Shell (Co-Chair SBLC)
Tim Fell (TF)	Synthace, BIA
Matt Goode (MG)	Research Councils UK
Tim Higginson (BIS,	Head of the BBSRC Sponsor Team
Julian Hitchcock (JH)	Lawford Davies Denoon
Alastair Kent	Genetic Alliance
Michael Paton (MP)	Health and Safety Executive
Nick Pidgeon	Cardiff University
Hilary Sutcliffe (HS)	MATTER

Clare Hamilton and Sarah Cundy (DEFRA) and Alex Johns, BBSRC-funded PhD student, on a placement with SBLC Governance Subgroup, also joined the meeting.

Apologies: Roland Jackson; Richard Kitney

Thanks to Alex Johns for preparing the minutes of this meeting.

Agenda 1 Welcome, minutes of the last meeting and feedback on actions

Joyce Tait welcomed the members of the SBLC Governance Subgroup and visitors to the fourth meeting.

Minutes of the meeting of 3rd meeting, 17th Nov., 2014, were accepted. All actions were either completed or are on the agenda for this meeting, with the following qualifications:

Action 1 from the meeting of 6th June: the appointment of a new member to join the Subgroup carried forward **(LC)**

Agenda 2 Health related issues for future consideration by the SBLC Governance subgroup.

Alastair Kent led the discussion, framed on the assumption that synthetic biology will be able to deliver new and innovative therapies for treatment of debilitating or intractable conditions, considering the context in which innovation arises and what hurdles need to be addressed to ensure appropriate and timely access of patients to treatments.

A number of things need to be done to realise the potential of this technology. Practitioners, those commissioning services and those communicating treatments to patients should be aware of treatments arising from synthetic biology. Understanding what changes need to be made and what can be achieved requires a realistic understanding of what is and what is not biologically possible, devoid of “the hope, the hype and the shroud waving”. As well as what is doable or not doable, what is “feared to be doable” should also be considered, whether the feared outcomes are biologically plausible, or whether they are far enough in the future that we will have time to create structures to mitigate any harmful effects.

For products to reach the market, regulatory frameworks need to be facilitative. At present regulation appears to assume firms marketing products are inherently dishonest and regulators have to catch them out through stringent testing. Synthetic biology may bring the potential to treat highly debilitating, otherwise intractable conditions which induce a large amount of grief for a small, dispersed population of patients. In these cases such stringent testing may not be possible or would not be affordable / would take too long. The need to consider the benefit-risk relationships was emphasised, including in some cases a greater degree of risk associated with some treatments.

The route by which regulators reach a decision on a product could be adapted to allow additional sources of data, facilitating faster approval than is possible through large scale double blind trials. This is already recognised by European Medicines Agency (EMA) and Medicines & Healthcare products Regulatory Agency (MHRA) which are broadening criteria from which evidence can be drawn looking at adaptive pathways and real world data. It was emphasised that regulation should be appropriate for the condition and treatment to which it is being applied and that existing regulation may be excessively burdensome in some cases.

Assuming a treatment passes regulation this does not necessarily mean that it will be made available to those in need. Bodies for health technology appraisal (NICE, Scottish Medicines Consortium etc.) are already swamped dealing with more conventional interventions. Also downward pressure on healthcare resources means that requirements for demonstrating efficacy and value requirements are likely to become more tightly defined or narrowly restrictive. For example there is currently a consultation underway by NHS England to consider the weighting criteria for evidence when assessing a product, with a proposal to consider only peer reviewed data. This could have the effect of precluding evidence from patient perspectives or any unpublished industry generated evidence. For consideration of treatments for ultra-rare conditions NICE recommends assessment by the Highly Specialized Technologies Evaluation Committee. However this committee is only able to consider three treatments per year with all other products having to go through the more standard routes assessed by clinical commissioning groups. These already have a backlog of over 100 proposals for service development and are liable to block expensive treatments.

Pricing models need to be considered for certain treatments, in particular those treatments where a single intervention could give rise to a cure. The example of a treatment for Duchene muscular dystrophy (DMD) was given. This treatment would convert DMD, a highly debilitating condition which results in death at around 20, to Becker muscular dystrophy which is weakly debilitating and gives a life expectancy approaching normal. This gives an increase of around 50 QUALYS for the patent. Under current cost assessments, treatments will be funded with a cost of up to £30,000 per QUALY gained. Therefore, the NHS could be expected to pay up to £1,500,000 for this treatment. Treatments such as this would be highly taxing for the drugs budget and could require a new model for payment such as staged pricing or a hire purchase model. Where synthetic biology derived treatments pass regulatory scrutiny and are funded clinicians will need to have the skill mix to apply the technologies. Doctors, nurses and laboratory scientists will require initial training as well as continual professional development to effectively apply these treatments, as well as possible recruitment of new staff such as bio-informaticians.

