Synthetic Biology Biosensors for Global Health Challenges

Workshop Report of the Flowers Consortium

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We would like to thank all the workshop participants for their contribution to the constructive and engaging discussions and for their contributions to the review process.

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Executive summary

Synthetic biologists seek to design, build and modify organisms at the genetic level. One category of engineered organisms, or devices, sense changes in the environment and respond by producing a change in state, such as colour. Two such 'biosensors' are in development within the Flowers Consortium, and both are envisaged to address threats to human health in the Global South. Biosensors are at an early stage in development, meaning that there is scope to shape their future trajectories.

Accordingly, researchers at King's College London convened a one-day interdisciplinary workshop with 30 experts working insynthetic biology, regulation, global health, international development and the social sciences. The workshop's purpose was to investigate the two biosensors and draw lessons for researchers and policy makers working in synthetic biology, especially when intervening in global health contexts.

Part one of the report summarises the discussions of the day. This executive summary outlines the overarching analytic themes from the workshop, which can be found in part two.

Understanding global health contexts

Overall, workshop discussions emphasised the complexity of the problems that the two technologies seek to address. This complexity arises from differing geographies, social dynamics, cultures, and histories. For instance, what is deemed to be a 'healthy' physique varies from location to location and is the result of cultural, dietary and environmental factors. Likewise, different cultures have different understandings of sickness and healing, which vary and change over time. Such insights mesh-well with an understanding of global health as resulting from webs of interaction between people, their cultures and the environments that they inhabit. Adopting such a position makes visible that there is unlikely to be a singular 'best' way of framing a problem. Rather, the extent to which a problem and solution are seen as appropriate will vary depending on the perspective taken and by whom.

All of these features are site-specific and have a significant impact on the characteristics that a technology must have to be successful. Thus, despite the importance of the idea of challenge led research to address global health, it is fundamental to understand to local specificities if a project is to make a worthwhile contribution.

Understanding the technologies

Building on our understanding of global health contexts, discussion around the two case studies emphasised that biosensors are not just neutral tools, but interventions into global health networks of organisms, organisations and environments. To be effective, a biosensor must necessarily be designed to address particular niches within this network and embed different design choices according to the objectives of its users. These design choices are likely to be competing and may be mutually exclusive.

Workshop participants also made clear that the implementation of each solution would affect different people in different ways, empowering some and disempowering others, supporting certain ways of making sense of the problem and marginalising others. And, because projects are increasingly geographically-

dispersed, with partners in different constituencies, the political implications are not limited to the locale of end use.

Whilst it may be tempting to view biosensors as primarily neutral technical devices, acknowledging the features above highlights that the choices embedded into these objects are political as much as technical.

Technologies in context

Four recommendations follow from this analysis. Researchers and policy makers involved in the governance of synthetic biology need to:

1. recognise the political choices embedded in the design and use of biosensors and make key decisions explicit in advance of their development;

2. generate knowledge of the complex social and cultural contexts alongside the development of such projects using established and emerging social science methodologies;

3. identify existing interventions that a biosensor seeks to improve on, replace or may inadvertently displace and analyse the implications of doing so;

4. integrate local knowledge into the design of the biosensor by conducting engagement with key stakeholders; and acknowledge that integration can be laborious.

Three avenues for further research

Part two of the report closes by highlighting three tensions that arise as emerging biotechnologies are being developed to address global health challenges.

Lock-in

On the one hand, certain aspects of a technology must be locked down in order for a project to advance, but on the other hand a technology must remain open to shaping as contexts change. There are several key points at which project ideas can be locked down, including initial project framing, circuit design and after gaining regulatory approval. Both projects are notable in that their initial framing was set in terms of synthetic biology seeking applications and problems to address, a framing that each team is progressively moving away from. Whilst this is a long-identified tension in social studies of science, we suggest that it is likely to become more important as research funders increasingly demand challenge-oriented projects in which those who seek funding have, at very early states, to claim a fit between their ‘solution’ and the problem it seeks to address.

Translational pathways

Relatedly, it is worth attending to the oft-assumed models of innovation and translation that shape biotechnology projects. At extreme ends, we see ‘bench to bedside’ and ‘bedside to bench’ models of translation. Noting that these are perhaps best seen as ideal types rather than representative models, it is nevertheless important to explore alternatives and attempt to diversify the models of translation and innovation apparent and available to researchers because: a) the assumed model of translation can significantly impact the ability of projects to integrate new knowledge into the design of the technology; b)

the funding assessment criteria for projects wishing to adopt alternatives in global health contexts appears to be opaque; and c) such models are coupled to institutional reward structures within academia which are skewed towards certain outcomes (e.g. funding income, intellectual property).

Regulatory frameworks

Finally, we address regulatory tensions in the governance of synthetic biology. Discussions throughout the workshop highlighted the political, social and technical characteristics of biotechnologies. Acknowledging that regulation surrounding genetically modified organisms is one of the primary points that social values around such organisms are codified means that it is important to pay attention to any challenges to regulatory definitions and frameworks. There is currently much discussion regarding the ability of novel gene editing techniques, such as CRISPR/Cas systems, to disrupt established regulatory regimes for biotechnologies. However, the workshop identified two additional challenges: the legislative distinction between 'deliberate release' and 'contained use'; and assumptions about the relationship between regulatory approval and environmental safety. Whilst noting the value of precautionary approaches, we suggest that identifying methods to incorporate broader social, political and environmental characteristics — beyond technical assessments — into the governance of synthetic biology technologies may help to address such regulatory tensions.

Contents

Introduction 8

Part 1: Summary of discussions 10

Global health and synthetic biology biosensors 11
Case study 1: An arsenic biosensor 17
Case study 2: A schistosome biosensor 34
Reflections 48

Part 2: Key themes and analysis 54

Lessons: Understanding global health challenges 55
Institutional reflexivity: Tensions 60

Supplementary material 63

Workshop programme 64
List of participants 65
Feedback received 66
Procedure to exclude a GMM from the scope of Directive 2009/41/EC 67
Further reading 68

Introduction

This document reports on a workshop on 'Synthetic Biology Biosensors and Global Health' organised by King's College London and held at the Royal Society of Arts on 13 October 2015. It was the third in a series sponsored by the Centre for Synthetic Biology and Innovation (CSynBI). The first two were on 'Synthetic Biology and Biosecurity' and 'Synthetic Biology: Containment and release of engineered micro-organisms'. Reports and slide presentations for all these workshops are accessible here[1].

Synthetic biologists are currently developing several different biological sensors – that is to say, biologically based devices to detect substances in the environment – and some of these are intended to be used in the Global South to identify threats to human health. Bringing the products of synthetic biology into these regions, and thereby intervening in complex interconnected social, environmental, political and technical spaces raises important questions for the design and envisaged deployment of these devices. The workshop presented here involved participants with a range of different sets of expertise: synthetic biologists, risk regulators, representatives from civil society organisations and social scientists. The aim was to bring together different perspectives on these issues in order to help build an approach to the development of biosensors for Global Health that was compatible with the emerging concept of 'responsible innovation'[2].

The underlying principle for this type of biosensor is to produce harmless genetically modified bacteria or cellular machinery that can detect a harmful agent and then emit a signal, for example a change in colour, pH, or fluorescence to indicate the presence of that agent[3]. Compared to other kinds of existing detection methods (e.g. using chemicals or microscopes) the hope is that synthetic biology biosensors might be cheaper, easier to use and/or more environmentally friendly. Two such projects are currently being developed within the UK Flowers Consortium for synthetic biology: an arsenic biosensor at the Universities of Cambridge and Edinburgh and a biosensor for the parasite that causes schistosomiasis, currently being developed at Imperial College London (ICL).

At the time of the workshop each project was at a different stage of development. While the Arsenic Biosensor Collaboration had produced a physical, functioning pilot, the schistosome biosensor team were exploring design options, use cases and technical feasibility. In line with the principles of responsible innovation, such differences presented an opportunity for the workshop discussions to inform the future development of each biosensor. In addition, the workshop focussed on these two case studies in order to identify and explore a range of more generic issues relevant to synthetic biology biosensors for Global Health.

1 http://www.kcl.ac.uk/sspp/departments/sshm/research/Research-Labs/CSynBI-Events.aspx

2 See here for the UK Engineering and Physical Sciences Research Council's perspective on responsible innovation: https://www.epsrc.ac.uk/index.cfm/research/framework/. See also: UK Synthetic Biology Roadmap Coordination Group (2012). *A synthetic biology roadmap for the UK*. Swindon, Technology Strategy Board; Stilgoe, J., Owen, R. and Macnaghten, P. (2013). 'Developing a framework for responsible innovation.' *Research Policy* **42**(9): 1568-1580; Owen, R., Bessant, J. and Heintz, M. (Eds.) (2013). *Responsible Innovation: Managing the Responsible Emergence of Science and Innovation in Society*. Chichester, Wiley.

3 The biosensors in this report can also be described as bioreporters. For consistency, we use the term 'biosensor' throughout.

The meeting was held under the Chatham House Rule in order to facilitate open and productive discussion. This means participants are free to use and disseminate the information presented, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed. For this particular meeting, participants have agreed to be listed (see Supplementary material) and the speakers at the workshop have given their consent for their names to be used in the summary of their talks, and where relevant also in the summary of discussion.

Part 1: Summary of discussions

The first part of this report summarises presentations made by seven researchers in the field of global health and/or synthetic biology and the discussions that occurred during the day, replicating as accurately as possible what was said by workshop participants, without commenting on those statements, and without endorsing any of the views expressed. The discussion in each case study contains both clarifications relating to the presentations and broader discussions relating to synthetic biology and/or global health. Arguments are reported even when they were only expressed by just one or a few participants. The aim is to represent the diversity of views expressed and not to seek to assign particular weight to any of the arguments reported. In the second part of this report the authors use their social science expertise to analyse those discussions and summarise what they consider to be the key findings, and reflect on the dynamics of those discussions.

Global health and synthetic biology biosensors

The day began with two short presentations, the first on Global Health and the second on Synthetic Biology Biosensors.

Global Health

Bronwyn Parry, GHSM, King's College London.

Parry's presentation introduced some of the key considerations to be addressed when developing global health interventions. It began by recognising that large inequalities in health are found throughout the world, and that these inequalities are a key motivation for many intervention attempts. A crucial point was that culture can influence what is even deemed a matter of health or disease in a given context, and that this can therefore influence what kinds of intervention are likely to succeed or fail.

Health inequalities between countries, measured with indicators such as infant mortality and life expectancy, are well known but still shocking. In many cases, diseases are concentrated in certain key regions. For example, in 2013 over 80% of malaria cases occurred in just 18 countries. The success rates of efforts to tackle malaria vary widely. Parry noted the Exxon Mobil malaria initiative 'Malaria No More' as an example of the kind of intervention that has proven successful in reducing cases of malaria, and which also illustrates the wide range of actors involved in global health interventions. Aside from traditional state actors, NGOs and health delivery agencies, this programme also saw philanthropic organisations and commercial companies playing significant roles, sometimes in the form of public-private partnerships. Parry recommended that synthetic biology initiatives in the global health arena be prepared to interact with this variety of stakeholders.

Parry also noted that diseases can have very uneven political geographies. Through the example of HIV, she explained how political issues such as intellectual property rights (IPR) can have a dramatic effect on access to treatment. For instance, the World Health Organization (WHO) estimated that of the 34 million people living with HIV, 26 million need antiretrovirals, but by the end of 2012 only around 10 million actually had access to them, circumstances thought to have been due, at least in part, to overly-restrictive IPR regimes. It is therefore important to consider how any technology solution developed by synthetic biologists might actually be rolled out, bearing in mind the important role of national and international political decisions.

Parry then turned to typical portrayals of global health issues, using examples of photographs of intervention work taken from the internet, arguing that they have a particular valence: that of 'white people going out to help people of other colours in developing countries'. Parry argued that this is patently not how we should conceptualise global health interventions. Global health is instead better understood as an iterative process involving ongoing conversation between different stakeholders. An important way in which this latter approach is superior to the former, argued Professor Parry, is that it allows us to recognise that how problems are understood and prioritised, and thus are seen as a matter for intervention, can vary from location to location. Anthropologists such as Robert Hahn have pointed out that "the culture of a society constructs the way members think and feel about sickness and healing"[4]. This highlights that the way in which

4 See: Hahn (1995). "The role of society and culture in sickness and healing." In Hahn, R. *Sickness and Healing: An Anthropological Perspective*, New Haven: Yale, 1995, p. 76-98.

people understand symptoms, disease progression and appropriate treatments is complex, and draws on deeply embedded local beliefs and values that can differ greatly between one place and another. Rather than arriving into the field with presumptions about what constitutes priorities for good health, researchers seeking to provide solutions need first to consider how those apparent solutions are going to be understood by their intended users. For example in regions where infections by intestinal worms are common, children with very bloated bellies are considered 'normal'. Conversely in Samoa, being what we in the UK would call 'obese' is a physical characteristic to aspire to. These are social and cultural constructs rather than simply being 'naturally' determined. In addition, if we look at the different explanations given for particular health concerns over time, we can see that theories as to the causes of a disease can change dramatically over time The historical lesson here for synthetic biology is that proposed solutions are bounded by the contemporary historical and political context.

Parry argued that many global health interventions are intrinsically 'ethnocentric', meaning that they are characterised by a belief in the inherent superiority of the intervener's own perception of the world that prioritises his or her idea of what a rational response should be. But, it is very important to remain reflexive about what different stakeholders and researchers consider to be problems and solutions, and to be willing to adapt and change one's views. Taking part in iterative conversations with different stakeholders can contribute to this.

Parry referred to the social anthropologist Marilyn Strathern, who has stressed that 'culture' is something that applies to all societies, including our own, and talks about 'bringing anthropology back home'[5]. Every society is made up of 'quirky tribes'. We can for example think of synthetic biologists and sociologists as 'quirky tribes', so it is important to reflect and gather insights about our own practices. This would help us to move away from the unidirectional notion of global health whereby 'we' go 'over there' to help 'them'. Indeed, Parry argued, global health is an issue right here in London: there is something like a 'third world' in every 'first world.' As argued by Hoogvelt[6], in every society in the world, you will find the 'elites', the 'contented' and the 'marginalised'. Global inequalities are no longer solely geographical divisions; they are embedded in global social structures.

> "The culture of a society constructs the way members think and feel about sickness and healing."
>
> *Hahn, 1995*

Parry argued that synthetic biology was positioned to make enormous potential contributions to vaccine development, diagnostics, drug synthesis and so on. But in order to make a meaningful contribution in global health contexts, lessons need to be learnt from successes and failures of the past. This means paying serious attention to the various social, geographical, political and cultural issues outlined in this talk. Many failures in global health have arisen when institutional goals and logics did not align with those of the targeted population. An example of this is the Global Malaria Eradication Programme (GMEP) launched by the WHO

5 See, for instance, Strathern, M (1996) *Shifting Contexts: Transformations in Anthropological Knowledge*. Abingdon: Routledge.

6 Hoogsvelt, A. (2001). *Globalization and the Postcolonial World: The New Political Economy of Development*, Palgrave Macmillan.

in the 1950s, which ultimately saw some successes but also many failures. In this case, the programme began with a large swell of optimism underpinned by large amounts of funding. Many experts and policymakers believed that worldwide eradication of malaria was feasible within a limited timeframe with the use and deployment of the right tools: namely the pesticide DDT[7] and the pharmaceutical drug chloroquine.

> "We need to move away from the unidirectional notion of Global Health whereby 'we' go 'over there' to help 'them'."
>
> *Bronwyn Parry*

The GMEP did indeed result in the eradication of malaria in some countries; but this optimism also led to disillusionment in other countries where effects were not seen as quickly. This in turn led to 'donor fatigue' and cuts to funding. Another problem was that this vast programme was established over and above national governments and was therefore detached from national health systems, which meant that it could not adapt to local conditions. It was based on a one-size-fits-all approach that, according to Parry, ultimately proved to be inadequate in achieving its stated goal of universal malaria eradication.

Parry's talk ended with three cautionary points to help avoid such failures, adapted from a recent paper by Liu[8]. The first was the need to pursue the inclusion of multiple publics from the outset. This is likely to produce better acceptance of products and processes and also, Parry argued, better science. The second was to avoid the 'magic-bullet' mentality that assumes we can helicopter in a technical 'fix' and that ignores the fact that health problems are the product of entrenched social and political inequalities that must themselves be tackled at the same time as the technological solutions are implemented. Technological fixes that ignore those contexts are likely to fail or even to exacerbate matters. Taking this into account could help to avoid results such as in the WHO malaria eradication programme that resulted in the rise of artemisinin resistance. Thirdly, understanding the barriers to successful implementation may require 'turning the telescope back on ourselves' (a reference to Marilyn Strathern): what are our own values, beliefs, and organisational expectations and how are these shaping the project in a particular way? This means that we need to study synthetic biology institutions themselves: what are the underlying priorities, assumptions and logics of those practicing synthetic biology? If we follow these guidelines, we can be hopeful that projects to develop biosensors for Global Health will actually deliver something meaningful.

7 Dichlorodiphenyltrichloroethane

8 Liu, J. A. (2015). Synthetic biology in Global Health: lessons from history and anthropology. *Journal of Responsible Innovation* **2**(1): 96-99.

Synthetic biology biosensors

Paul Freemont, CSynBI, Imperial College London.

Freemont's presentation began by emphasising that synthetic biology envisions merging engineering design practice into the systematic construction of biological systems and cells at the genetic level. At the core of synthetic biology is the aim to construct biological systems using the systematic design process of engineering. Synthetic Biology's vision of 'making biology easier to engineer' rests on the understanding that engineers have for some time dealt with and attended to systemic complexity, in order to achieve robustness and stability in their technological products. Freemont explained that, as complex biological systems display similar features, synthetic biology aims to incorporate engineering principles (such as system control, redundancy, modular design and structural stability) into research and innovation practices. However, certain features of biological systems make them less tractable than the systems that engineers have typically focussed on: they are much more complex, consist of multiple scales (from the atomic scale up to human beings and ecosystems) and operate over time. In short, they are alive.

Freemont then moved on to biosensors explaining that they have been in use for some time – an example being blood sugar level monitors. A basic definition is that biosensors are analytical devices for the detection of substances of interest (analytes). Synthetic biology aims to produce biosensors that are quick, simple, and cost effective in comparison to existing detection methods. They should also allow for high specificity with regard to the analytes they detect, thanks to the molecular level at which recognition takes place.

