Written evidence from Engineering Biology Interdisciplinary Research Centre, University of Cambridge (ENB0034)

The University of Cambridge's Engineering Biology Interdisciplinary Research Centre is a centralised hub for Engineering Biology research in Cambridge. It brings together researchers, commercial partners and external collaborators. It supports researchers working across disciplines - at the intersections of biology, engineering, computer sciences, design and bioethics.

1. What are the UK's key strengths in the area of engineering biology?

The UK's key strengths are in the extremely high-quality scientists in this area at several universities spread throughout the UK. The UK excels in the fundamental sciences that underpin Engineering Biology including engineering, computational modelling, genomics, molecular sciences and genetics. This, combined with shrewd early investment into Synthetic Biology, including the 'Synthetic Biology for Growth' program and the 'Synthetic Biology Road Map', established the UK as a global lead in Synthetic Biology. This programme established centres of excellence, including the plant-focussed OpenPlant centre, led by the University of Cambridge, that trained many graduate students and postdoctoral scientists and helped to establish new interdisciplinary research groups. This augmented the UK's already exceptional reputation for producing high-quality graduates and post-graduates in life-sciences and engineering. The UK is also home to world-leading hubs for bioinformatics, genetics and molecular biology (Wellcome Sanger genome campus, Laboratory of Molecular Biology, Roslin Institute, Crick Institute) with historical visibility and an ongoing legacy (Human genome project).

There are many smaller pockets of exciting and innovative science going on around the UK in e.g. genetic engineering of plant and animal cells, tissue engineering, engineering devices such as microfluidics that will revolutionise the ability for "high throughput" science. Additionally, there are exciting and innovative developments in areas of Engineering Biology such as hardware, software and computational modelling. All of this work is highly interdisciplinary.

2. What are the key applications for engineering biology?

Can you give examples of particularly exciting or interesting applications? In particular, applications which could be taken forward or are being worked on in the UK?

The UK has shown the power of synthetic biology through many proof-of-concept projects, and engineering biology allows these to be taken to the next technology readiness level. The ability to biomanufacture small molecules and biologics, including new-to-nature and designer molecules has been critical: Engineering Biology can be used to introduce new pathways into production hosts, including plant and microbial expression systems, for the sustainable and scalable production of valuable chemicals currently obtained from petrochemicals, from fragile environments or rare plants.

The UK is also very strong in agricultural biotechnology, including the development of improved crops for a changing climate. Engineering of agricultural species has made remarkable progress in the past five years. UK academic institutes are actively engaged in advancing the technology readiness levels of the resulting plants and farmed animals. Similarly, the technologies behind the development of GM (transgenic) crops continue to improve in precision. Notably, important agricultural traits such as disease resistance (to reduce or eliminate the need for pest- and fungicides), as well as the biofortification of plants with vitamins, will at times be best achieved using *cis*-genic and *trans*-genic technologies where genes from closely or distantly related, respectively, are transferred into a new species.

On what timescales might the different applications for engineering biology be realised? Which applications are emerging now, and what is on the horizon in the next 5–10 years or further ahead?

Key opportunities over the next 5-10 years include:

- Foundational open technologies, "nuts and bolts" that allow positioning in a unique way to build the infrastructure.
- DNA synthesis that can speed up research and innovation, several UK companies working on these technologies.
- Better quantitative and predictive modelling: we have more data than we know what to do with but an inflection point is coming in terms of how we can use it.
- Big advances in de novo design of proteins, especially catalysts or more diverse functions
- Advances in protein engineering eg light-controlled and chemical-hybrid proteins that have novel and controllable functions
- Advances in microfluidics and multiplexing, with high throughput uses
- Organ-on-a-chip models for engineering therapeutics
- Designing synthetic microbial communities for healthcare applications, such as gut microbiota modulation

How does the UK compare to other countries, such as Germany, the US, or China, in terms of investment and policy activity, as well as areas of specialism?

Despite early investment through the UK SynBio for Growth program the UK has now lost its competitive edge in this area. Due to the scarcity of funding after the initial investment, the UK's efforts have been eclipsed by what has now been established in Asia, the USA, the EU and Australia with significantly larger investments and commitments. Similarly the large Synthetic Biology Research Centres that established large centres of expertise were dissolved without ongoing investment with loss of talent and expertise. The post-Brexit context has aso meant that the UK's participation in Horizon and other funding schemes has been compromised, as have the sustained development of international partnerships.