Finally the organisational infrastructure of healthcare providers should better reflect the biology of pathologies, for example at the molecular level Retinitis pigmentosa is related to Alzheimer's disease. Currently these diseases are treated by different groups of clinicians (ophthalmologists and neurologists) and communication between disciplines is limited. To be applied effectively synthetic biology may require greater interaction between disciplines.

The question was raised how different is synthetic biology to other medical innovations and a comparison was drawn with robotic surgery in that they were both expensive and could suffer from public perception issues. The scope for synthetic biology was seen as being applicable

to a broader range of conditions and impacts for clinicians, with robotic surgery only affecting the surgeon whereas synthetic biology could affect a greater range of medical personnel.

As different therapies reach the market, different groups will be affected at different times and the importance of low hanging fruit to give quick wins and demonstrate the potential of synthetic biology was emphasised. Technology to detect very low bacterial counts in fluid samples to monitor treatment of neonatal meningitis is one potential example of such a potential quick win which could have a significant impact both in terms of improving clinical outcome and decreasing the cost of treatment. Genetics and biotechnology are moving forward rapidly and the major barrier to new treatments reaching the clinic is not the science, but the rolling out of the technology in a manner that is acceptable to clinicians and regulators. There is a need for pump priming funding and, although money for this may not be readily available to the health service, the relevant equipment may be available in other labs - perhaps a mechanism should be established to access this equipment for medical use.

The importance of both technology push and market pull was emphasised. Industry may have the product and the market may be available but unless appropriate actors from both groups are linked the product may not reach the market. Patient groups are important in creating market pull and Herceptin was noted as a case where patient demand had succeeded in making the product available. Once the product was brought to market clinicians began to understand where this drug would be effective in treatment of HER2+ tumours and the product could be used effectively. Patient groups are becoming increasingly engaged with research and greater consultation with these groups could drive market pull and accelerate synthetic biology products reaching the market

The issue of appropriate regulation being required was raised by the emergence of technology to insert DNA into human somatic cells in a heritable manner, potentially ready for market in approximately 2 years. This could have significant ethical implications in terms of germ line transmission and the release of transgenes into the environment.

The need for an effective communication strategy was noted to discuss with researchers what is doable, with clinicians what they need and with the public to consider public opinion and to prevent a “grey goo” fallacy in the minds of the public.

In discussion it was noted that the majority of the public tend to have a positive view on healthcare technologies and that if aware of the products would likely want them. If the science is available this creates technology push, and market pull should help drive regulators and clinicians to take up these products.

The question of where decisions are likely to be blocked and who will champion the technology was discussed. It was noted that at a regulatory level the EMA is in discussion with ABPI and EFPIA on how adaptive licencing should work. Financing these treatments should be discussed with NICE to consider the HTA framework for assessing these technologies and how cost and clinical effectiveness could be measured. NICE had been considering value based pricing but a decision had been shelved. Commissioning would be the responsibility of the NHS and the value of using low hanging fruit to forge a pathway for commissioning of products resulting from synthetic biology was noted.

Pilot projects on adaptive licencing for specific patient care are currently underway. If successful this would provide a good example of more flexible regulation. However if unsuccessful this could result in regulatory agencies being less likely to allow more flexible licencing criteria.

George Freeman’s MedTech Review regarding the capability of the health service to adapt quickly to new innovations was noted. There should be an aspiration to get this done quickly and use it to get political capital available to accelerate changes in regulation.

It was noted that although the regulation for synthetic biology in the clinic would be at a European level, this would be debated in parliament. In order for quality debate to occur the

facts must be in place to evidence the role of synthetic biology in the clinic. In the absence of this evidence the debate could easily be hijacked by those against this technology.

Bringing together clinicians and researchers should promote the technology push and market pull required to help synthetic biology reach the clinic, for example linking synthetic biology and cell therapies.

Finally the role for industry in bringing products to the market and shaping regulatory pathways was noted. In the NHS (England and Scotland) Stratified Medicine Initiative, Thermo Fischer and Illumina play a big role based initially on in-house work before moving into hospitals. This could contribute a model for bringing future products to market.

Action 1 the SLBC needs to be proactive in laying the ground for a parliamentary debate ensuring an evidence-based approach and ensure appropriate facts available to facilitate this.