Freemont explained that there are two main types of synthetic biology biosensor, which he characterised as living and non-living (see figures below and facing). Whole-cell biosensors are composed of living cells, and make use of the inherent sensing machinery of the cell. Novel genetic circuits are incorporated so that when triggered by an analyte of interest, they emit an output (typical outputs being fluorescence and bioluminescence). The primary advantages are that bacterial replication makes this cheap, and complex systems can be designed. The primary disadvantages are that whole-cell biosensors comprise genetically modified organisms (GMOs), and that there may be difficulties in ensuring robustness and reproducibility.

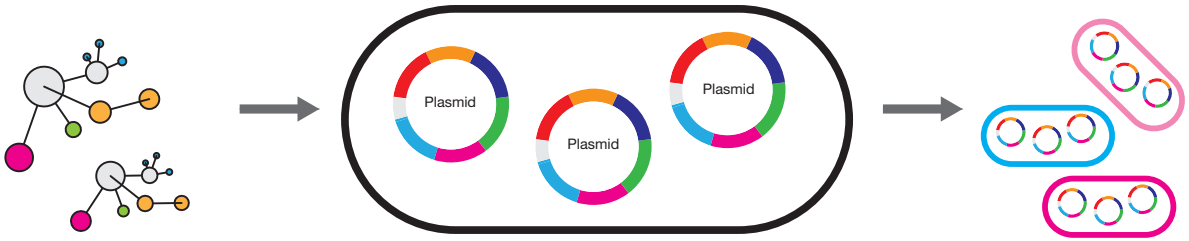

Figure 1: Principle of whole-cell biosensors. Adapted from Goers, L et al (2013) 'Engineering Microbial Biosensors'. in Harwood, C, Wipat, A. (eds) Microbial Synthetic Biology. Academic Press: Burlington.

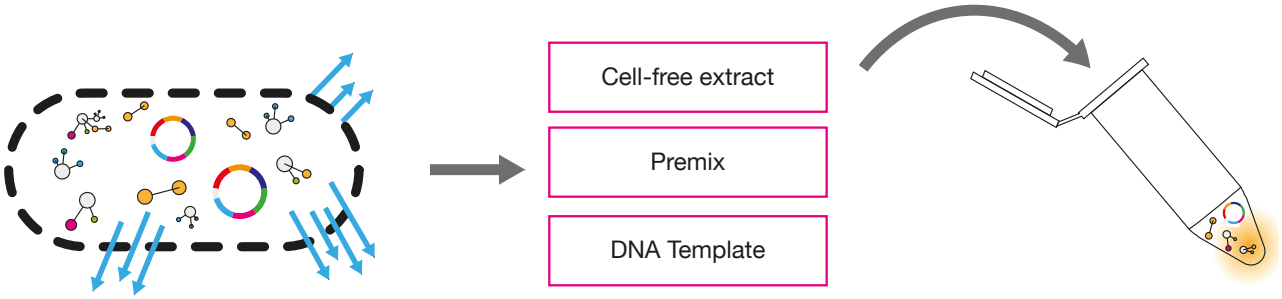

Figure 2: Cell-free biosensors made from lysed cells have three essential components: A cell-free extract containing machinery for transcription and/or translation; A premix containing buffers, energy and resources (cofactors, amino acids); and DNA templates from plasmids or PCR products. Adapted from presentation given by Paul Freemont. See also, Lu (2017) Cell-free synthetic biology: Engineering in an open world. Synthetic and systems biology. http://dx.doi.org/10.1016/j.synbio.2017.02.003

In vitro cell-free biosensors do not carry out their sensory operations within a cell, but rather within the biochemical cell extract, and can be considered non-living. Currently used outputs are very similar to those employed by living biosensors. Freemont suggested advantages including: cell-free systems do not meet the regulatory definition of a GMO; they do not replicate; and, they are more robust. A major disadvantage is that they are currently very expensive. One important article published in 2014 demonstrated that cell extracts could be freeze-dried and applied to filter paper, which opens up room for many new applications[9].

Freemont then listed some of the potential applications for synthetic biology biosensors, ranging from environmental and consumer product monitoring to home health tests and the monitoring of industrial processes. The design of such sensors requires attention to technical details as well as a range of social and environmental factors, including the *location* of the target molecule (intra or extracellular), the *concentration dynamics* of the target (will its concentration levels be constant or are they likely to change over time?), *relevance* to the process being monitored (does the concentration of the detected compound actually reflect the process we want to monitor?), *specificity* (if the target compound is similar to other compounds, might these also be detected by the biosensor, and will this result in 'false' readings?), and lastly *need* (do current detection methods exist and what advantages could a biosensor have over those existing methods?).

Freemont then went on to describe three classes of synthetic biology biosensor: transcription based, translation based, and post-translation based. He concluded by reiterating that these types of synthetic biology biosensors are using natural biological systems refactored for detection and that cell-free paper based approaches currently showed particular promise.

9 Pardee et al. (2014) 'Paper-based Synthetic Gene Networks', *Cell* **159**:4, 940-954.

Opening discussion

Expense of cell free systems

Following these two introductory talks, group discussion first focused on why cell-free systems were so expensive. This appears to have been an evolving process largely shaped by what these cell extracts were being used for: commercial manufacturers, which charge a considerable price, have over the years found it necessary or advantageous to supplement them with components that make them more amenable for use as research tools for molecular biology (in, for instance, studying fundamental principles of transcription and translation). However, simplified extracts are now being developed both commercially (with cost-savings of ~95%) or in-house, where for instance researchers at ICL are themselves experimenting with methods to produce cheaper extracts.

Comparison with existing medical point-of-care DNA diagnostics

One participant mentioned that there are many companies worldwide developing cheap, rapid, point-of-care DNA medical diagnostics and wanted to know how synthetic biology sees itself in relation to this established industry. A synthetic biologist responded by arguing that because synthetic biology is based on the engineering of biology, it can produce more complex systems than other technologies currently being used for diagnostics. For example, it should be technically feasible, using synthetic biology 'logic gates' to have a paper-based biosensor able to detect five different analytes simultaneously and produce different coloured outputs, depending on which ones are present.

The role of industry in agenda setting

Questions were asked about who dictates the research agenda and what the role of the commercial sector might be. In response it was explained that Imperial College hosts the government-funded national UK Innovation Knowledge Centre, SynbiCITE,[10] that aims to ensure that academic research labs are well-connected with firms in order to accelerate the commercialisation of synthetic biology. Strategies were also being set by research funding bodies and governments. The UK government had commissioned a 'roadmap' in 2012 that had constituted an important component of national strategy and that was being 'refreshed' during 2015[11]. The 2012 roadmap had led to the establishment of the UK Synthetic Biology Leadership Council that brings together synthetic biologists and other stakeholders, including industrial partners. It was also acknowledged that unless people in different countries actually want synthetic biology products, these will not be taken up. This means that it is important for researchers to engage with other communities. There was a sense that certain synthetic biologists had demonstrated a willingness to be a part of such a process.

10 http://www.synbicite.com/

11 In February 2016, the UK Synthetic Biology Leadership Council published the "Biodesign for the bioeconomy: UK Synthetic Biology Strategic Plan 2016".

Case study 1: An arsenic biosensor

This session was devoted to discussion of an arsenic biosensor being developed by members of the Flowers Consortium at the Universities of Cambridge and Edinburgh. Talks were given by experts on the problem of arsenic contamination, the arsenic biosensor project itself and the regulatory process that this device was going through. This was followed by a general group discussion.

Arsenic contamination: occurrence, causes, impacts and mitigation

Peter Ravenscroft, independent consultant

Ravenscroft's talk provided an overview of the global problem of arsenic contamination, its effects on health, and impact on agriculture. It also described the problems that are likely to be encountered by the Arsenic Biosensor Collaboration team (or any arsenic sensor project for that matter) when they go out into the field.

Ravenscroft explained that the most common way in which arsenic gets into groundwater is through 'reductive-dissolution.' Arsenic present in mountains that are subject to rapid weathering is released when rocks are dislodged and transported into rivers at the mountain base. Decomposition of biological matter in the rivers creates chemically reducing conditions in the water that release the arsenic from the rock. Contamination is found on all inhabited continents, but the most affected areas occur along the fringes of the Himalayas, in North and Central America and parts of South America. Arsenic occurs throughout the world, including in wealthy countries such as the USA. When viewing maps of arsenic contamination, it is important to bear in mind that the extent of arsenic contamination in surface and ground water is not directly correlated with the local scale of human health impacts (see Table 1). The most affected populations include Bangladesh, India, Pakistan, Myanmar, Nepal, China and Vietnam. Approximately one third of the exposed people in the world live in Bangladesh, but importantly, there are many countries in the world that have simply not been tested. This was why much of Ravenscroft's talk – and indeed much scholarship in the area of arsenic contamination – focused on research in Bangladesh.

A key feature of the history of arsenic detection throughout the twentieth century has been its discovery in certain regions, and then its subsequently being largely ignored. Different countries and international organisations have set standards for levels of arsenic contamination in food and drinking water; these decisions have been influenced by the extent to which any given country wants to politicise the issue, or feels capable of responding to it based on what is considered achievable. In many cases, standards for acceptable limits have been based on the practical level of detection at the time. Arsenic consumption – through both drinking water and eating food grown in contaminated soil – results in a wide range of serious health problems, including cancers, heart problems and other conditions leading to premature death. Ravenscroft noted that at present the levels of deaths caused by arsenic poisoning are not sufficiently recognised, because arsenic causes a host of different diseases and health problems and those diseases are recorded on death certificates without any mention of the role of arsenic. One feature of arsenic that Ravenscroft emphasised was its latency: effects occur long after exposure, sometimes decades later.

The talk explained that arsenic is not just a problem of contaminated drinking water, but also of agriculture and food production. When arsenic accumulates in the soil, growth of some crops – rice in particular – can be heavily impeded by arsenic. Moreover, arsenic contamination of the food chain poses serious health problems. Mitigating arsenic in the food chain is even more complicated than for drinking water. The issue of food supply contamination is central, but is even more politically sensitive because without a viable alternative food supply, the effects of arsenic on rice production are often believed to be insurmountable. It would for example be untenable to suggest to people in Bangladesh that they should not eat rice.

The main mitigation technologies aim to either remove arsenic from water or to help people avoid contaminated water in the first place. Removing arsenic from groundwater can be done through oxidation, coagulation-filtration, lime-softening, adsorption, membrane technologies, electrolytic methods and phytofiltration. Arsenic can be avoided by using alternative groundwater sources, through sharing of safe wells or by using deep tube wells. In some cases however, these deep tube wells have not themselves been tested or have not been maintained to a sufficiently high standard and so, the problem could have worsened. Ravenscroft also noted the political dimensions of mitigation which may mean that the benefits of mitigation are not necessarily evenly distributed. For example, there have been cases where newer, safer wells have been located at the end of a village where government supporters live. In short, testing on its own is of limited use unless there are available options for decontaminating or for avoiding the contaminated water and using alternative sources.

Ravenscroft nevertheless argued that testing was important to raise awareness of the dangers of arsenic poisoning. In the 1970s (prior to when the government began a large series of tests), the number of shallow wells being drilled increased rapidly. By the mid 1990s to the mid-2000s however, when the government began testing, the number of shallow wells being drilled dropped dramatically. After this series of testing was completed and the government stopped testing, the rate of shallow well drilling again increased steadily (see Figure 3, facing page). Testing, Ravenscroft argued, is about monitoring and maintaining awareness, and ensuring that mitigation efforts are concentrated where they are most needed.

Country	>10ppb	>50ppb
Argentina	unknown	2.0
Bangladesh	50	27
China	15	5.6
India	30	11
Mexico	0.2	0.4
Nepal	2.5	0.5
Pakistan	5.0	2.0
USA	30	3.0

Table 1: Numbers of people exposed to arsenic contaminated drinking water (millions of people; parts per billion). In the US and EU, the maximum recommended level is 10ppb; In India, Bangladesh and China the standard is 50ppb. Source: Ravenscroft, P., H. Brammer & K.S. Richards (2009) Arsenic Pollution: A Global Synthesis. Wiley-Blackwell

Affordable and easy to use testing is key but some existing technologies have been considered controversial, as they are not considered sufficiently reliable. Current test kits, which use toxic and hazardous chemicals, cannot be operated on a commercial model for the level of testing that is required due to the very low ability to pay and the small number of tests that can be completed in a day. In the history of testing in Bangladesh, the number of labs working on testing and the sensitivity of the testing kits, has increased. However, Ravenscroft emphasised that there are currently no

testing kits available for use by the general population: all testing currently must be performed by government representatives or other institutional experts. In short, in countries like Bangladesh there is no system of accessible and affordable arsenic testing.

Ravenscroft ended the talk by pointing out that the UN had recently established a new Sustainable Development Goal to promote access to safe and affordable water (SDG 6). Riding on this kind of momentum, keeping the problem in the political and public eye and making testing available to the general public, would be crucial. Ravenscroft's opinion was that the synthetic biology arsenic biosensor (described in the following talk) offers the possibility to significantly reduce the cost and time devoted to safe testing, and could thus help overcome the limitations of existing options.

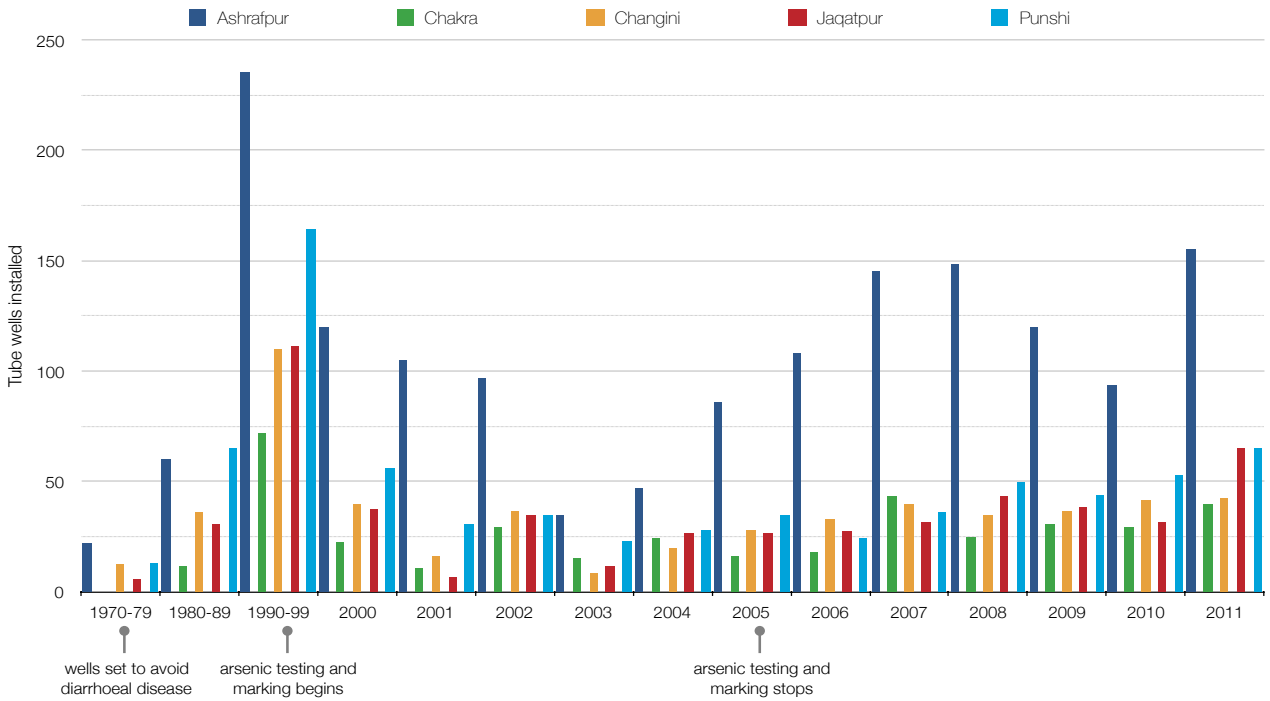

Figure 3: Shallow tube wells in five large villages in the Ashrafpur Union, Bangladesh. The expansion of shallow tube well (STW) installation in Bangladesh up to the late 1990s was driven by a motivation to reduce diarrhoeal disease. However, in the 1990s, widespread testing for arsenic demonstrated that 98% of STWs were contaminated. These wells were marked (usually with a red cross) and drilling of new STWs declined dramatically. Later, when arsenic testing and marking of wells stopped and very little mitigation had taken place, awareness of arsenic contamination declined and households began drilling and using more STWs again. Source: Adapted from Asia Arsenic Network (2012). Report on Fact-finding Survey on Water Sources in Ashrafpur Union, Chandpur District: 20 February – 22 March 2012. Available at: https://drive.google.com/file/d/0B24GorVR0_ZHemxGSDJmTF9JV0k/view

The Arsenic Biosensor Collaboration

Lalitha Sundaram, CSER, University of Cambridge

Sundaram's talk explained the work of the Arsenic Biosensor Collaboration, a joint-project between researchers at the Universities of Cambridge and Edinburgh. The Collaboration also involves other partners, in particular non-governmental agencies in Nepal (ENPHO) and in Bangladesh (ICDDR,B) as well as consultants with specialised expertise (David Grimshaw, James King, David Nugent and Peter Ravenscroft). The project had received funding from the Wellcome Trust.

The concept for the project first emerged through the work of the 2006 Edinburgh iGEM[12] team, which won the award for 'Best Real World Application' with their design of an arsenic biosensor that used a change of pH as the output. In 2009, the Cambridge iGEM team, with their *e.chromi* project, found a way to make an output that was variable in colour and visible to the naked eye (and won the top prize in the competition, as well as, jointly, the Human Practices prize). The combination of these two projects provided the background to the subsequent Arsenic Biosensor Collaboration. This project has pursued extensive stakeholder engagement from the beginning, with collaborative partners in Nepal and Bangladesh and with potential end-users. As the product involves the use of a genetically modified organism (GMO) the team also applied for regulatory approval at an early stage.

Field-testing kits currently in use for arsenic are chemical, and their operation requires considerable expertise. Their results, argued Sundaram, are difficult to read and the chemical processes involved use mercury and can produce arsine gas, both of which can have negative health impacts themselves. The key design features that the biosensor project therefore aimed for were that the biosensor should be cheap, easy-to-produce, easy-to-use, and be sensitive to bioavailable arsenic only (other tests that are not biological may not be able to make this distinction).

Early-stage fieldwork in Nepal provided key pieces of information. The team discovered that a graded signal output was less desirable to local stakeholders than a quasi-digital one. Gradients of pH or colour were seen as being too difficult to interpret and so a 'traffic light' system that would clearly indicate whether particular concentration thresholds had been exceeded would be preferable. The Nepalese stakeholders had also emphasised that they did not wish to have to treat the water in any way before testing it (e.g. by boiling). The team also learnt that it would be very desirable to incorporate a test for coliform into the biosensor so that both coliform and arsenic could be tested at the same time. Coliform bacteria, Sundaram explained, are used as an indicator of water being contaminated with sewage and thus being at risk of contamination with pathogenic bacteria. Testing for coliform is already commonly carried out in the field using a simple-to-use H_2S test, and associating it with the arsenic biosensor could help with the uptake of arsenic testing, especially if the testing costs could be kept similar to that of coliform-only test kits. Nepalese stakeholders had also stressed to the team that being able to collect and analyse data from individual tests of numerous wells in a centralised manner would be of considerable use.

Sundaram then described how the team has been working to incorporate all these findings into the design of their biosensor. With respect to the output, the team was developing gene circuits that generate coloured

12 The International Genetically Engineered Machine (iGEM) competition is a competition for undergraduate students that has played a key role in the global development of the field of synthetic biology. Based on a kit of biological parts, teams work over the summer to design and build biological systems and operate them in living cells. For further information, see: www.igem.org

spots. There would be a blue positive control (similar to the first line in a home pregnancy test) and then, if particular thresholds of arsenic had been exceeded, red spots would appear (see Figure 4).

This, Sundaram emphasised, is a whole-cell biosensor. The bacterium used as the 'chassis'[13] is the naturally occurring non-pathogenic soil bacterium *Bacillus subtilis*. Under certain environmental conditions this bacterium can form spores that are highly resilient in a wide range of different environments (e.g. surviving freezing and boiling temperatures). These spores therefore have a long shelf life and can be transported or stored without the need for a cold chain or any specialised equipment. *Bacillus subtilis* is not pathogenic and is part of the South East Asian diet: it is used in Japan to produce the fermented bean product Natto, as well as Kinema, which is consumed in Nepal.

> "Decisions about what kind of test data should be made public and to whom it should be shared is a thorny issue that the Arsenic Biosensor Collaboration is taking time to think about "
>
> *Lalitha Sundaram*

It is also important to consider safety aspects, and the fact that the bacteria are genetically modified. Sundaram explained that the team has been working to make the bacterial strain used in the biosensor attenuated, using criteria used for live organisms used as vaccines. The aim was to make the bacteria unable to persist in the environment, unable to complete its life cycle and unable to revert to wild-type. Overall the intention was to make it even more debilitated than it already is and to ensure that it remained fixed in that debilitated state. Particular attention was paid to how the bacteria were contained. Sundaram described that there were two levels of physical containment on top of the genetic containment described above. The whole device – approximately the size of a credit card - is submerged in the water that is to be tested. Upon submersion, the device self-regulates the water intake and self-seals. Another level of containment can be added, through the placing of a sticker over the back of the biosensor. Sundaram noted that, when the team took a non-GM dummy version of the biosensor out to the field in Nepal, they were able to explain its use to a young girl, who then carried out the process of testing without any problems after only a few minutes of informal training.

In order to facilitate large scale testing programmes, Sundaram then explained that the team has developed a prototype mobile phone app for recording test results and linking them to a centralised database. A QR code is incorporated on the back of each biosensor, which is thus used in tandem with the phone app. This allows the results to be mapped and centrally collected, thus generating useful information about the geographical distribution of arsenic contamination (or, if tests are performed seasonally, the temporal variation in contamination).

13 The term synthetic biologists use for the organism in which their genetic systems are incorporated.

The information that this app collects includes a well's GPS location coordinates, the type of water source (deep or shallow well, river, household tap etc.), the arsenic concentration range, the coliform result, and the date and time of testing. Because the data are collected via a mobile phone, information about the user is also collected (their phone number and location when uploading results, for example). While much of this information is clearly very valuable as a resource for policy makers, there are concerns that some of it may be sensitive. In particular, it will not always be clear whether someone is happy to have the result of tests on their well made publicly-available. This is one area where discussions with stakeholders are on-going, as there could be important social implications; There is often stigma associated with arsenicosis, as well as with owning/using an arsenic-contaminated well. The biosensor cannot solve this problem, but it is important that it does not exacerbate it. There can also be complex relationships of religion or caste or land/well-ownership that are tricky to navigate. In the case of a communal well, it can be difficult to identify and communicate with all the users, unless you paint the spout red or green. This was an approach that had been taken in the past and was seen by some to be problematic, potentially leading to stigma for the affected communities.

Beyond such ethical responsibilities, Sundaram emphasised, there are also legal responsibilities. As a university project involving human subjects (as well-owners and users), any future trials must be conducted under ethical review that ensures the transparency of methods, informed consent, lack of harm and clear benefit to participants. With respect to data privacy, some national regulations emphasise that it is illegal to withhold information regarding public health, while other regulations emphasise the illegality of making private data public. For example, the 2013 Bangladesh Water Act states that it is a criminal offense to withhold information about water quality. In contrast, the 2007 Nepalese Right to Information Act has a variety of provisions for exemptions regarding the publication of private data, in particular pertaining to data about public health (which would seem to apply to arsenic contamination), or information that "jeopardizes the harmonious relationship subsisted among various casts or communities".

Decisions about what kind of data should be made public and who it should be shared with are clearly thorny issues that the team is taking time to think about. One of the ways in which data will likely end up being protected is through stratification of the databases, with different levels of granularity available to individuals, communities, and local government/institutions. At each level, groups could be provided with the information necessary for their level of decision-making. For example, three or four households could develop a well-sharing plan, where one well is used for household cleaning and the other for consumption. Community-level decisions might include installing a water filter at a school. District level information could be used

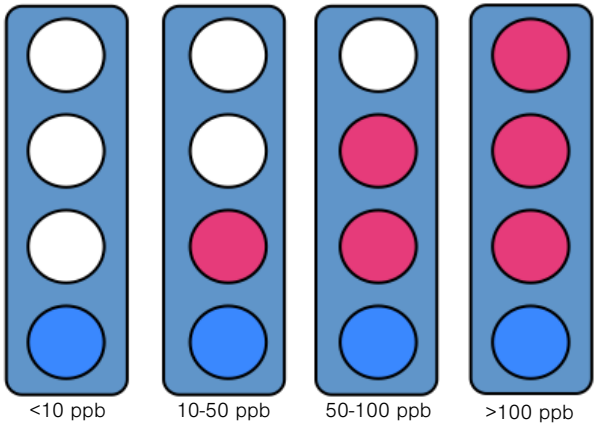

Figure 4: 'Traffic light' output for arsenic biosensor

Figure 5: Members of the University of Cambridge arsenic biosensor team collected water samples from villages in Nepal and Bangladesh. Note the red cross on the well, indicating that it had previously been identified as contaminated with arsenic. Credit: Jim Ajioka.

to determine the best location for deep tube wells or allocation of piped water. As Sundaram pointed out, it is key to note that the biosensor will need to allow for flexibility in order to be adapted to different local circumstances.

Trustworthiness of the data is also an issue. For example, would governmental authorities be willing to trust and use data generated by individuals (a 'crowd-sourced' approach), or would they only trust data generated by institutions?

There are further considerations regarding how the technology will be used and who will be conducting the testing. According to one scenario, staff from an institution could travel to a village to test a number of wells one day and would report the result the next day, perhaps while travelling to another village. This is very different to the scenario where an individual visits a shop and buys a single kit because they want to test their own well. This has implications for the design of the biosensor (for example, it is important for the colour output to be at its brightest at the time when the tester is reporting the results).

Disposal – currently envisaged as being through incineration – is a further issue that requires consideration, again with regard to different kinds of tester. An institutional tester could be required to always return to the office with the same number of testing kits as they left with, so that disposal could be monitored. Individuals, however, would likely be less assiduous in the proper disposal of sensors. It is also known that in the kinds of areas where the biosensor would be

used, nothing is thrown away - local populations tend to repurpose everything.

In order to overcome some of the issues identified, the project is working in close collaboration with actors already involved in mitigation and testing. Sundaram ended the talk by noting that tapping into this local ecosystem is crucial. The regulatory aspects of the project – equally crucial – were covered in the following talk by Simon Warne.

Risk assessment and regulatory issues

Simon Warne, UK Health and Safety Executive

Warne's talk concerned the regulatory process for the arsenic biosensor. In the European Union (EU) there are two key Directives that seek to ensure the safe use of genetically modified micro-organisms (GMMs): one for 'contained use' (2009/41/EC) and one for 'deliberate release into the environment' (2001/18/EC). Contained use is defined as "an activity involving genetically modified micro-organisms in which specific containment measures are used to limit their contact with, and provide a high level of safety for, the general population and the environment". It generally applies to the use of GMMs in laboratories and factories, and these premises need to be registered with regulatory authorities (in the UK this is the Health and Safety Executive) before work involving GMMs can begin. Deliberate release on the other hand is defined as the "intentional introduction into the environment of a GMO for which no specific containment measures are used" and generally applies to genetically modified organisms (GMOs) used outside laboratories and factories - crop plants grown in agricultural fields, for example. Prior consent must be obtained from regulatory authorities before any such release, and this involves procedures at the level of the European Commission.

Warne noted that it can be difficult to maintain a sensible and workable regulatory definition in the face of rapid scientific and technical change: he used the recent development of genome editing technologies as an illustrative example. Under the Contained Use Directive, a "genetically modified micro-organism (GMM) means a micro-organism in which the genetic material has been altered in ways that does not occur naturally by mating and/or natural recombination". This definition is then clarified in Directive's Annexes that list techniques that constitute genetic modification (e.g. cloning of DNA into plasmids or the direct introduction of naked DNA), those not considered to result in genetic modification (e.g. in-vitro fertilization, or transduction), and yield organisms that are excluded from the Directive (e.g. organisms created by classical mutagenesis using radiation or chemicals). As new methods have been developed, these have had to be accommodated in the regulatory system. Moreover, EC Directives are drafted following negotiation and the wording is deliberately open-ended so that Member States can adapt the way in which they convert the Directive into national legislation so that it meets national interests. There is therefore some flexibility in the wording of legislation within each Member State, but if countries diverge too far from what the European Commission regards as the spirit of the Directive they can take a legal ruling to 'rein things back'.

The European Commission appears to be moving towards a more stringent position in interpreting this definition, where organisms produced by *any* process leading to a change in genetic material would be covered, unless that process were specifically listed in the Annex.

Warne then moved onto possible precedents for whole-cell biosensors involving GMMs. The first was that of a Finnish company that produced a test kit for identifying antibiotic residues in milk. Their test was based on a GM strain of *Streptococcus thermophilus* and involved

Definition of "contained use":

In UK Genetically Modified Organisms (Contained Use) Regulations 2014 (Regulation 2(1)):

> "Contained use" means an activity in which organisms are genetically modified or in which genetically modified organisms are cultured, stored, transported, destroyed, disposed of or used in any other way and for which physical, chemical or biological barriers, or any combination of such barriers, are used to limit their contact with, and to provide a high level of protection for, humans and the environment.

In EU Directive 2009/41/EC on the contained use of genetically modified micro-organisms (Article 2(c)):

> "Contained use" means any activity in which micro-organisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment.

Definition of "deliberate release"

In EU Directive 2001/18/EC (Article 2.3):

> "Deliberate release" means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment".

In the UK Genetically Modified Organisms (Deliberate Release) Regulations 2002:

> There is no definition of "deliberate release" in this Regulation, and since it implements EU Directive 2001/18/EC the definition above applies.

Box 1: UK and EU Regulatory definitions of "contained use" and "deliberate release"

taking ampoules into field sites and opening them in order to expose the modified bacteria to the sample of milk. Marketing of this biosensor was authorised under the Deliberate Release Directive, even though there was no suggestion that the GMM would be intentionally released into the environment.

The second precedent described by Warne was that of a 'mobile laboratory' used in Germany. A caravan was registered as a Contained Use premises, and within this vehicle biosensor test kits could be used[14]. Warne's view was that this quite flexible interpretation of the Contained Use criteria was unlikely to be repeated. In the US there is a process for the approval of experimental releases of GMMs that do not present an unreasonable risk to health of the environment, the Environmental Protection Agency's TERA[15] procedure.

Warne then explained how, following discussions between staff at the HSE and the arsenic biosensor team, it was decided that the most appropriate approach would be to apply for authorisation under the Contained Use regulations. This was based on the fact there was no intention to release the GMO into the environment but was also influenced by the assumption that it would take a long time to obtain approval under the deliberate release regulations.

Thus, the team is attempting to get the GMM in their biosensor listed as a GMM that is exempt from the Contained Use Directive as per the provisions laid out in Article 3 of Directive 2009/41/EC which applies to GMMs that have been established as safe for human health and the environment. GMMs that meet this criteria are to be listed in Annex II, Part C but to date, no such organisms have been listed in this Annex. If approved, the GM *B. subtilis* strain used in the arsenic biosensor would be the first exempt organism listed. It is important to note, though, that exempted organisms are still defined as GMMs, and would still be bound by Article 4 of the Directive that requires Member States to ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment that might arise from the contained use of GMMs. Annex II, Part B of Directive 2009/41/EC sets out the criteria for establishing the safety of GMMs for human health and the environment that would be exempted (see supplementary material for further details). The process – as detailed below – has been slow, because the application for exemption is breaking new ground and setting a precedent for the future.

The talk then described the case that the arsenic biosensor team have put together in order to demonstrate that the arsenic biosensor GMM is suitable for exemption. This includes a set of mutations that seek to ensure that it can only survive in controlled laboratory conditions along with the two layers of physical containment described in the previous talk. The UK's Scientific Advisory Committee on Genetic Modification (SACGM) discussed and endorsed the application in November 2014[16], and it was then forwarded to the European Commission. At the time of the workshop, it was being considered by the European Food Standards Agency (EFSA). This was something of a surprise because that Agency generally deals with GM crops and

14 This ARSOlux biosensor was described in detail in the report from a previous workshop of the Flowers Consortium. Note that the authorization was for experimental field trials conducted in Germany and that the company did not apply for the authorization to commercialize the biosensor. See: Marris, C. and Jefferson, C. (2013). *Workshop on Synthetic biology: Containment and release of engineered micro-organisms: Scoping Report.* London, King's College London, pages 14-17, available at http://www.kcl.ac.uk/sspp/departments/sshm/research/Research-Labs/CSynBI@KCL-PDFs/Publications-page/SB-Containment-and-Release-Workshop-Scoping-Report-Final.pdf.

15 Toxic Substances Control Act Environmental Release Application

16 See Minutes of the 28th meeting of the Scientific Advisory Committee on Genetic Modification (Contained Use) held on Friday 14th November 2014, available here: http://www.hse.gov.uk/aboutus/meetings/committees/sacgmcu/2014/minutes-141114.pdf

foods, but the Commission decided that this was where the most relevant expertise was to be found. EFSA was due to give a ruling on the arsenic biosensor case by December 2015.

The talk concluded by mentioning that it would not have been worth all the effort that has gone into this application for exemption if it did not offer the opportunity for future projects to be granted approval in a more streamlined way. It was also noted that the definition of 'contained use' in UK regulations and in the EC Directive are slightly different and might allow for a more liberal interpretation in the UK. The UK regulations define contained use as involving GMMs "where physical, chemical, or biological barriers, or any combination of such barriers, are used to limit their contact with, and provide a high level of safety for, the general population and the environment". Under this definition, even just one of the containment methods (physical or biological) built into the arsenic biosensor might be sufficient to gain approval[17].

Discussion in the arsenic biosensor case study

Social inequality and arsenic contamination

One participant asked what kinds of persons are most affected by arsenic contamination. Ravenscroft explained that the poor are most vulnerable, because their diet would likely be less varied, and because a lack of social influence often translated to not having ready access to water from a safe source. Gender was also a factor, as men (who typically do more physically-intensive labour) will drink more water. For women the effects are also social by, for example, affecting dowry values. In some situations, affected women and children are socially isolated on a pseudo-voluntary basis, to reduce shame in their communities. It is also important to bear in mind the massive inter-generational effects of arsenic: children's lives and opportunities will be affected by the health status of their parents. Children growing up in affected households will grow up less educated and earn less. Thus, the poverty cycle will be re-iterated.

Given such social inequalities in exposure to arsenic contamination, one participant asked whether it might be more effective to target the social inequalities rather than arsenic contamination; or was it perhaps possible to tackle both at the same time? Ravenscroft explained how taking social inequalities into account could indeed influence decisions about the most effective interventions to mitigate exposure to arsenic. For example, a single well in Bangladesh may be accessible to approximately 100 people in a village with more than 1000 inhabitants and may be subject to 'elite capture': meaning that it will be located in a place that is most easily accessed by the wealthier elite. In contrast, some of the more expensive and slower to implement solutions, such as piped water, can capture the whole community and therefore enable a fairer distribution of benefits.

Political geography of arsenic contamination

Another participant focussed on the question of arsenic contamination being marginalised as a political issue, and whether or not there is a comparison case of a toxic substance that has actually been dealt with well, and which arsenic might be able to learn from. Ravenscroft used mercury as a comparison, where mitigation had been considered economically practical and was implemented in the USA. In contrast, arsenic contamination in the USA has not been tackled because mitigation of health effects is achieved through a highly

17 Note that the UK leaving the EU, which is currently underway, adds uncertainty to any future relationship between European Commission and British GMO regulation.

varied diet, and because the majority of Americans are not relying on their tap water every day for hydration.

Questions about the regulatory process for the arsenic biosensor

One participant asked why no organism had yet been included in the Annex of exemptions of Directive 2009/41/EC. Was this because no applications for exemption had been submitted or because applications had been submitted but had failed to obtain approval? A respondent explained that there was believed to have been a Belgian application that got to a very early stage in the process but had 'run out of energy'. The fact that no applications have been pushed through the system explains why the procedure is unclear.

Another participant asked about international guidelines, and which bodies are currently invested in the question of GMO release. One answer was that the UN Convention on Biological Diversity regulates the movement of GMOs across international borders.