Action Joyce Tait and Lionel Clark

Action 2 The Knowledge Transfer Network will offer workshops in support of the SBLC to bring together clinicians, researchers and regulators providing information for parliamentary debate.

Action James Brown

Agenda 3 Recent developments related to the UN CBD and Protocols: potential Governance Subgroup contribution

Sarah Cundy led the discussion on the outcome of CBD COP 12 as laid out in Decision XII/24. The decision asks stakeholders to submit responses to a set of seven questions giving background information on synthetic biology. Responses must be submitted to the Secretariat before 30/04/15. The call for submission and submitted documents can be found at: https://bch.cbd.int/synbio/notifications/.

The 7 questions are:

(i) How to address the relationship between synthetic biology and biological diversity;
(ii) The similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques;
(iii) Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques;
(iv) An operational definition of synthetic biology, comprising inclusion and exclusion criteria;
(v) Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols;
(vi) Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes
(vii) The degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology.

The UK government response will be included in a 'mixed' EU response. This will consist of a "chapeau" giving the overall European response, to which the responses of individual member states will be annexed. The focus of the UK response will be on the regulatory

landscape. This could be usefully complemented by responses from the synbio community of the potential benefits of the technology.

Submitted responses will act to inform further debate which will consist of two parts, an AHTEG (Ad Hoc Technical Expert Group) and an online discussion forum. The AHTEG will comprise 5/8 experts from each of the 5 regions (Africa, Asia-Pacific, Central and Eastern Europe, Latin America and the Caribbean and Western Europe and Others), as well as observers. In order to be considered to become a full member of the AHTEG (i.e. representing a Government) one has to be nominated by the national focal point of a government. Anyone can be nominated to become a member, although those put forward tend to be government officials. Nomination does not ensure membership. The nominees are chosen by the Secretariat to give a balance of skills and expertise. Michael Paton will be the UK nominee for the AHTEG. A limited number of observers will also be involved. Nominations of observers can be submitted by "by other Governments, indigenous people and local communities and relevant organizations" with places awarded by the secretariat. Observers can fully participate in discussions but not in decision making.

The supporting online discussion forum is open to all and will take place between April and June. The discussions that take place in the forum will support the work of the AHTEG. Active participation in the AHTEG is also a key selection criterion for the AHTEG. Anyone may partake in the forum and the importance of the SLBC taking an active role was emphasised. Also individual members may separately represent their own institutions on this forum.

It was noted that depending on the activity of the forum, taking an active role can be time consuming but this can be helped by groups working together to argue a point. Also the importance of activity throughout the duration of the forum was emphasised, with activity early in the forum important to frame the debate and continued activity to insure important facts are not missed.

For ease of reference, information on how to join, or nominate members to the forum can be found at: https://bch.cbd.int/onlineconferences/nominationOrgs_ra.shtml.

The worst possible scenario resulting from COP XIII would be a complete moratorium on synthetic biology, including contained use in those countries that are Parties to the CBD. It was noted that this would not include the United States of America, although even there research would be stunted as export of technologies would be difficult. It was noted that this outcome would be unlikely, and a more realistic outcome would be extra regulation on top of the Convention and associated protocols.

At present, synthetic biology is not clearly defined. This lack of a clear definition could significantly affect both the debate and resulting regulation. Many definitions used are vague and thus would encompass aspects of biotechnology and GM not classically considered synthetic biology. Given that the European knowledge-based bioscience industry is valued at approximately €2 trillion the cost of any moratorium would have to be carefully considered by regulators.

The idea of using the lack of a definition for synthetic biology to filibuster any detrimental regulation was discussed. There was concern that this would create uncertainty within industry. It was considered whether regulation imposed sooner would be preferable to the risk of draconian regulation being imposed at a later date. For one industry member, maintenance of the status quo in spite of uncertainty would be preferable to extra regulation being imposed. It was noted that attempting to filibuster regulation would require significant input into the debate. The role of using examples to convince nations of the useful nature of synthetic biology was raised and it was noted that filibustering would increase the number of examples available to convince nations of the utility of synthetic biology.

Action 3 The SBLC to submit its own response to the secretariat, independent of the UK government response as this would have more freedom in what could be included.

Action: SBLC Governance Subgroup

Action 4 In order to insure a balanced representation, it was recommended members partake in the online forum in support of the AHTEG representing their own institutions.