Another participant asked about whether or not EFSA is going to respond well to the argument that the arsenic biosensor qualifies for Contained Use[18] because it is kept within a container. Are they likely to accept that it does not constitute Deliberate Release? In response Warne explained that it remains unclear whether one can have Contained Use outside of purpose-built facilities such as laboratories and factories. A number of workshop participants felt that in a technical sense the arsenic biosensor fulfils the requirements of containment, but in terms of the spirit of the Directive this was less clear. A member of the arsenic biosensor team pointed out that SACGM had asked for further details regarding the nature of the container, which suggests that physical containment was being considered as a significant factor in the decision.

It was suggested that one reason why the case of the arsenic biosensor has proven so difficult for regulators is that the directives in question have been most closely associated with GM crops. For crops the difference between Contained Use and Deliberate Release into the environment is very much clearer, but because many synthetic biology applications envision the use of genetically modified *micro*-organisms we are now witnessing a blurring of these divisions. This had been a key topic at a previous workshop of the Flowers Consortium[19]. In addition, novel approaches such as paper-based biosensors are challenging previous understandings of 'deliberate release into the environment.' It was however pointed out that modifying an EU Directive or issuing new legislation would be a very slow process; and that in the current political context it could lead to even more stringent regulations.

There was a discussion about what would happen to the project if the European Commission ultimately did not approve the application. This was thought to be a possible outcome because some specific EU Member States are known to be very reticent about GMOs. The arsenic biosensor team's conversations with the authorities in Bangladesh and Nepal have centred around the need for approval to be given in either Europe or the USA, as Nepal did not at the time have regulations covering GMOs. The team has therefore considered applying for approval by the US Environmental Protection Agency (EPA) to conduct a field trial (not for manufacture or marketing), in addition to their EU application under the Contained Use

18 'Contained Use' and 'Deliberate Release' are used here with capital letters to indicate that we are talking about the legal definitions for these concepts as set out in EC Directive 2009/41/EC.

19 See: Marris, C. and Jefferson, C. (2013). *Workshop on Synthetic biology: Containment and release of engineered micro-organisms: Scoping Report.* London, King's College London, pages 14-17, available at http://www.kcl.ac.uk/sspp/departments/sshm/research/Research-Labs/CSynBI@KCL-PDFs/Publications-page/SB-Containment-and-Release-Workshop-Scoping-Report-Final.pdf

Directive. If this is granted there is still a chance that the project can go forwards. Another possibility would be to apply for an EU authorisation for commercialisation under the Deliberate Release Directive, even though the team and the UK regulatory agencies believe this is not necessarily the most appropriate route. This route would apparently take a year or so and would involve decisions processes at the EU level but at least there is a known regulatory procedure that has already been implemented.

> "Used biosensor kits will be thrown on the rubbish dump where children play."

As far as anybody present knew, the regulatory procedure under the Deliberate Release Directive had however never been used to authorise the *commercial* release of genetically modified *bacteria*: it has only been used so far for the commercialisation of GM *plants. Experimental* field releases of GMMs had been authorised in specific EU Member States, including trials of the ARSOlux biosensor conducted in Germany. It was however pointed out that *medicinal products* made from or consisting of GMOs go through a different regulatory route in the EU; and that some GMMs used in medicines (e.g. GM viruses and bacteria used in vaccines) had been evaluated and approved for both clinical trials and marketing in the EU.

Coliform test more of a biological hazard that the arsenic biosensor

During the discussion it became apparent that the disposal of the bacteria collected from the environment and being detected by the coliform test component of the biosensor was potentially a more important safety issue than disposal of the arsenic biosensor bacteria. The bacteria used in the arsenic biosensor are not pathogenic and have been engineered to drastically reduce their chances of persisting in the environment. This is the basis for the application to make it exempt from the Contained Use Directive. In contrast, the coliform test involves amplifying potentially pathogenic bacteria in quantities that might present a risk to human health. While these coliform tests are not new, they are currently used only by trained members of NGO or governmental testing teams. There are precedents for local communities to conduct these tests, but nevertheless the instructions for disposal will require consideration.

The local context of waste disposal

Some participants pointed out that in developing countries all rubbish is typically thrown in ordinary rubbish dumps with little particular consideration for the health hazards posed by particular kinds of refuse (e.g. used medical equipment such as syringes used for HIV tests). We should therefore not expect waste disposal instructions designed for the UK context to be followed and it was important to take into account, when considering the safety of the device, the way in which the biosensor would be disposed of in such locales. There is also an issue of scale: if the arsenic biosensor is successful, millions of test kits are likely to be used and it then becomes very likely that at least some of them will not be disposed of properly: this would also be true in a wealthy country in the Global North. The Arsenic Collaboration Team responded that it has indeed considered this, by engineering the bacterium to minimise the possibility of it persisting in the environment following any potential release, and conducting laboratory experiments to test, for example, how long they can survive in soil and how the engineered bacteria compete with wild bacteria.

International safety regulations: who wields the power?

Some participants brought up the topic of international collaborations on safety regulations in order to stress the importance of international bodies as a way of counterbalancing powerful states such as the US. Others brought it up in order to stress how the lack of regulation for GMOs in developing countries, combined with the lack of scientific capacity in biotechnology in those countries, presents a serious challenge for the introduction of synthetic biology products in those countries.

It was also pointed out that international harmonization of safety regulations for synthetic biology is an issue currently being discussed by parties of the United Nations Convention on Biological Diversity, that already regulates the 'transboundary movement' of 'living modified organisms'. One workshop participant who had been present at a recent meeting of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) reported that it seemed as though issues raised by NGOs during the open debates (e.g. indigenous rights, farmers losing their livelihoods, the cultural context of technology, the role of industry, exploitation) were not raised by representatives from developing country governments who were also present. Instead, it seemed that these representatives were quiet during the debates, but in private conversations they expressed a lot of interest in getting access to synthetic biology technologies.

Overall, a key point to emerge from this discussion was that decisions about who gets to sit at the table at international negotiation forums will to a large extent determine how the agenda is set, which issues get raised, and whose interests are prioritised.

What are users expected to do with a positive test result?

Some participants wanted to emphasise that while better testing technology is clearly important, the real challenge was what to do with the results of the test. The arsenic biosensor team was congratulated for having developed technology that works well to identify contaminated water, but were asked how they envisioned the testing kits having an influence on access to clean water and what they saw as the potential for infrastructural improvement in water supply.

Using the example of HIV testing in the past, one participant asked about the value of urging local populations to test for arsenic in their drinking water if they do not have access to an affordable method to treat the water. In response Sundaram stressed that it was important that awareness, testing and mitigation measures went hand in hand. At the local level, there are things that individuals can do. Learning which wells are unsafe can help people decide which water source to use for drinking, and which for washing. Another use can be in helping to decide whether or not to pay for piped-in water. Also, arsenic contamination is seasonal, so at different times of the year arsenic contamination in water from a particular well will vary, and access to a cheap and easy to use testing kit could allow villagers to test the same well over time. The issue of mitigation was one reason why it was important for the team to work with a Nepalese partner such as ENPHO that is already involved in mitigation and awareness-raising.

Stakeholder engagement: when, who and how? Who are the legitimate stakeholders?

On several occasions during the morning, the discussion returned to the relative legitimacy of NGOs, governments and local users with respect to their influence on the design of a biosensor project, on safety regulations, and more generally on public debates.

Some participants felt that the public debate around synthetic biology was overly dominated by NGOs, and that they unfortunately 'held the moral ground' but that they did not necessarily represent the views of governments and other stakeholders or of the general population. Other participants were of the view that NGOs play a crucial role to counterbalance the powerful interests of governments and private corporations, which are not necessarily well aligned with the welfare of the general population. One member of the arsenic biosensor team suggested that engaging with the actual people who are affected on the ground in order to get them on board was perhaps the best way forward, rather than focusing on official organisations.

A member of the arsenic biosensor team expressed the belief that the design of synthetic biology products can – and should – include stakeholder engagement right from the start. They cited the importance of the change in output signal (from a gradated colour change to a traffic-light system) as one that had required a great deal more work to implement (involving the engineering of separate bacterial strains for each of the different threshold levels of contamination as opposed to a single strain) but which is essential to create a workable technology appropriate to its purpose.

Who controls the data? Not just a privacy issue

> "If data is not freely shared, then power lies in the hands of those who can access it."

The arsenic biosensor incorporates a data collection system. Participants wanted to know more about how this data is going to be shared. One participant stressed that the issue was not only about the potential disclosure of private information such as the user's phone number or home address, because there are also broader political considerations. Governments will need access to the testing data in order to inform their decision-making. At the same time, some of the data might be of interest to the commercial sector. This raises ethical questions about who controls the data. If data is not freely shared, then power lies in the hands of those who can access it.

A number of participants wanted to learn more about when and how the arsenic biosensor team had engaged with stakeholders, and who these were. Team-members explained that in the case of Nepal the first point of contact was an NGO, the Environment and Public Health Organisation (ENPHO). ENPHO is part of the National Arsenic Steering Committee, responsible for testing programs in the past, which had been conducted with partners such as UNICEF and the Japanese International Cooperation Agency. At the local level, the team had also spoken to governmental departments involved in water supply and sanitation, as well as village Water User Service Committees, that are locally-elected in each village. During these visits the team were also able to speak to people from the villages. Thus the team had spoken with the kinds of people doing the testing and those having their wells tested.

Another participant suggested that a restrictive focus on data privacy was driven by a Euro-centric legalistic position. Instead, wider sharing of data could be seen more positively as a duty of care. For example, if you report results only to the male head of a household, you may be neglecting your duty of care towards his children. In this regard a powerful precedent for the sharing of information had been set in Bangladesh by the government during its early 2000s testing, when wells were painted red or green to publicly

indicate whether the water was below or above safety standards for arsenic. In addition, it may not be up to the arsenic biosensor team, or anyone participating in this workshop, to decide what level of information should be made public. What the team can do is design a system that has the capability to depersonalize the information and then let local authorities decide what should be done.

A member of the arsenic biosensor team emphasised that data uploading and sharing could be part of a process of communication and engagement with the users. It could, for instance, be a way to see where tests are being conducted, how many are being conducted, and whether or not the biosensor is being used correctly.

One participant pointed out that from a historical perspective, public health initiatives have frequently trodden on difficult ground with respect to boundaries between public and private spheres. For example, when the UK government decided to introduce piped water into people's homes in the nineteenth century, there was a lot of concern that this would be an invasion into privacy (as the saying goes, 'an Englishman's home is his castle'). These difficult issues are exacerbated when there is a mixed economy of water provision, with provision coming from both the private and the public sectors, but they have been successfully tackled in the past.

GM and its publics

A number of participants felt that the arsenic biosensor project was likely to be received negatively in light of the history of public controversies around genetically manipulated (GM) crops and foods. When this issue was raised, a number of discussion points followed.

Some participants felt that communication surrounding GM crops and food to the public had not been handled well and had led to unwarranted public fears, especially about potential negative impacts from eating GM food. The danger, in their view, is that such public fears will carry over to synthetic biology biosensors and lead to 'knee-jerk' negative reactions. It was therefore important to get the communication aspect right this time, in order to get people on-board and to ensure that members of the public do not put synthetic biology biosensors in the same 'bucket of feelings' as GM food. In their view the scale of the public reaction against GMOs remains considerable, and despite the extent of the containment features that have been incorporated into the arsenic biosensors, existing prevalent negative public attitudes towards GMOs is likely to be the largest impediment to the success of the arsenic biosensor. There was a belief among many participants that it will be difficult to communicate that this technology is very different to the cases that have, often rightly, been highly controversial.

Other participants stressed that communicating in a transparent manner about these kinds of technological innovations, including about their potential risks, was important in order to enable members of the public to make informed decisions; and that this was very different from communicating simply in order to convince them to accept your device.

Many participants felt that there were legitimate concerns about the safety of GM foods; and some felt that the role of large multinational corporations such as Monsanto had played a negative role in the development of GMOs and in the communication strategies deployed. A number of participants felt that only some public concerns about GM foods had been legitimate, but that those concerns did not apply to the arsenic biosensor case. For example, there were legitimate questions about whether GM products such as GM tomatoes or salmon were needed. It was pointed out that on all these dimensions, the arsenic biosensor could be assessed more positively than GM crops and foods.

While all participants who expressed themselves agreed that the arsenic biosensor seemed to be extremely safe, for some participants, issues such as disposal (see above) were still significant and real safety issues, not just public communication issues.

> "A win for the arsenic biosensor wouldn't just be a win for the arsenic biosensor: It would be a win for synthetic biology and the kind of institutional and funding arrangements that led to its creation."

Championing a way of doing science alongside the product of science

One participant argued that understanding the GM controversy as a 'mess' that is rooted in irrational public fears fails to recognise that it can be entirely reasonable for members of the public to examine the kind of world that is produced by particular scientific practices. For example, discussions at this workshop had demonstrated that a win for the arsenic biosensor was not just seen as a win for that particular project, but more generally as a win for synthetic biology, and beyond that, a win for the kind of institutional and funding arrangements that supported its development. It would therefore be entirely legitimate for people to scrutinise every facet of this technology, 'all the way down to its core'. This participant then went on to explain that, in the case of the arsenic biosensor, the surrounding social and political contexts could actually be used to the advantage of the project. By emphasising how this biosensor is not like previous GMOs with regard to interventions in national labour markets, food supply, ownership by large industrial partners, biodiversity protection and so on, the team could be even clearer about what this technology could mean for people in a way that would be entirely to the Arsenic Biosensor Collaboration's advantage.

Another participant argued that the public controversy about GMOs has not been only or mostly about safety. Key questions raised in the GMO debate were also: Who is doing it? Why are they doing it? What kind of needs are being addressed? Who sets the agenda? For GM crops and foods, this participant argued, the answers to these questions have commonly been that the GMOs have been produced by a few large firms and aimed at a narrow range of crop traits and this – the participant continued – was at the heart of the controversy, just as much as safety. As such, the arsenic biosensor project can be championed not only because it is safe, but also because it can distinguish itself along these other dimensions. In this context, any research team developing biosensors for global health needs to be transparent about the nature of any links their project has with industry.

Case study 2: A schistosome biosensor

This session was devoted to discussion of a schistosome biosensor that was at an early stage of development by members of the Flowers Consortium at Imperial College London. Talks were given by experts on the problem of schistosome occurrencee and the biosensor project. A general group discussion followed.

Schistosomiasis: occurrence, causes, impacts and mitigation

Joanne Webster, Centre for Emerging, Endemic and Exotic Diseases, Royal Veterinary College

Webster's talk gave background information as to the epidemiology of and current challenges faced by researching the neglected tropical disease schistosomiasis (bilharzia). Currently, about 240 million are infected worldwide and infection can lead to a number of different health effects including serious damage to the bladder. In some regions of Africa this is very common and most children are affected.

Schistosomiasis is a blood-borne fluke (flatworm) that is transmitted through fresh water between definitive hosts (where it reaches maturity and reproduces) and an intermediate snail host (see Figure 6). Depending on the species of schistosome, the definitive host can be humans, other mammals such as cattle, or birds. This means that it is a disease of both humans and animals and has an impact on agriculture as well as on human health. Different species that infect either humans, cattle or birds are present in different parts of the world. Webster noted that this means that it would be very useful to have a device that could identify not just the presence of schistosomes in water, but be able to distinguish between species.

The environment for schistosomiasis, Webster explained, is changing, due to a number of different factors, including a vaccination program for water buffalo in SE Asia, global warming, the construction of new dams (which provide bodies of fresh water for the snails) and changing agricultural practices (where for instance herders follow their animals all day - including into the water - rather than letting them roam alone). Despite the worms' long life span (seven years on average), we can, argued Webster, expect schistosomiasis to adapt to these changing environments.

There is an effective drug treatment for schistosomiasis - praziquantel (PZQ) - but large-scale use of this drug is generating pressure on the fluke to develop resistance. The Schistosomiasis Control Initiative was set up at Imperial College London 12 years ago, and between 2003 and 2015 the SCI administered over 100 million PZQ treatments in sub-Saharan Africa. The success of these programmes influenced the WHO strategic plan on schistosomiasis: while it had previously focused on controlling morbidity rather than on reducing the incidence of infections, it now had adopted the more ambitious goal of eliminating schistosomiasis as a public health problem by 2025. Pharmaceutical companies have been closely involved in these programmes and Webster cited Merck's pledge to donate 250 million tablets of PZQ a year by 2016 as an example.

Webster then cautioned that it may not be realistic to talk about eliminating the disease altogether. In China, for instance, where the particularly serious species *S. japonicum* resides, there has been a very intensive programme spanning more than 50 years

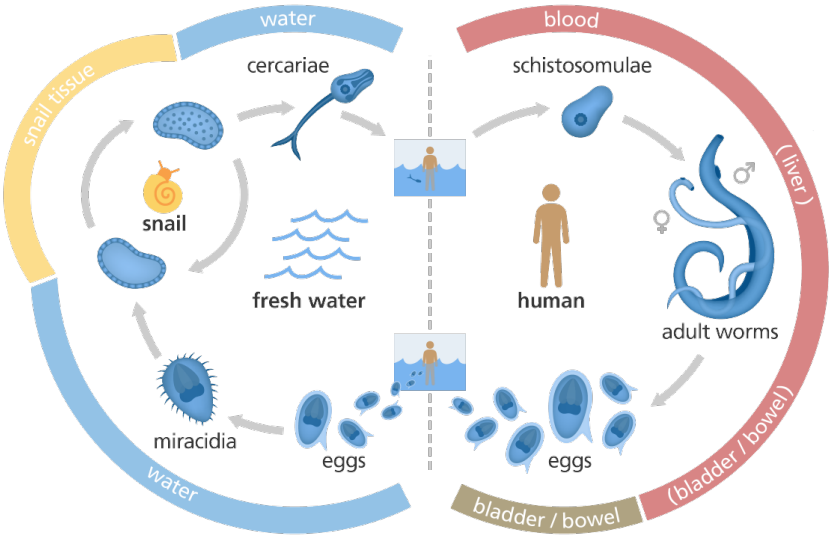

Figure 6. Life cycle of the Schistosome species showing the different life stages and hosts. Credit: Genome Research Limited (CC BY 3.0)

that has included drug treatment, health education, molluscicides, modification of the environment, and behavioural change, but schistosomiasis has remained endemic in some regions and is re-merging in others. Webster used this example to illustrate the dynamic and complex nature of the situation: one reason for the inability of the programme in China to fully eradicate schistosomiasis appears to be that while it had been assumed that water buffalo were the primary animal reservoir, wildlife also play a significant role, with wild rodents acting as 'super-spreaders.' That is, depending on the conditions, the parasite can switch host. Moreover, worms that infect these rodents are shed from snails at dusk, which is when the rodents are present, whereas the worms that infest water buffalos are shed from the snails in the morning, which is the prime time for the cattle to come into the water[20].

In Africa, Webster explained, mitigation efforts have focused on *S. haematobium* because this species' host range is thought to be restricted to humans (and some primates). Therefore, controlling the worm in humans through mass drug administration was expected to lead to elimination of the disease. Taking Niger as an example, this strategy has worked in some regions and the prevalence has been drastically reduced. However, in other regions, prevalence has remained very high despite a very thorough drug administration

20 For further details see: Lu, D., Wang, T-P., Rudge, J., Donnelly, C.A., Gua, C. & Webster, J.P. (2009) Evolution in a multi-host parasite: Chronobiological circadian rhythm and population genetics of Schistosoma japonicum cercariae indicates contrasting definitive host reservoirs by habitat. *International Journal for Parasitology* **39**: 1581-1588; and Rudge, J.W., Lu, D-B, Feng, G-W, Wang, T-P, & Webster, J.P. (2008). Population Genetics of Schistosoma japonicum within the Philippines Suggest High Levels of Transmission between Humans and Dogs. *PLoS Neglected Tropic Diseases.* **2** (11), e340

programme. There were concerns that this might be due to the development of drug resistance by the parasite, but this is not the case. Treatment of infected children with PZQ is still effective but there is very rapid bounce back about six weeks after treatment. This was puzzling because *S. haematobium* takes eight weeks to mature and start laying eggs. It turned out that, contrary to textbook knowledge about schistosomes that states that they pair up with a mate from the same species and remain paired for the rest of their lives, schistosomes are in fact quite promiscuous and can also form pairs between different species and, in some cases, these hybrids produce viable offspring. In Niger, research revealed that *S. haematobium* was mating with other (zoonotic) schistosome species that take 6 weeks to mature[21].

Webster then described ongoing research in West Africa which now focuses on situations where human behaviour – including mitigation measures – could be leading to changing behaviours in the parasite (such as hybridisation). Potential consequences now being investigated include new sites of infection, broader host ranges, switches in host, increased transmission potential, higher virulence, and altered drug resistance. These, Webster emphasised, will need to be taken into account in monitoring and control programmes, and the complexities involved suggest that it may not be realistic to envision entirely eliminating schistosomiasis from Africa. Moving away from Africa, Webster noted that there had also been reported instances of schistosomiasis in Europe – in Corsica, Spain and Portugal, for instance, where the cause appeared to result from hybridisation of human and animal schistosomes[22].

These findings also mean that it would be particularly useful to have a schistosomiasis biosensor that was able to distinguish between species, and to identify hybrids. Another lesson is that dealing with both human and animal health together may be the most effective approach to deal with this infectious disease that is both very ancient (it is present in Egyptian mummies) and 'emerging'.

Schistosome biosensor project

Alex Webb, CSynBI, Imperial College London

Webb explained the origins, aims and ambitions of the schistosome biosensor project at Imperial College London (ICL). The idea emerged in 2010 from the ICL iGEM team that aimed to develop a platform to detect a range of different parasites, not just schistosomes. Parasites and their eggs release specific proteases at different stages of their life cycle and so this seemed to be a good target for a biosensor. The ICL team is working on the development of both a whole-cell biosensor and a cell-free biosensor.

The project follows the iterative design-build-test scheme emphasised in synthetic biology. The team started by researching the proteases released by different parasites in order to identify a specific target for the

21 For further details see: Huyse T, et al. (2013) Hybridisation between the two major African schistosome species of humans. *International Journal of Parasitology* **43**: 687-689; Koukounari A, et al. (2010) The impact of single versus mixed schistosome species infections on liver, spleen and bladder morbidity within Malian children pre- and post-praziquantel treatment. *BMC Infectious Diseases* **10**:227; Webster BL, et al. (2013) Introgressive Hybridization of Schistosoma haematobium Group Species in Senegal: Species Barrier Break Down between Ruminant and Human Schistosomes *PLoS Neglected Tropical Diseases* **7**(4): e2110; Leger E & Webster JP (2017) Hybridisations within the Genus Schistosoma: implications for evolution, epidemiology and control. *Parasitology* **144**: 65-80; King KC, et al. (2015) Hybridization in Parasites: Consequences for Adaptive Evolution, Pathogenesis, and Public Health in a Changing World. *PLoS Pathology* **11**(9): e1005098.

22 For further details see: Moné H, et al. (2015) Schistosomiasis Haematobium, Corsica, France. *Emerging Infectious Diseases* **20**(9): 1595-1597; Boissier J, et al. (2014) Schistosomiasis reaches Europe *Lancet Infectious Diseases*. **15**(7): 757-758

biosensor. They found potential motifs that were specific to the parasites *Trypanosoma cruzi* (Chagas disease), *Plasmodium falciparum* (malaria) and *Schistosoma* (schistosomiasis). Schistosomiasis was chosen because it is a neglected tropical disease that affects more than 200 million people worldwide each year, with important consequences (as described in the previous talk by Joanne Webster).

When the cercariae make contact with the skin of their host they release a cocktail of enzymes. One of these is called cercarial elastase. It breaks down the skin and enables the parasite to infect the host. The ICL biosensor is designed to detect this enzyme.

The design of the biosensor was first envisaged within a bacterial cell: *E. coli* thanks to its tractability in the lab. It was built such that the engineered (and introduced) detection and signal genetic modules would be expressed on the surface of the bacterial cell. The biosensor relies on three components: a synthetic peptide attached to the outside of a bacterial cell wall, fluorescent markers, and elastase produced by *S. mansoni* (Figure 7). The synthetic peptide is a tagging molecule to which fluorescent markers can bind, and contains a site (motif) that has previously been identified as cleavable by *S. mansoni* elastase. This modular design means that it could be easily adapted to detect a different parasite by changing the motif that allows the peptide to be cleaved.

A two-stage process is envisaged where the biosensor is first immersed in a water sample and then a fluorescent marker is added to the solution. In stage one, if *S. mansoni* elastase is present, the tagging molecule will be cleaved from the biosensor. If *S. mansoni* elastase is absent, the tagging molecule will remain. In stage two, if *S.mansoni* elastase has cleaved the tagging molecule, there will be nothing for the fluorescent marker to bind to and the bacterial will stay colourless. If the molecule remains, then the bacteria will turn red. Thus, the presence of *S. mansoni* is indicated by a lack of colour and the absence of *S. mansoni* is indicated by a red colour.

For experimental purposes, the team has built multiple different biosensors: one contains the motif specific for cercarial elastase, another, used as a positive control, has a motif specific to the commercially available TEV protease and the third contains a motif with no specificity and is used as a negative control. The first chassis used was *E. coli*, because it is easier to manipulate in the laboratory. These three biosensors were exposed to three different commercially available proteases: TEV protease, Enterokinase, and PreScission protease. The results showed that the TEV biosensor was specific to its intended target and was able to detect very low amounts of enzyme. There were no off target effects: the TEV biosensor was only cleaved by the TEV protease; and the other two biosensors were not cleaved by any of the three proteases.

The team also incorporated their biosensor design into *Bacillus subtilis*, because products made in this bacterium have been granted 'generally recognised as safe' status for use in food by the US Food and Drug Administration (see also previous talks by Simon Warne and Lalitha Sundaram). It was hoped that using bacteria with GRAS status would help to address concerns from regulatory agencies when taking this into the field, although it is unclear whether such a status would apply to a non-food application[23]. *B. subtilis* is a gram positive bacterium whereas *E. coli* is gram negative. This means that the cell walls are different and the biosensor design had to be adapted.

The initial strain of *B. subtilis* used turned out to have too many native proteases, which meant that the

23 For a discussion on this topic, see Webb AJ, Kelwick R and Freemont P (2017). Opportunities for applying whole-cell bioreporters towards parasite detection. *Microbial Biotechnology*. **10**(2): 244-249

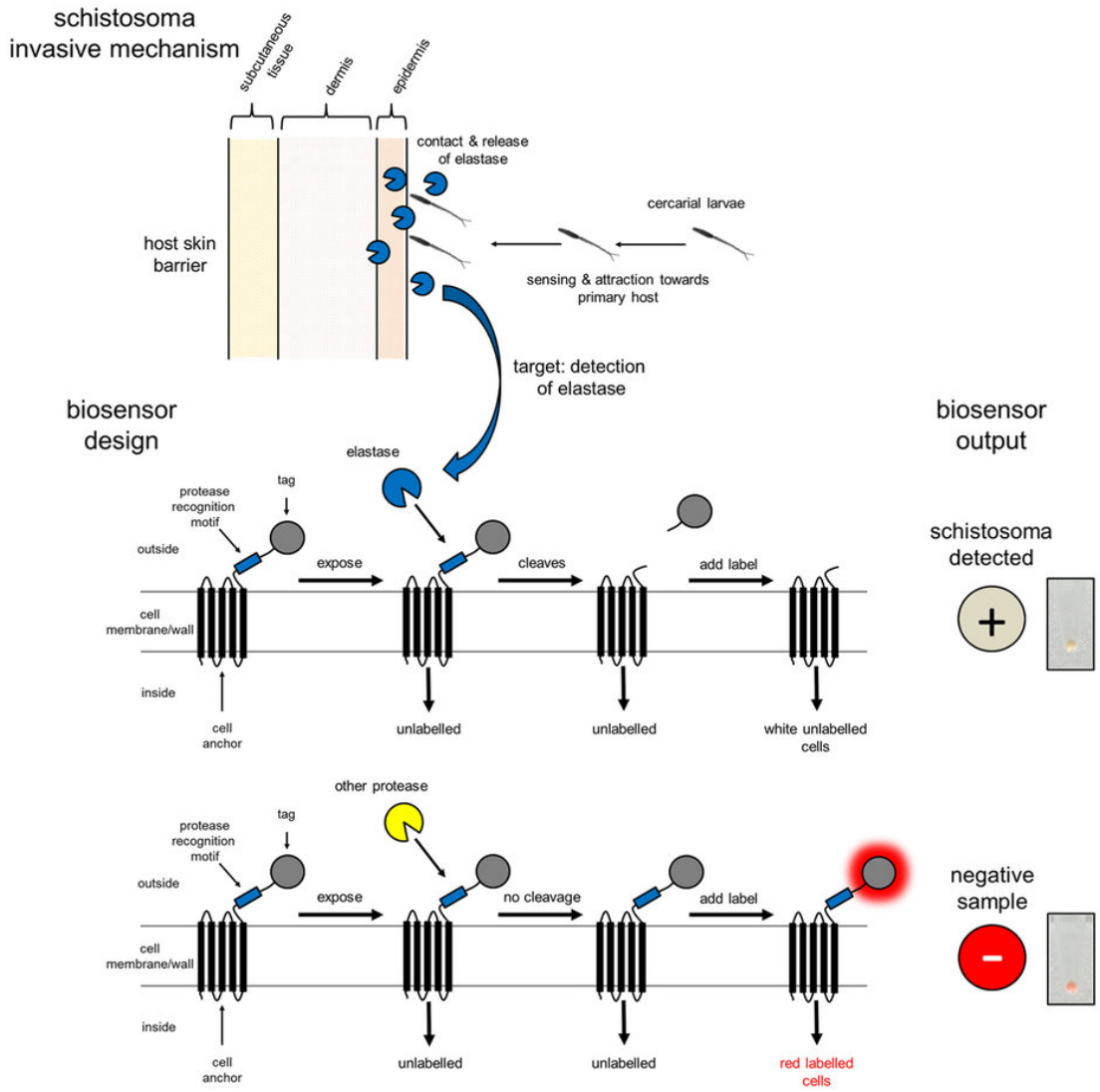

Figure 7. Design of the schistosome biosensor, showing the protein, embedding in the membrane wall with protease recognition motif and tag. Cleavage, by a schistosome elastase, of the tag at the protein recognition motif ultimately leads to loss of colour. Credit, Webb A, Kelwick R, Doenhoof MJ, Kylilis N, MacDonald JT, Wen KY, McKeown C, Baldwin G, Ellis T, Jensen K and Freemont P (2016) A protease-based biosensor for the detection of schistosome cercariae. *Scientific Reports*, 6: 24725 (CC BY 4.0)

bacteria themselves were able to cleave the biosensor motif. Another strain (WB800N) was therefore used, that has had eight genes for proteases knocked out by mutation. After several design iterations, experiments with the TEV biosensor in *B. subtilis* showed that was specific to TEV and fairly sensitive, though not as sensitive as the biosensor in *E. coli*.

The next stage in the research was to see whether or not they could detect the actual elastase implicated in schistosomiasis. Biological samples were obtained by mechanically breaking up cercariae from infected snails and lyophilising the supernatant. These were supplied by Prof. Mike Doenhoff from the University of Nottingham (also present at the workshop). When the three *E. coli* biosensors were exposed to these biological samples, all three were cleaved although the elastase biosensor was more sensitive. In other words, there were significant off-target effects. This may be the consequence of the method of preparation of the biological samples because when the cercarial worms are crushed in order to produce the sample, multiple proteases are released. A different method of sample preparation is therefore being investigated with Doenhoff. However, this hypothesis is challenged by the fact that tests using biological samples with the biosensor in the *B. subtilis* chassis did not show off-target effects[24]. An experiment showed very promising results with one biological sample (only the elastase biosensor was cleaved) but no effect at all with two other biological samples. This is because one sample contained more elastase than the others[25].

These results were considered to be encouraging enough to investigate another issue: would the whole-cell *B. subtilis* biosensor still work after being freeze-died and then revived? This is important if the biosensors are going to be shipped across long distances. Experiments were performed and the results showed that the cells did survive and maintained their plasmids after such treatment.

Turning to issues of usability and future developments, Webb noted that the biosensor would likely be easier to use by people in the field if the output was a *gain* in colour, rather than a *loss* of colour. The team is investigating new designs to deal with this. This may also mean that fluorescent tagging would be unnecessary, possibly making the biosensor more sensitive and cheaper to produce and use.

Finally, the ICL team has decided to investigate the possibility of using a cell free system. As explained in the earlier talk by Paul Freemont, a cell-free system is made by breaking open bacterial cells. The cells are killed but all the bacterial machinery required to express genes, make proteins and fold them is present and active. The plasmid containing the genes for the biosensor can then be added, together with chemicals that provide energy. The team believed this approach may address concerns (embodied in the regulatory landscape) about using genetically modified bacteria in the environment, but there may also be technical benefits to such a system: preliminary experiments have been conducted to validate the principle for such a cell-free system and the results are promising.

Webb concluded his talk by noting that Webster's talk had spoken of a need to develop a biosensor that could help differentiate between strains of schistosomiasis. This should be possible if specific motifs can be identified.

24 Subsequent research from the Schistosome biosensor team has explored these questions in more detail, with differences in cell architecture appearing to play a role. Webb AJ, et al. (2016) *Scientific Reports*

25 *Ibid.*

Discussion in the schistosome biosensor case study

Existence of schistosomiasis hybrids

Following Webster's talk one participant asked if the changes in livestock farming are one of the main drivers of increased hybridisation between schistosomiasis strains, because (as was described in the talk) farmers are now moving their cattle over larger distances. Joanne Webster responded that her current hypothesis is indeed that this is one of the main drivers, especially because farmers are now routinely following their animals into the water, thereby increasing the interaction between human and animal parasites. Research is currently underway to test this hypothesis. Another participant asked whether knowledge about the existence of different species and hybrids was due to the availability of new detection technologies. Joanne Webster responded that this had been suspected for years, but the use of DNA barcoding and whole-genome sequencing (which is too expensive to do widely), had demonstrated the presence of hybrids, and also how dynamic the situation was.

> "Is this biosensor for a researcher to find out the fundamentals of parasite biology or is it for public health initiatives on the ground?"

Current testing methods

Another participant asked how detection of schistosomes is currently conducted. Joanne Webster explained that typically they use sentinel rodents that are deployed in the field and then collected for tests to be conducted on, but this process can take 6-8 weeks. In China cercariae meters are used.

Detecting the presence of a schistosome versus distinguishing between species

During the discussion it became apparent that there are two different possible goals: one is to just detect the presence of any schistosome, and the other is to identify the specific species present. The initial design of the biosensor aimed to detect *S. mansoni* as a proof of principle. If it turned out that different species produce sufficiently different variants of the elastase, then the biosensor could easily be modified to detect different strains, because of its modular nature. In this scenario, the biosensor system could contain a series of tests for different variants. At this stage there is little knowledge globally about any differences between the elastase produced by different species and it may be necessary to change the biosensor's target to detect other species. The initial design focused on elastase produced by *S. mansoni*, which is known to be 98% similar to *S. haematobium,* so it unclear how easy it will be to design biosensors based on targeting elastase that can distinguish between species.

Contacts at the Upstream Alliance[26] had indicated that being able to ascertain whether snails were infected with any schistosome would in itself be useful, and once a device has detected cercariae, other features of the environment can be used to determine the species; but Joanne Webster believed that ultimately some level of typing would be necessary. One participant expressed the view that tackling this issue should be seen as a more crucial component of Responsible Research and Innovation than thinking about possible environmental risks and user-friendly features such as which kind of coloured outputs the biosensor should produce. A member of the team felt that at this stage, the project is just trying to demonstrate proof-of-concept for the biosensor and the protein target could be changed later on.

> "People on the ground aiming to reduce infection might require a simpler version, whereas a lab would want something engineered to be more sensitive"

Stakeholder engagement

Another participant asked if any stakeholder engagement has been attempted. Alex Webb explained that the team's primary point of contact has been the Upstream Alliance, a US-based international partnership of scientists and private and state funders seeking to reduce the prevalence of schistosomiasis by repopulating aquatic ecosystems with African prawns, which are voracious predators of the snails that carry the schistosome parasite. As yet the Imperial College team had not spoken to anyone from regions in Africa where their sensor would be deployed, but have relied on the expertise of Professor Mike Doenhoff (a workshop participant) and those in the Upstream Alliance, who themselves collaborate with people in these regions[27].

Who is this biosensor for?