Action: SBLC Governance Subgroup

In a related discussion there was a call for the SBLC to lobby for harmonisation of standardised biological parts. Harmonisation of standards for assessing genetic parts could reduce uncertainty associated with given parts as they would be understood and well qualified. There are several different "standardised" libraries (BioBricks, iGEM part library, etc.) but formal, international standardisation is required to create harmony between libraries. An ISO type standard was recommended and it was noted that BSI have an initiative under way to develop such a standard. Given that biology is context dependent and that inserting certain combinations of genes may have unexpected consequences, standardisation would give us the best footing to understand these effects. It was recommended to pass this on to the leadership council.

Action 5 The SBLC should lobby for the creation of a harmonised specification for genetic components.

Action JT and LC

Alex Johns presented a brief analysis of some of the key arguments used by NGOs against synthetic biology developments, including calling for a full moratorium on release and commercial use of synthetic biology organisms or products. Four types of arguments are used against synthetic biology: safety concerns regarding both human health and the environment; economic impacts; changes in land use; and intellectual property and benefit sharing.

- With regard to safety, most synthetic biology products approaching the market are derived from engineered microorganisms. NGOs state concern over the efficacy of biocontainment practises and uncertainty regarding how these organisms would behave after an environmental release, intentional or otherwise.
- With regard to economic effects, synthetic biology is currently being used for production of high value compounds such as vanillin or artemisinin and NGOs are concerned that this will adversely affect farmers in developing states who previously would have produced these products from botanical sources.
- With regard to land use changes, NGOs claim that use of feedstocks such as sugar in industrial fermentation will displace land used for food production or encroach into virgin land, primarily affecting those most productive lands in equatorial regions.
- With regard to IP and benefit sharing, NGOs are concerned that synthetic biology will facilitate "biopiracy" as advances in DNA sequencing and synthesis facilitate the reproduction of genetic resources, evading controls on trans-boundary movements and creating legal loopholes to avoid liability. They also fear that patent thickets could be used to block indigenous groups from using their native resources.

Agenda 4 Update on Ecover / Solazyme

Due to time constraints this item was postponed.

Agenda 5 Update on the discussions on the definition of Synthetic Biology

Julian Hitchcock presented for discussion the European commission document 'Final Opinion on Synthetic Biology I, Definition'. This document is the result of an EC consultation on the definition of synthetic biology, the purpose of which is to inform two further opinions on risk assessment methodologies and safety aspects; and research priories. This document attempts to answer the question what is synthetic biology and what is its relationship with GM.

In this document they produced the definition “SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms”. They describe this as an operational definition and that it should unequivocally be able to define whether a product is synthetic biology or not. However this assertion is questionable.

It is noted that synthetic biology is covered by existing GM regulations 2001/18 and 2009/41 and will likely remain so for the foreseeable future, stating “the definition has the advantage that it does not exclude the relevant and large body of risk assessment and safety guidelines developed over the past 40 years for GM work and extensions of that”. Furthermore it is noted synthetic biology should not require any change in existing core regulation.

The problem of identifying quantifiable inclusion or exclusion criteria was noted and instead a list of guiding principles was offered. These principles cover any organism, system, material, product or application of the genetic material in a living organism and the factors used are complexity of the genetic modification, the speed of the modification and the degree of computational modelling used. This assures us it will be able to separate synthetic biology form GM but again this is debatable.

The document summarises regulations pertinent to synthetic biology, listing : GMO regulation, GMO medicinal products, biological risks to occupational health, medical devices, gene therapy and tissue engineering, clinical trials, cosmetic products, and chemicals and products for food and feed uses. It was noted that this list was incomplete in places or out of date, but it highlighted that synthetic biology is already regulated and new regulation is not required.

It was emphasised that everything on or near market is covered by existing regulation and that there are no plans to generate new regulation at an EU level for release or contained use. The European Commission is however working on updating definitions in order to capture new techniques such as gene editing under existing regulation.

This document was produced by an advisory committee and not the European Commission itself, however the Commission can be expected to draw heavily on documents such as this.

There are many definitions for synthetic biology (this document highlights several) and different definitions serve different purposes. The one given in this document is purely for the purpose of safety and risk assessment for the subsequent documents. It was noted that DEFRA would have to continue using definitions contained within regulations.

The lack of distinctions, descriptions or gradations which could be used to clearly separate synthetic biology from systems biology, GM or other fields was noted. Such distinctions would not be feasible given their overlapping nature, broad scope and varying opinions on what is synthetic biology.

No actions arose from this discussion.

Date of next meeting: 18th June, 2015, Room C17, BIS Conference Centre, 1 Victoria St., 13.30 – 16.30.