One participant asked about the intended purpose and envisaged user of the biosensor, pointing out that this would determine who the relevant stakeholders are. If the purpose is to map and monitor the prevalence of different species of schistosomes around the world, then the primary stakeholders would be schistosomiasis researchers such as Joanne Webster, who is easily accessible to researchers at Imperial College since she is right here in London. Since Webster had stated that her priority is to be able to differentiate between species and to be able to study the presence of hybrids, this would provide a specific brief for the project. Alternatively, if the purpose is to enable some kind of public health intervention on the ground, the relevant stakeholders would be different and they might not care so much about which species is present. It may be possible to engineer the biosensor so that it can fulfil both goals, but it would be useful to clearly distinguish them. These were two

26 http://www.theupstreamalliance.org/about.html

27 The original iGEM project engaged with global health experts, designers, and synthetic biologists at the Schistosome Control Initiative, The Royal College of Art, London School of Hygeine and Tropical Medicine and the BIOS research centre, now incorporated into the Department of Global Health & Social Medicine at KCL.

different scenarios and the team were unsure about which direction to pursue[28].

A member of the team agreed that this is an important issue to consider, as they might want to create a more basic version of the biosensor that is easier to use (e.g. does not need a cold chain) but is less sensitive for use by the people in the field, and a different one that is more sophisticated and more sensitive, for use in a laboratory setting.

Another participant sugested that there could also be an intermediate scenario, where the biosensor would be used to assess the relative success of different kinds of public health interventions, for example treating children with drugs only during term time or also during the school holidays; or testing the impact of different kinds of behaviour change.

Potential for false positive test results

One participant asked whether the design of the biosensor would allow the bacteria to distinguish between the protease from the parasite and the proteases of different bacteria present in the water sample. Alex Webb responded that, as previously highlighted, the team were currently investigating this problem, and that the ideal field solution would include controls to test for this.

The delivery of the biosensor to the field

Another participant asked how the team see the biosensor being rolled out in low resource contexts, where there is no easy access to sophisticated laboratories. The response was that freeze-dried *Bacillus* could be sent out in a vial and when a sample of water was added this would revive the bacteria and the biosensor gene circuit would be expressed. Some of the biosensor components need to be located on the cell surface and this poses an additional challenge. One way to circumvent this issue would be to use a cell-free system. Overall, however, this project was not as far advanced as the arsenic biosensor project and was just beginning to tackle these issues.

What would users do with positive test results?

A participant asked what could be done in situations where the presence of schistosomiasis is detected in the water. A member of the team expressed the view that the biosensor was 'just a tool' and that people on the ground could decide how best to use it for public health. Joanne Webster explained that experience had shown that killing the snails with pesticides is not a feasible solution and expressed the view that eliminating the parasite entirely was not a realistic aim, except perhaps in some islands. She stressed that a biosensor would be particularly useful to identify areas where the parasite is being transmitted. People and livestock can then be treated with drugs to try to break the parasite's life cycle; but experience had shown that once an area had been cleared, re-infection often occurs. A rapid and cheap biosensor would be useful to quickly identify the source of re-infection.

> "Some of these tools require infrastructure that simply isn't there"

28 The team have subsequently begun to narrow these option down, identifying an epidemiological route as fruitful. See Webb et al (2016) *Scientific Reports*

When is elastase released?

One participant recalled that the elastase the biosensor is designed to detect is only released by the cercariae when they make contact with the skin of their host because it is part of the invasion mechanism. This means that even if the parasite is present, the enzyme may not be detected in the water. Alex Webb responded that the elastase is continually produced by the cercariae and it is possible that it may be released without direct contact with the host. The team is considering designing a trap that includes a membrane to attract the parasites and make them release the enzyme as if it were infecting a host. The biosensor would then be used to test a water sample from that trap. This is an approach that has been previously demonstrated but it would also make the technology less easy to use.

Regulation of whole-cell and cell-free systems

One participant asked about what the team were considering in terms of regulatory procedures being considered to ensure safety. Webb responded that this would partly depend on the results of the arsenic biosensor application discussed in the morning sessions, but that the cell-free version could be a good alternative strategy. The whole-cell system could be used to validate designs, but the cell-free system may be better for use in the field because in his opinion it would be safe to release into the environment. Cell-free systems do not contain viable cells, just the cell machinery necessary to express the genes. They do however contain DNA, and potential plasmid DNA that could perhaps be taken up by native bacteria.

A member of the schistosome biosensor project team solicited views on whether the cell-free system would be better than the whole-cell approach with respect to the issue of 'release' into the environment. Warne explained that in his opinion a cell-free biosensor would lie outside of existing GMO regulations, because it would not be regarded as containing a microorganism that can replicate and transfer genetic material. Another participant argued that the question of asking 'would cell-free be better' can mean different things, because different people will use different criteria to define what is better. For instance, is it just considered 'better' because it might be easier to get through safety regulations?

A related discussion followed about which option might be cheaper, and which would be easier to incorporate into a user-friendly device. Ultimately this would depend on the precise design for the biosensor and at this stage a number of technical options were being investigated, so it was not possible to make any categorical statement about which option would be cheaper. It was pointed out that the cell-free system was useful during the design stage as it enabled researchers to iteratively test alternative designs faster than using whole-cells systems. Additionally, the term 'cell-free' covers many different things. For example, transcriptional and post-translational biosensors (described in Paul Freemont's talk) would not involve the use of DNA. Members of the team explained that a key anticipated advantage of cell-free systems was the much shorter time needed to obtain results. The cell-free systems currently being tested in the lab gave results in approximately 30 minutes. In contrast, the whole-cell system involved growing bacterial cells overnight then setting up the test, leaving it overnight again, and then conducting another operation that took two hours.

One member of the team also suggested that giving local users access to a living self-replicating organism was a powerful thing. People could interact with it in a somewhat similar way to microorganisms used in home brewing (although in practice local users were not really expected to interact with the living organism as it was intended to be kept within a sealed tube, similar to the one that had been designed for the arsenic biosensor).

Relative safety of cell-free systems

A participant pointed out that as the schistosome cell-free biosensor is using plasmid DNA, this might be transferred to naturally competent bacteria. If used outside a lab, you would not be deliberately releasing a GMO into the environment, but you could be unintentionally creating a GMO in the field. If so, why not include something in the plasmid DNA, such as a 'kill gene', to help prevent the survival of organisms that take up the DNA? Members of the team explained that they had been thinking about this. They could for example build on previous work at Imperial College's Centre for Synthetic Biology and Innovation to design a 'GeneGuard'[29] that would severely reduce unintentional plasmid propagation from an engineered bacteria. It would also be possible to ensure that the biosensor DNA does not contain elements that would give an organism a positive selection advantage, such as antibiotic resistance genes routinely used during the design stage. Another option that had not been tested yet was to use linear DNA fragments instead of circular plasmids. A participant highlighted that linear DNA fragments could still pose a problem if homologous recombination regions were present.

It was also pointed out that any novel GMO created would be inside a sealed vial and would not pose an environmental risk as long as it remained contained in that vial. However, this meant that, as with the arsenic biosensor, disposal issues will have to be considered. A team member suggested that barcoding the biosensor organisms could perhaps provide the means to track the extent of dissemination in the environment.

The overall tenor of this discussion was that the cell-free system approach could be considered a viable strategy, but that it could still pose safety concerns and one participant suggested that there would still need to be guidelines to ensure safety, even if it did not fall within current regulatory definitions of a 'genetically modified organism'.

This issue was returned to on several occasions during the session. Later on one participant argued that the fact that cell-free systems would not be defined as a GMO by regulatory authorities meant that they might be more applicable and acceptable for certain kinds of applications, for example products used in a clinical environment. Another participant questioned the correlation between broader acceptability and whether or not a product is regulated.

Managing expectations in Global Health

One of the participants drew attention to the grand claim of the WHO that schistosomiasis was to be eliminated. Such claims had been made in the past for a number of diseases and it could be argued that they can have detrimental effects. They pointed out that one of the important messages from Responsible Research and Innovation was that it was important to manage expectations in order to avoid creating unreasonable expectations about what can be delivered. Joanne Webster explained that she considered grand claims about eliminating schistosomiasis by 2020 to be bizarre, and is concerned that such claims do indeed set us up for failure. However, policy people she collaborates with tend to think that such claims are necessary to gather political support and increased funding for an issue. In that context stressing the complexity and dynamic nature of the biology of the disease may not be helpful.

Engagement with local stakeholders

One participant drew attention to the fact that at the time a lack of funding was preventing the schistosome biosensor team from visiting the African regions in

29 See: Wright, O., Delmans, M., Stan, G.-B. and Ellis, T. (2015). GeneGuard: A Modular Plasmid System Designed for Biosafety. *ACS Synthetic Biology* **4**: 307–316.

which their biosensor is intended to be used. Were there lessons here for researchers who are not used to attempting such research, and the problems with getting funding to do so?

A member of the team agreed that this was a challenge and there were important questions that they wanted to address: did local people really want such a biosensor? Would it be useful? What features would they want to be incorporated? At the same time, it would be important to stress that the team were only working with prototypes at the moment and simply wanted to carry out field tests. Visiting regions of the world where the biosensor might be used would also give the team an idea of the local laboratory facilities, although this could also be obtained by speaking with Joanne Webster and members of the Upstream Alliance. Discussions with this group had for example revealed that local labs are typically on a flatbed truck, and this had changed the way in which members of the team envisaged what would be technically possible in the local context. Another participant noted that it was often difficult to judge which factors – the technical or the social – had the most impact on funding decisions.

'Bench to bedside' or 'bedside to bench'?

One participant suggested that the project appeared to follow a 'bench to bedside' logic of translation, where scientists work in a lab to try to resolve a technical problem and then take their research to 'the bedside'. It was argued that we know from past experience that such approaches take a very long time, and that very few things that are designed on the bench actually get to the bedside[30]. It may therefore be better to start at the bedside: to go out there to see how people manage their water supply, the skills they have, and the kinds of equipment they already use. You could then bring back some of what is 'out there' back into the lab. For example, you could bring infected water back to the lab. You could try to replicate some of the local conditions in the laboratory, instead of necessarily having to travel there, which is quite expensive. A key point is that the design of the biosensor would be built on the basis of knowledge about how people in the affected regions live and work, rather than developing a device in the lab and then finding out later that you need to go through many iterations of tinkering for the device to work in local conditions.

One participant disagreed that the traditional 'bench to bedside' model of translation was not effective. They felt that industrial translation was a well-trodden path that traditionally involves partnerships with large companies who have expertise in how to translate research projects into successful products such as medical devices. The projects being discussed today were only one part of the process and the next stage would be industrial translation.

Vertical technological interventions in Global Health

The point above was emphasised by another participant who argued that experience has shown that 'vertical'[31] technological interventions in Global Health, that focus on one particular disease, have not been very successful when they are not connected in meaningful ways to more upstream causes of the problems being

30 Morris, Z.S., Wooding, S. & Grant, J., (2011). The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of the Royal Society of Medicine*, **104**(12), 510–520.

31 Debates about the most appropriate approaches for the delivery of health sometimes make a distinction between 'vertical' and 'horizontal' approaches: "Horizontal approaches tend to incorporate several health interventions as part of a comprehensive primary care approach, usually delivered through government health facilities. Vertical programmes, on the other hand, tend to deliver selected interventions, often independently, with specialised management, logistics, and delivery mechanisms." (Victora CG, Hanson K, Bryce J and Vaughan JP (2004) Achieving universal coverage with health interventions. *The Lancet* **364**(9444): 1541-1548). Note that this distinction was familiar to only a few workshop participants.

addressed. This means that it is very important not only to conduct stakeholder engagement but also to take into account the social and environmental context. This participant felt that the way in which the project had been described seemed to address some of the environmental context, but not the social context.

In response a member of the team reiterated that the team had begun to make arrangements to try and visit groups working *in situ*, but that the specific social context was still unclear. In that respect, there was a lot of scope for further development of the biosensor to be shaped by growing knowledge from this context. They also explained that the goal of the biosensor is to detect the presence of parasites, not to eliminate the parasite or provide a cure. Detection would be part of a bigger picture. With respect to environmental factors, the biosensor would provide useful information about the presence of different species of schistosomes in different areas in the world, and how these might be shifting in response to environmental factors such as global climate change.

Webster explained the Schistosomiasis Control Initiative (SCI) follows a horizontal approach where all the drug treatment programmes are implemented through local school teachers and village chiefs and that as far as possible local people are being trained to do the collecting, sampling and measuring themselves (though this was not feasible for the final stage of genetic typing). Experience had shown that local people were interested and keen to get involved. She believed that this was one reason for the success of the SCI. The local scientific partners know the local village leaders and the infected sites and therefore provide crucial expertise. This meant that if and when the schistosomiasis biosensor is shown to work, it could be integrated into these existing control programmes.

Later, Webster also explained that the SCI works with local ministries of education and of research, who play the leading role in their own countries. In each country there are scientific co-investigators, and she and her colleagues travel to those countries regularly. Certain research funders, such as DFID require projects to be interdisciplinary and to include social sciences as well as clinical sciences and veterinary sciences; and this was the general trend.

The biosensor is just a tool that can be used for different purposes

Following on from the above, a team member also explained that, because of the way in which it was being designed, the biosensor was a tool or technology that could be used for many purposes. For example, it could perhaps be used to detect bacterial infection or to identify proteases that could be used in washing powders. In the case of schistosomiasis, there were still several different ways it could be used including, for instance, in epidemiological studies[32].

When should the biosensor leave the lab?

Members of the team also expressed the view that until the biosensor was shown to work in laboratory conditions, there was little point taking it to the field, where conditions would be very messy. The team realised that there would be substantial work to be done in due course to further optimise the biosensor for it to work in the field compared to laboratory conditions. Also, until the researchers know that the device is likely to work, it may be a waste of limited resources (such as research funding and money and local people's time) to conduct stakeholder engagement; it may be better to wait until you have a technical object that works.

32 As of 2017, the team are now pursuing such a route.

A team member described two extreme situations to highlight the tension. If the team travelled to a country in Africa before having a working prototype or data to show proof-of-concept, asking people to tell them what they want, they could be accused of 'going on a nice jolly.' The other extreme would be for researchers to stay within their labs saying that they were working on something that is useful to society but with no contact to the world outside. Clearly teams working on global health projects need to tread a middle ground, where a more horizontal kind of engagement occurs as it is clear that the idea is technically feasible. They noted that the schistosomiasis biosensor project had probably reached that point now. Indeed, the team had already had conversations over Skype with local experts and this had proved very useful. For example, when these local stakeholders explained the technique they currently employ to collect the parasites using a filter, the team began to envisage how their biosensor might be incorporated into their protocol.

This led again to a discussion about whether or not, and at what stage, it would be useful to engage with stakeholders and potential users. One participant suggested that early engagement might help clarify what was wanted, what the different potential uses might be (it could for example help determine whether a whole-cell biosensor that requires growing the bacteria for 48 hours would be feasible and in which places). Others felt that it was better to wait until the researchers had obtained some firm results and published papers, and were ready for industrial translation. The question of when to engage was a recurring theme throughout the day.

Reflections

The final session of the day began with five-minute invited 'responses' from three participants with expertise in the use of technologies in Global Health contexts. Their goals were to summarise key points from the discussions so far, and to identify issues that they felt were important but which had not been raised. This was followed by a closing discussion.

Watu Wamae, African Centre for Technology Studies and Cambridge-Africa

> Began by saying that having such biosensors, even if they only raise awareness without providing a treatment should be considered a significant step

> Returned to the question of 'who defines the problem?' and whether developing a technology first and then going out there to see what problem it can solve is an appropriate approach; and argued that the answer to these questions will depend on the kinds of problems being addressed.

> Recommended that 'end users' should be seen in terms of producers rather than simply users: technologies tend to work better in situations where people feel they can engage with them and reconfigure them when needed. This could mean being able to repair the technology when it breaks down, or reconfiguring it so that it is better adapted to different contexts.

> If there is no suitable infrastructure (e.g. laboratories) then the focus should perhaps be on helping to create that infrastructure. Projects should engage with what little knowledge base exists and help to build it up so that it can become a crucial 'face on the ground.' This would help avoid a situation where the technology is seen as coming from the outside. This may take longer but is likely to produce solutions that are more organic. Once this infrastructure is there, bringing in a new technological solution (e.g. a new drug or a biosensor) is less problematic. The SCI programmes described by Joanne Webster were a good example of how engaging with existing local infrastructures such as deworming programmes in schools run by Ministries of Education enabled local people to be trained and to take responsibility for the success of the control programmes.

> Stressed the useful role that social scientists can play to understand how the local social context might affect the desired impact of the technology.

David Grimshaw, ICT4D Centre, Royal Holloway, University of London

> Stressed that we have a lot of previous experience of successful stakeholder engagement, for example in the field of nanotechnology. This experience suggests that there is an alternative to the notion that 'we have to prove the science first'[33].

> The ultimate outcome of successful stakeholder engagement isn't necessarily a technology or the solution to a particular problem. Getting different communities to engage with each other to systematically look at a nexus of problems

33 See: Grimshaw DJ (2012). Toward Pro-Poor Nano-Innovation (Zimbabwe, Peru, Nepal) in *Nanotechnology and Global Sustainability*, D. Maclurcan and N. Radywyl (Eds.) CRC Press: London.

and solutions can be seen as an important achievement in itself.

> From his experience of stakeholder engagement with nanotechnologies in Peru, Zimbabwe and Nepal, Grimshaw had learnt that it can be more fruitful to begin discussion by focusing on the problem at stake and the interplay of related cultural, social and economic issues, rather than with the technology. In other words, to take the stance of a 'technology agnostic'. When this was done in Nepal, it led to a reasonable diagnostic of the problems and inter-relationships between them, from different points of view.

> One important group of stakeholders - that was not represented at this workshop - was local scientists. It is important to recognise that they can be competent enough to understand the potential of the technology being discussed and to engage with scientists from universities in the Global North.

> Quoting Amartya Sen[34], Grimshaw stressed his belief that development is about developing the capability of local people to lead the life they would choose for themselves.

> Suggested that the so-called 'translation' process and stakeholder engagement should be seen as a design process, and design always starts with people. A key starting point is: who are you designing for? The design process involves built-in processes to obtain feedback and learning.

> Aid-dependency was a key issue that had not been addressed so far in the discussions, and that is particularly predominant in Nepal.

> The timescales typically adopted by research funding bodies are problematic for these kinds of projects. A project that involves stakeholder engagement and the need to apply for regulatory approval, such as the Arsenic Biosensor project, cannot be realised within a 3-year grant. In Grimshaw's opinion, research funders do not generally appreciate the importance of stakeholder engagement in actually getting something usable and used in the field, and do not recognise that this requires specialist expertise. As a result, it can be difficult to obtain funding for activities that go 'beyond the laboratory'[35].

Mohga Kamal-Yanni, Senior health & HIV policy advisor, Oxfam GB

> Reiterated what the two previous speakers had said with respect to the role of local stakeholders: it is important to recognise the capacity of local communities in the Global South to be involved not as consumers of science but as producers of science. These people can also produce benefits for humanity.

> Transparency and better/earlier communication of the value and risks of ongoing work are essential. This should not be seen as a PR exercise, and it is important to treat the audience as adults who can understand what is at stake and make rational decisions. Their rationality might be different to our rationality, but it is still rational. This is particularly pertinent if the project is ultimately intended to benefit those people.

34 See: Sen A (1999). *Development as Freedom*. Oxford University Press, Oxford.

35 See Grimshaw DJ (2016) Inclusive innovation: Beyond the laboratory. In Agola, N.O., Hunter, A. *Inclusive innovation for sustainable development: Theory and Practice.* Palgrave Macmillan UK

> If we are interested in producing high quality products that are usable, accessible and affordable we need to pay attention to intellectual property rules and to international free trade agreements. Experience with medicines, for example for HIV/AIDS and cancer, has demonstrated how IP restricts people's access to affordable medicines because it generates monopolies and leads to high prices. Developing wonderful medicines means nothing if the people who need them cannot access them. They might as well not have been invented. Free trade agreements also play an important role because they generally strengthen IP. The latest trade agreement being negotiated is the Transatlantic Trade and Investment Partnership (TTIP) and this includes sections that would provide stronger protection for pharmaceutical and other firms.

> It is important to consider the role that will be played by industry. If products are going to be manufactured on a large-scale, industry will necessarily be involved. However, there are different models for industry involvement. For instance, the Drugs for Neglected Diseases Initiative (DNDi) works with pharmaceutical companies and research institutions in India and Brazil to pursue affordable medicines for neglected diseases. Some large pharmaceutical firms from the Global North issue voluntary licenses to generic comapanies in the Global South, but the licensing terms are often opaque. Additionally, companies in emerging markets can often produce products more cheaply than big pharma.

> Who is going to pay for these biosensors? Campaigns by NGOs have played an important role in the establishment of the Global Fund for HIV/AIDS, TB and Malaria by making these diseases into political issues; and continued lobbying has been necessary to ensure that donors continue to replenish this fund.

> The way in which new technology is integrated into local health systems is crucial. Horizontal - health system based - rather than vertical - disease specific - approaches are more likely to lead to sustainable, usable and affordable products.

> Reflecting on the tenor of discussions at the workshop that day she explained how surprised she was that some participants seemed to assume that all NGOs necessarily attack science. Speaking about her own organisation (Oxfam), this was not and had never been the case. More stakeholder dialogues could perhaps help dispel such misunderstandings. Groups such as NGOs should not be seen as antagonists, but collaborators who approach the problem from different perspectives and can enable scientists to see things that they would not otherwise have seen.

Closing discussion

The role of iGEM[36] in framing synthetic biology projects

One participant reflected on how it is interesting to note that both of the projects discussed began life as iGEM projects[37], where the emphasis is primarily on

36 The International Genetically Engineered Machine (iGEM) competition is a competition for undergraduate and postgraduate students that has played a key role in the global development of the field of synthetic biology. Based on a kit of biological parts, teams work over the summer to design and build biological systems and operate them in living cells. For further information, see: www.igem.org

37 The arsenic biosensor started as Edinburgh's iGEM 2006 project, which won the 'Best Real World Application' prize (http://2006.igem.org/University_of_Edinburgh_2006). The schistosome biosensor project started as Imperial College's 2010 'Parasight' project, which won the 'Best Human Practices Advance' prize (http://2010.igem.org/Team:Imperial_College_London#).

finding problems that synthetic biology could solve and on developing applications for synthetic biology. This participant was impressed at the way in which both projects had broadened this agenda but nevertheless what we had heard about the experience of both projects demonstrated how problematic it can be to start with the question of 'what problems can we find that synthetic biology can solve?' This was perhaps particularly problematic in the area of Global Health because this is a field that is complex and requires overlapping disciplinary expertise. Synthetic biology may be a component in addressing Global Health problems, but will not be the whole solution.

Who sets the research agenda?

There was a wide-ranging discussion about how research agendas are, or should be, set, and by whom. One participant believed that researchers set the agenda, and felt that this was appropriate. In contrast, another participant noted that such decisions were political and needed to come out of conversations that take in a wide array of perspectives and stakeholders. As a researcher, they did not feel that they would want to impose the agenda. This question permeated the following discussion.

One participant argued that the very idea of anybody setting the agenda for scientific research was worrying. For example, the work of Watson and Crick on the structure of DNA had not been supported by their institution and yet it is now recognised as one of the most important scientific discoveries of the twentieth century.

Addressing Grand Societal Challenges requires attention to the broader context

One participant noted that one way to set the agenda was for funders to set 'Grand Challenges' but that these were often not popular with researchers, with many believing that they led to bad science and forced researchers into interdisciplinary projects when they did not see the need for interdisciplinarity. This participant argued that if one took a 'Grand Challenge' approach, dealing with schistosomiasis would arguably be high on the agenda. But having decided on this as a goal, an array of different interventions would be needed, beyond a biosensor, such as stopping shepherds going into the water with their flocks or stopping people from defecating in the water, so the biosensor would need to be built into a coherent programme of transformation. The biosensor is important, but it needs to be thought of in a broader context if we are trying to address a grand societal challenge. If not, it is likely that the device, however fantastic in technical terms, will only have a minimal impact on health outcomes. This linked in with the earlier comment about how highly technical solutions that are vertically dropped into the situation often fail and can even produce antagonism. It was well known that this was often the approach adopted by the Bill & Melinda Gates Foundation. It was important to learn from past experience where this had not proved successful.

Good solutions for us, but only 'good enough' solutions for them

Another participant followed this up using the example of malaria. The common approach is to use technological solutions such as bed nets and pesticides. However, we know how to eradicate malaria, because we have done it in the Global North (for example in Montreal where malaria was once endemic): by

covering stagnant water, providing sanitation and other infrastructure that also provides a better quality of life for people. These are the 'good' solutions, yet we insist on providing only 'good enough' solutions to regions in the Global South, instead of more 'upstream'[38] solutions such as tackling inequities between and within countries. Technologies have a role to play, but if they are disconnected from these larger issues their impact will not be as beneficial as it could be.

Innovation competitions as a means to set the research agenda

There was a discussion about whether innovation competitions could be a useful model for setting research agendas. One example was the 2008 Granger Foundation $1 million Challenge Prize for Sustainability for removing arsenic from contaminated well water in Bangladesh, where the winner had developed the Sono filter. One participant argued that the filter was very effective at removing arsenic from water, but over time it had became clear that it was not necessarily the most effective method to reduce people's exposure to arsenic, because it was relatively expensive and therefore not distributed equitably[39]. They suggested that this was perhaps linked to the fact that the competition adopted an engineering perspective.

Two workshop participants reported that they were engaged in the ongoing Longitude Prize challenge that is offering £10 million to help solve the problem of global antibiotic resistance. In this case the challenge had been set in consultation with members of the public. They felt that the prize was unlikely to generate a solution to the problem, but that it had served to focus attention on the issue and to bring together people to tackle it.

Intellectual property

One participant took the opportunity to clarify that intellectual property was not discussed that day in relation to the arsenic biosensor simply because they felt it was not part of the agenda that day. Nevertheless, at the root of it, synthetic biology is intended to be an open source technology that is open to everyone. That is the ambition. There will be IP issues, and these are complicated by university obligations, and funding body obligations. IP is not always about freedom to make money but freedom to operate. The arsenic biosensor team are working with the latter understanding.

> "No one in this room has the legitimacy to set a research agenda on their own"

Another participant suggested that the open source ambitions will likely impinge upon their chances of scaling up. Large industrial partners typically ask first what your IP portfolio is, and such companies simply

38 In the literature on Global Health, authors sometimes distinguish between 'upstream' and 'downstream' social determinants of health.' Downstream determinants pertain to medical care and personal behavior, while upstream determinants include working and living conditions in homes and communities as well as economic and social opportunities and resources. Some authors argue that most interventions tend to target 'downstream' determinants and not enough attention is paid to 'upstream determinants.' See for example: Braveman PS, Egerter, Williams DR (2011). The social determinants of health: coming of age. *Annual Review of Public Health* **32**: 381-398.

39 See: Shafiquzzaman M, Azam MS, Mishima I, Nakajima J. (2009). Technical and Social Evaluation of Arsenic Mitigation in Rural Bangladesh. *Journal of Health, Population, and Nutrition* **27**(5):674-683.

will not be interested in open source. You will therefore likely end up having to rely upon governments and organisations such as the Gates Foundation.

During the whole day, it appeared that some participants felt that avoiding partnerships with large firms and not applying for patents was the best way forward, whereas others felt that collaborations with large firms would be necessary and desirable in order to commercialise biosensors.

Manufacture

Another participant emphasised that the nature of some of these technologies, for instance cell-free, does open up room for very different kinds of manufacturing processes that perhaps do not require the involvement of large industrial partners.

One participant emphasised that having a vision for the kind of manufacturing process, and industrial partner or business that you want to become, needs to be considered as early as possible because it will direct a number of different translation decisions. Another participant emphasised that translation is precisely the kind of process that has been the subject of much study in the social sciences, and this evidence base can be used to inform the decisions for these biosensors going forwards. Translation is an exceedingly difficult process that takes far longer than most people realise and which often simply does not succeed.

Giving people in the Global South the chance to participate in synthetic biology research

One participant pointed out that a number of participants had talked about synthetic biology as though the intention was to see this science adopted and flourish in the developing countries within which these projects worked. They wanted to know more about this ambition and whether or not it was feasible. One participant responded that absolutely this was part of the ambition but was again a very complex issue. iGEM is one vehicle for achieving this and efforts are being made to include teams from Asia and Africa. The work of the BBSRC/EPSRC OpenPlant Synthetic Biology Research Centre[40] was also cited, as evidence of how synthetic biologists are trying to create the basic parts and hardware for these new technologies in such a way that they are available to everyone. They have also been involved in meeting with companies to try and develop bioparts that can survive a wide range of environmental conditions, making them accessible to countries that might not otherwise have the cold storage facilities necessary.

The latter point was used for further discussion on increasing participation in the international research process through those involved in initiatives such as iGEM. At this point one participant made reference to the efforts of DIY biologists who often face harsh limitations on their access to equipment, and who might be able to offer suggestions regarding how to organise a more dispersed research network in the future. Another participant explained that in some regions of the world, electricity can only be provided for limited parts of the day and even then supply can be intermittent. So in that respect there is some scientific research that simply could not be conducted in those regions. In response to this point, one participant explained that perhaps rather than assuming their laboratory work needs to be of the same kind as that which goes on in Cambridge, there may well be numerous other kinds of research that could be pursued in these other regions of the world.

40 https://openplant.org/

Part 2: Key themes and analysis

The first part of this report summarised the presentations and the discussions that occurred during the day, replicating as accurately as possible what was said by workshop participants, without commenting on those statements, and without endorsing any of the views expressed. In this second part of this report, the authors use their social science expertise to analyse those discussions, summarise what they consider to be the key findings, and reflect on the consequences of those discussions.

Lessons: Understanding global health challenges

Problems are not easily isolated

Workshop participants' discussions are littered with examples that draw attention to the complexity and multiplicity of global health challenges. Arsenic contamination is subject to physical geography (e.g. rainfall), which changes over the course of a year, meaning that the distribution of well contamination also changes over the year. Between just two localities, one can find very different histories of arsenic contamination which affect how the problem manifests for people. During discussion of the arsenic biosensor it became clear that the 'health challenge' was not just one of access to water, but also one of agriculture, education and social exclusion. Likewise, the challenges of addressing schistosomiasis as a phenomenon are evident. Many of the challenges that schistosomiasis presents stem from interactions between: the parasitic worms; treatment, management and intervention programmes; farming practices; physical geographies; and the movements of a wide range of animals (wild rodents, buffalo and snails, for example). This means that there are many possible users, several species with different biologies, and several different points of intervention for a biosensor project.

The global health context of each biosensor project is uniquely distinct and extremely complex. Despite the importance of the idea of global health, it is fundamental to understand the local specificities if a project is to make a worthwhile intervention.

Before advocating a synthetic biology based solution to a global health challenge, it is necessary to evaluate its benefits and potential drawbacks in relation to other potential approaches with which it may interact or even displace. Such an evaluation must look beyond techno-economic approaches to also include cultural and social dimensions.

There are always multiple possible solutions

There are multiple ways of 'framing' the problems that each biosensor aims to address. Multiple solutions are also possible. For example, arsenic contamination can be addressed through: diversification of dietary sources; removal using a range of technologies; well sharing; and / or infrastructural provisions of clean, piped water. Similarly, attempts to eradicate Schistosomiasis are being made through destruction of the parasitic worm but morbidity can also be controlled through the treatment of infected people. Alternatively, the incidence of infection can be reduced through changing practices, in this case by adapting farming practices. There have been examples when attempts to introduce a high-tech or mainstream solution to a health problem can actually degrade or reduce the capacity of locally developed approaches[41]. Indeed, given limited resources, sometimes the introduction of one approach may effectively exclude others that local stakeholders find more acceptable or appropriate. If a technologically advanced approach such as that using synthetic biology is to be justifiable, therefore, it is important to review other approaches and explore whether this new approach is likely to be cheaper, easier to use, safer or more locally effective than other potential solutions, and also to evaluate whether it can, or even must, work in synergy with other approaches.

41 See, for example the accelerated scale-up of water cisterns in the social technologies network by the Brazilian Government, Fressoli M, Abrol D, Smith A, Ely A, Dias R (2014) When grassroots innovation movements encounter mainstream institutions: implications for models of inclusive innovation. *Innovation and Development*, **4**(2): 277–292.

Solutions are political as much as technical

Both projects aim to produce a technological solution to a global health challenge. However, both the framing of the problem and the framing of the solution are as much political as technical. The implementation of each solution would affect different people to different degrees, empowering some and disempowering others, supporting certain ways of making sense of the problem and marginalizing others.

In Bangladesh, arsenic contamination resulted from a previous technological intervention, and places poor farmers in one of the most vulnerable positions: not only are they are unable to vary their diet, they also perform laborious work and therefore consume more contaminated water and food. Similarly the 'solution' of arsenic testing has resulted in stigmatisation for some whose wells are found to be contaminated, whereas for others, contamination has been reduced by the installation and control of a deep tube well.

Testing has wider political consequences because continued metricised monitoring can maintain the question of arsenic contamination as a matter of concern for political elites. However, implementing a regime of testing, and associated data collection, also has consequences, introducing monitoring, and raising questions of the ownership and control of water supplies. Further, political dimensions are not limited to the geographical boundaries of the intervention, but also to the locale of production: the Arsenic Biosensor has become an accidental precedent case for contained use regulation in the European Commission.

> Innovating responsibly requires making politically-laden choices explicit in advance, reflecting on their desirability with key stakeholders, and offering ways of ameliorating those socio-political consequences deemed to be problematic. Well-established methodologies such as actor and controversy mapping would be reasonable base requirements[42].

Thus, testing is not a neutral act. While it may seem merely a technical option, introducing a regime of testing will have wider political, social, cultural and material consequences for the populations involved. Those who advocate building a biosensor for testing, and introducing it in a local context, are thus inevitably also intervening into local and even national politics.

42 See, Bijker WE (2009) How is technology made? – That is the question! *Cambridge Journal of Economics*, **34**(1): 63–76.; Whatmore, SJ (2009) Mapping knowledge controversies: science, democracy and the redistribution of expertise. *Progress in Human Geography*, 33(5): 587–598.

Identifying pre-existing interventions to act as comparators – illustrating the different issues, understandings and framings – can help to successfully navigate complex health systems.

Biosensors are interventions into global health systems

Biosensors are not just passive tools, but intervene into complex relations among many actors who may understand and frame the problem and potential solutions in different, and even conflicting, ways. Existing testing kits for arsenic contamination provided a benchmark for design goals and constraints of the arsenic biosensor. They also provided indications as to the kinds of users that the biosensor will be used by and the social context in which they will be deployed. Crucially, they highlighted the problems that are posed about the value of testing – for arsenic but also for waterborne pathogens – if no solution is available, either in the form of an alternative source of water, or through some means of decontamination or purification of existing water supplies.

However, as the case of schistosomiasis shows, it is not always simple to identify such comparators. Existing detection methods for schistosomiasis include: sentinel rodents which are released, caught and tested; Cercariae meters; a range of medical patient tests; and PCR-based detection for known transmission areas. While issues such as the presence or absence of a cold-chain to move the biosensor have been considered, it is not yet clear how the schistosomiasis biosensor will fit into this existing testing regime. There are multiple possible options to this end, indicated by the question of whether the aim is to assist public health experts to identify different species of schistosome or just to detect schistosome presence for citizens. The design of a biosensor will differ depending on which of these objectives is prioritised.

Public and stakeholder knowledges are fundamental to good design

Much has been written about the role of perceived public concern and participation in shaping synthetic biology and emerging technologies more broadly. These two cases provide lessons regarding the value of public and stakeholder *involvement* in a way that may help to move discussions beyond solely 'concern about public concern'[43]. They do so by demonstrating substantive rather than instrumental rationales for engagement, that is, they engage outsiders on the basis of their knowledge rather than on the sole basis of 'smoothing through' a technological intervention[44]. The example of the arsenic biosensor shows the benefits of such an approach: the team developing this sensor has pursued partnerships and engaged broadly, and field visits to specific locales have enabled them to take account of a wide range of unanticipated issues. Some of these, such as the sensor output, have been 'designed-in' to the technological device itself.

Sensitive engagement on the basis of expertise can provide a valuable way of making sense of complex problems and their potential solutions, but only if it comes with a genuine commitment to respond to the lessons of that engagement. Such a commitment may entail lengthy and expensive modifications to prototype interventions, and should not be made lightly.

It is important to note that such processes of local field research and consultation require significant thought and preparation. For example, research has demonstrated that factors such as the person chosen to lead the engagement will shape access to particular groups within the communities and the responses given. Thus, care must be taken with the framing of such engagement work, ideally based on learning from previous work and its evaluation. It is necessary for all involved to believe that engagement is genuine, and not merely 'box ticking' and that insights from such engagement will be incorporated into the project, even where they are technically difficult. For example, in the case of the arsenic biosensor, the realisation that it was desirable to move from a gradated sensor to a traffic light system in the arsenic biosensor required a significant amount of technical work, but did achieve its objective.

The example of the Schistosomiasis Biosensor shows the difficulties, and yet the necessity, of identifying the most appropriate intervention in the face of numerous possibilities in a complex challenge involving multiple human and animal actors and their forms of life. Well thought out public and stakeholder engagement, if pursued with a substantive rationale focussed on shaping and reshaping the intervention, is necessary in such situations to identify and resolve such key questions as who the appropriate 'user' might be, what the appropriate way of framing the problem might be, and how it will be embedded as one element within a complex treatment system.

43 Marris, C (2015) The construction of imaginaries of the public as a threat to synthetic biology. *Science as culture*, **24**(1): 83–98.
44 Marris C, Rose N (2010) Open Engagement: Exploring Public Participation in the Biosciences. *PLoS Biology*, **8**(11): e1000549

Institutional reflexivity: Tensions

Technical fixes and lock-in

There is a long-running tension in social and technological change, which demonstrated in the above discussions about problem framings and solutions, and the value of integrating public and stakeholder knowledge into technological design. On the one hand projects must be made tangible and technical at an early stage, and not remain merely abstract ideas, which means making decisions and committing to particular framings. Yet, on the other hand, even some of the most basic assumptions built into those technical decisions must remain malleable, as new evidence and new ways of thinking emerge from engagement[45].

In the current examples, it is notable that both biosensors emerged amalgamations of entries into the International Genetically Engineered Machine competition (iGEM). The competition was established, and continues to act as, a field-building institution for synthetic biology[46]. As such, it plays a significant role in both the agenda setting and framing of synthetic biology projects. Teams are encouraged to enter the competition, develop particular 'genetic parts' and build them into 'devices' which can be used to address problems. It thus positions the technical objects of synthetic biology as solutions to social challenges. The role of iGEM is important because beyond the institutional capital that the competition generates, it provides ways of making synthetic biology tangible. Yet, in a non-trivial way, it also embodies an approach in which synthetic biology is a solution in search of potential problems to which it can be applied.

As each biosensor has moved from inception to application, it has proven necessary to move away from purely technical notions of problem and solution. It was after these projects had moved from iGEM projects to research council or charity-funded project that most of the significant changes, developments and social research took place. The Arsenic Biosensor team, funded by the Wellcome Trust, needed to change the genetic circuit designs in response to user feedback. As the projects continue to develop, activities such as the pursuit of regulatory approval and the receipt of research funding will begin to embed professional, financial, scientific and material capital, 'locking-in' more of their features. Nevertheless, even some rather basic features of the proposed solution may require modification. For example, it is conceivable that a protease-based biosensor may not be the most effective intervention for schistosomiasis.

This tension, between the need for closure and inevitable lock-in on the one hand, and the need for continuous adaptability on the other, is likely to become more important as research funders increasingly demand challenge-oriented research in which those who seek funding have, at very early stages, to claim a fit between their 'solution' and the problem it seeks to address. Challenge based funding schemes must find ways to recognise, and indeed support, this need for flexibility and responsiveness.

45 This is a version of the longstanding 'Collingridge Dilemma' (Collingdridge, D. (1980) *The Social Control of Technology*. New York: St Martin's Press) and the notion of 'technological lock-in' which have both been extensively discussed within the field of science and technology studies.

46 For example in 2016 it reportedly attracted approximately 3000 attendees from approximately 270 organisations, who raised approximately $15m in capital during the course of the year to fund their projects.

Regulatory definitions are being challenged

Biotechnologies are capable of challenging deeply held and common-sense categorisations of ourselves and the world that we inhabit (e.g. what is natural or unnatural). Regulation is one of the primary ways that social values regarding such technologies are codified. However, the workshop discussions suggest that several longstanding regulatory distinctions are either currently being challenged, or are likely be challenged in the future, by developments in molecular biology. Questions about whether current regulatory frameworks are appropriate and sufficient are therefore vital to address.

First, as alluded to above, the distinctions between regulatory pathways such as 'contained use' and 'deliberate release' are being challenged. The Arsenic Biosensor Collaboration's decision to pursue a path under the Contained Use EC Directive was one which was recommended to the project team by regulators but also one which felt more of an 'honest' definition, because the team did not feel they were deliberately releasing their engineered organism into the environment. Whilst this pathway has shaped the development of several containment mechanisms, it is not clear that such a pathway has produced an organism that is any more or less dangerous than if the team had pursued a deliberate release route.

Second, cell-free biosensors were presented as a solution to regulatory hurdles and concerns regarding the safety of whole-cell biosensors. However, it is not clear that such biosensors present an ecological threat that is different to whole-cell systems, despite potentially falling outside current regulatory frameworks for GMOs, in that these types of biosensors are not 'genetically modified organisms'. A product falling outside the scope of current regulation is not necessarily a mark of its safety. Conversely, as is seen with the arsenic biosensor case, being mired in a regulatory 'thicket' is not necessarily reflective of any inherent risk to the environment or human health.

Much debate regarding applications using modern molecular biology hinges on disputes about whether regulations should target the 'product' or the 'processes' used to produce applications. One problem is that both refer to highly technical assessments in tightly controlled conditions which fail to account for the wider social and environmental factors that would apply if translated to the domain of their intended use. Recognising the multiple characteristics that can be used to deem a device to be 'better' implies that an assessment that looks beyond technical evaluations in tightly-bounded experimental conditions would be desirable. Recent attempts to adopt precautionary positions in relation to gene drives go some way to achieving this[47], but there are precedents, embodied in certification standards and social sustainability assessment, that do *not* separate product from process and that if implemented carefully, may be fruitful avenues for exploration[48].

Competing models of innovation and translation

A significant amount of discussion in the workshop stemmed from participants' differing assumptions about the most appropriate models of technological intervention into Global Health challenges. These can be summarised as 'bench to bedside' on the one hand,

47 Kaebnick, G.E. et al. (2016). Precaution and governance of emerging technologies. *Science*, **354**(6313) 710–711.

48 Outside the area of health, see for instance emerging social sustainability analyses developed within Raman, S. et al. (2015) Integrating social and value dimensions into sustainability assessment of lignocellulosic biofuels. *Biomass and Bioenergy*, **82**: 49–62 and Wiek A et al. (2012) Sustainability and Anticipatory Governance in Synthetic Biology. *International Journal of Social Ecology and Sustainable Development*, **3**(2): 25–38.

and 'bedside to bench' on the other. In the former, the assumed model of intervention is of a technology being developed in a laboratory and then being 'dropped in' to its context of use. In the latter, a technology would be developed alongside prolonged engagement with end users or ideally would be developed by such end users incorporating knowledge and existing local processes of innovation. Corresponding parallels can be drawn between these approaches and vertical / horizontal models of health intervention; a vertical intervention would likely seek to deliver a single intervention whereas a horizontal intervention would work with agencies and actors in the context to deliver a suite of interventions and modification to best address the challenge / cluster of challenges.

These assumed models of translation and intervention are important to unpack for several reasons. First, they represent significantly different, but rarely aired, mentalities underpinning global health projects. The underpinning model will significantly impact the ability of a project to respond to the 'lessons' drawn from this workshop. For instance, if a vertical approach is taken then it will be almost impossible to incorporate knowledge of the local context into the design of the project's intervention. Second, neither model is without its problems. Against a backdrop of pathways to impact on the one hand, and a widely perceived 'valley of death' in the move from research to innovations on the other, Morris et al. attempted to trace which research proceeded down a translation pathway to implementation in practice[49]. The authors faced significant challenges, both in undertaking that work of tracing, and in identifying clear methods that could be used to assess pathways to impact. In the absence of such methods, funding was often delivered to projects on the basis of promises, founded on premises of linear translation processes that were not grounded in empirical research evidence. Similar promissory mechanisms have been described as intrinsic features of new and emerging fields. Conversely, bedside to bench / horizontal methods of intervention face not just the challenges encapsulated in the *Collingridge Dilemma* discussed earlier, but also face difficulties in achieving funding support from traditional sources which are seemingly more committed to funding basic research because of a belief in the alternative approach.

Such tensions are fundamental to address because assumed models concerning translation to applications are endemic within contemporary research funding policy where they are coupled to institutionalised reward structures in science and innovation (for instance in the form of intellectual property, a license to commercialise, professional promotion and the continuation of research funding)[50]. This means that global health projects appear to be caught within an external institutional tension that is difficult to contest. The implication is that this will remain a barrier to building responsive research systems; systems which are open to alternative models of funding, innovation (for instance grassroots innovation, appropriate technology and social innovation), purpose and conceptions of value beyond the economic. Yet it is precisely being open to these alternatives that the concept of responsible innovation demands[51].

49 Morris ZS, Wooding, S & Grant, J (2011) The answer is 17 years, what is the question: Understanding time lags in translational research. *Journal of the Royal Society of Medicine*, **104**(12): 510–520.

50 Nuffield Council on Bioethics (2012) *Emerging biotechnologies: Technology, choice and the public good*, London: Nuffield Council on Bioethics.

51 Raman, S (2014) *Responsive research: Putting the innovative back into agendas for innovation*, Nottingham: University of Nottingham; McNie EC, Parris, A & Sarewitz, DR (2016) Improving the public value of science: A typology to inform discussion, design and implementation of research. *Research Policy*, **45**(4): 884–895.

Supplementary material

Workshop programme

8:30-9:00	Arrival and registration
9:00-9:10	Welcome
Session 1: Introduction	
9:10-9:35	Introduction to Global Health
	Prof. Bronwyn Parry, SSHM, KCL
9:35-10:00	Introduction to Synthetic Biology Biosensors
	Prof. Paul Freemont, CSynBI, Imperial College London
Case study 1: Arsenic Biosensor	
10:00-10:30	Arsenic contamination: occurrence, causes, impacts and mitigation
	Peter Ravenscroft, independent consultant
10:30-11:00	Arsenic Biosensor Collaboration
	Lalitha Sundaram, Department of Pathology, University of Cambridge
11:00-11:30	Break
11:30-12:00	Risk assessment and regulatory issues
	Dr Simon Warne, Health and Safety Executive
12:00-13:00	Discussion of the arsenic biosensor case study
13:00-14:00	Lunch
Case study 2: Schistosome Biosensor	
14:00-14:30	Schistosomiasis: occurrence, causes, impacts and mitigation
	Prof Joanne Webster, Centre for Emerging, Endemic and Exotic Diseases, Royal Veterinary College
14:30-15:00	Schistosome biosensor project
	Dr Alex Webb, CSynBI, Imperial College London
15:00-16:00	Discussion of the schistosome biosensor case study
16:00-16:30	Break
Broader discussion	
16:30-17:50	Identification and discussion of Generic Issues
17:50-18:00	Wrap-up and close
18:00-20:00	Reception

List of participants

Jim Ajioka, Department of Pathology, University of Cambridge

Dominic Berry, Science, Technology and Innovation Studies, University of Edinburgh

Jane Calvert, Science, Technology and Innovation Studies, University of Edinburgh

Martin Cannell, Department for Environment, Food & Rural Affairs (Defra)

Mike Doenhoff, Faculty of Medicine & Health Sciences, University of Nottingham

Paul Freemont, CSynBI, Imperial College London

Chris French, School of Biological Sciences, University of Edinburgh

David J. Grimshaw, ICT4D Centre, Geography Department, Royal Holloway, University of London

Stuart Hogarth, Department of Sociology, University of Cambridge

Kirsten Jensen, CSynBI, Imperial College London

Mohga Kamal-Yanni, Senior health & HIV policy advisor, Oxfam GB

Hanna Kienzler, Department of Global Health & Social Medicine, King's College London

Richard Kelwick, CSynBI, Imperial College London

Richard Kitney, CSynBI, Imperial College London

Nicolas Kylilis, CSynBI, Imperial College London

Elsa Leger, Centre for Emerging, Endemic and Exotic Diseases, Royal Veterinary College

Claire Marris, Centre for Food Policy, City, University of London

David Nugent, Elucidare Limited

Jan Oltmanns, School of Biological Sciences, University of Edinburgh

Bronwyn Parry, Department of Global Health & Social Medicine, King's College London

David Radford, School of Biological Sciences, University of Edinburgh

Peter Ravenscroft, independent consultant

Nikolas Rose, Department of Global Health & Social Medicine, King's College London

Lalitha Sundaram, Centre for Existential Risk, University of Cambridge

Watu Wamae, African Centre for Technology Studies and Cambridge-Africa

Simon Warne, Health and Safety Executive (HSE)

Alex Webb, CSynBI, Imperial College London

Joanne Webster, Centre for Emerging, Endemic and Exotic Diseases, Royal Veterinary College

Ke Yan Wen, CSynBI, Imperial College London

Orr Yarkoni, Department of Pathology, University of Cambridge

Feedback received

All of the feedback received was highly positive, and all those who supplied feedback particularly emphasised the way in which open discussion was cultivated. One wrote that there was “interesting input from a variety of sources with widely different backgrounds”. Those who suggested ways in which it could have been improved suggested that scientists from the developing countries discussed could also have been included, and that some way of keeping record of the points being made (to avoid later confusion) through perhaps the use of a whiteboard would have been helpful.

Those who provided feedback all agreed that the workshop would have an effect on their future work. One participant wrote that they “will take into account the issues discussed when designing future projects of this nature, as well as in completion of existing projects”.

Another wrote that it was a “well run day” with an “Excellent moderator”.

Procedure to exclude a GMM from the scope of Directive 2009/41/EC

The introduction to **Part B of Annex II of Directive 2009/41/EC** on contained use of genetically modified micro-organisms (GMMs) states that:

> Types of GMMs listed in Part C in accordance with the regulatory procedure with scrutiny referred to in Article 20(2) are excluded from the scope of this Directive. GMMs will be added to the list on a case-by-case basis and exclusion will relate only to each clearly identified GMM. This exclusion applies only when the GMM is used under conditions of contained use as defined in point (c) of Article 2. It does not apply to the deliberate release of GMMs. For a GMM to be listed in Part C, it must be proved that it meets the criteria given below.

Article 20(2) of Directive 2009/41/EC states that:

> Where reference is made to this paragraph, Article 5a(1) to (4) and Article 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

Decision 1999/468/EC lays down,

> "the procedures for the exercise of implementing powers conferred on the Commission"

Article 5 (1) to (4) and Article 7 of Decision 1999/468/EC set out the regulatory procedure for the use of the "regulatory committee" that delivers opinions on draft measures prior to Member States voting on whether or not to adopt draft measures.

Criteria establishing the safety of GMMs for human health and the environment (**Directive 2009/41/EC, Annex II, Part B**) (GMMs that do not meet these criteria may not be included in Part C):

2.1. **Strain verification/authentication.** Identity of the strain must be precisely established. Modification must be known and verified.

2.2. **Documented and established evidence of safety.** Documented evidence of the safety of the organism must be provided.

2.3. **Genetic stability.** Where any instability could adversely affect safety, evidence of stability is required.

3. Specific criteria

3.1. **Non-pathogenic.** The GMM should not be capable of causing disease or harm to a healthy human, plant or animal. Since pathogenicity includes both toxigenicity and allergenicity, the GMM should therefore be:

3.1.1. **Non-toxigenic.** The GMM should not produce increased toxigenicity as a result of the genetic modification nor be noted for its toxigenic properties.

3.1.2. **Non-allergenic.** The GMM should not produce increased allergenicity as a result of the genetic modification nor be a noted allergen, having, for example, allergenicity comparable in particular with that of the micro-organisms identified in Directive 2000/54/EC.

3.2. **No harmful adventitious agents.** The GMM should not harbour known harmful adventitious agents such as other micro-organisms, active or latent, existing alongside or inside the GMM, that could cause harm to human health and the environment.

3.3. **Transfer of genetic material.** The modified genetic material must not give rise to harm if transferred; nor should it be self-transmissible or transferable at a frequency greater than other genes of the recipient or parental micro-organism.

3.4. **Safety for the environment in the event of a significant and unintended release.** GMMs must not produce adverse effects on the environment, immediate or delayed, should any incident involving a significant and unintended release occur.

Further reading

Arsenic Biosensor Collaboration

de Mora, K, Joshi, N, Balint, BL, Ward, FB, Elfick, A & French, CE (2011) A pH-based biosensor for detection of arsenic in drinking water *Analytical and Bioanalytical Chemistry*, **400**(4): 1031-1039. doi: 10.1007/s00216-011-4815-8.

Grimshaw DJ (2016) Inclusive innovation: Beyond the laboratory. In Agola NO., Hunter A *Inclusive innovation for sustainable development: Theory and Practice.* Palgrave Macmillan UK

Schistosome Biosensor

Kelwick R, Webb AJ, MacDonald JT and Freemont P (2016) Development of a Bacillus subtilis cell-free transcription-translation system for prototyping regulatory elements. *Metabolic Engineering* **38**: 370-381. doi: 10.1016/j.ymben.2016.09.008.

Webb AJ, Kelwick R, Doenhoof MJ, Kylilis N, MacDonald JT, Wen KY, McKeown C, Baldwin G, Ellis T, Jensen K and Freemont P (2016) A protease-based biosensor for the detection of schistosoma cercariae. *Scientific Reports*. **6**:24725. doi: 10.1038/srep24725

Webb AJ, Kelwick R and Freemont P (2017) Opportunities for applying whole-cell bioreporters towards parasite detection. *Microbial Biotechnology.* **10**(2): 244-249. doi: 10.1111/1751-7915.12604.

Responsible Innovation

Marris C (2015) The construction of imaginaries of the public as a threat to synthetic biology. *Science as Culture* **24**(1): 83-98. doi: 10.1080/09505431.2014.986320.

Ribeiro B, Smith RDJ & Millar KM, (2017) A mobilising concept? Unpacking academic representations of Responsible Research and Innovation *Science and Engineering Ethics*. **23**: 81-103. doi:10.1007/s11948-016-9761-6

Stilgoe, J., Guston, D. (2016) Responsible Research and Innovation. In Felt, U. et al. eds., *The Handbook of Science and Technology Studies* 4th ed., Cambridge, MA and London, UK: MIT Press

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