Policy activity in the US in particular has been much stronger, comparatively, with an executive order "Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy" in 2022, Bold Goals for U.S. Biotechnology and Biomanufacturing report in 2023, Building a Resilient Biomass Supply plan in 2024.

3. <u>How can Government policy support the development of engineering biology?</u>

The current Government has been supportive of Engineering Biology and has recognised the role of this area of research in the growth of the bioeconomy. It is important that any subsequent government:

- Ensure that educational programmes remain cutting edge and produce interdisciplinary graduates with training in computational biology, engineering, maths, biology and chemistry;

- Fund basic research to ensure that new and fundamentally transformative developments in this rapidly-developing field are not missed;
- Fund early-stage translation projects to enable progression from the earliest TRLs;
- Ensure that the UK is attractive to leading scientists in the field, especially post-Brexit;

What should the role of UKRI be in supporting engineering biology? Which research councils are most involved in funding it? Are there areas where more could be done to support interdisciplinary research? What would the best mechanisms be for achieving this?

The initial investment into the Synthetic Biology Research Centres (SBRCs) and Biofoundries was allowed to expire with no communication of future plans. This resulted in loss of talent and dispersion of expertise. The subsequent 'Transition' and 'Breakthrough' funding calls were last-minute and, as expertise had already been lost from most scientific teams, required the recruitment and training of new staff. This made it impossible to maximise success from these very short projects, which particularly impacted projects that use organisms with longer life-cycles, including plants and animals. The pattern has continued with the last-minute short term Mission awards. A key challenge is retaining highly-skilled technical staff who rely on temporary contracts with limited security. Such timelines also negatively impact the ability of academics to engage with industry as they do not allow sufficient time for agreements on intellectual property to be reached.

There is an insufficient number of sufficiently long, well-resourced awards. Post the initial SynBio For Growth awards, UKRI has funded short (12-24 months) awards (e.g. Breakthrough/ Transition/ Mission Awards) or a very small number of awards for very large centres (SynBioResearch Centres/Mission Hubs). Short, low-amount funds are insufficient for the vast majority of Engineering Biology Projects.

<u>What is most needed are regular (>1 per year) calls for 3-4 year projects that fund teams of 2-4 principal investigators from different disciplines e.g. biology, chemistry, engineering, mathematics.</u>

As a separate, related, issue: The government needs to support sustainable and curated facilities, tools and databases. This could include long term repeating grants specifically for developing and maintaining tools and software for the community. Far too many tools are poorly documented and maintained, as there is no incentive to do so.

Finally, to effectively tackle the grand challenges of engineering biology, it's imperative to establish physical spaces that facilitate interaction between engineers and biologists. These should feature open, frictionless interfaces that encourage collaboration among researchers from different disciplines and departments. UKRI should fund such cross-disciplinary spaces.

Is the UK getting the best value out of its existing facilities, such as the biofoundries? If not, why not?

The UK has four public biofoundries in London, Norwich, Manchester and Edinburgh. These can support the development of pilots, which can benefit academics and start-ups/SMEs seeking data to support scale-up. However, large-scale research is, by its nature, costly. Currently, there are insufficient funding opportunities for research projects of a scale that enables the use of these facilities. Post the initial SynBio For Growth awards, UKRI has funded short (12-24 months) awards (e.g. Breakthrough/

Transition/ Mission Awards). These projects are too short and too poorly resourced to enable use of the biofoundries.

4. How can the UK maximise the economic potential of developments in engineering biology?

How does the UK's approach to engineering biology, commercialisation and translation compare to other nations, such as Germany, China and the US? Are there specific areas the UK should look to focus on in order to gain or maintain a competitive advantage?

Incentives are needed to attract longer-term investment in Engineering Biology for new spin-out companies. A key reason why the UK lags behind the USA in major biotechnology companies is often the restricted investment provided at the outset. More incentives to capitalise on new developments would allow for greater investment and longer-term funding of new companies. There is a lack of investment, especially beyond seed funding and Series A. Scaling up can be very expensive and often requires a move to the US because the UK investors tend to be lower scale.

There may be areas where the UK's approach could borrow from successful strategies implemented elsewhere. In the US for example, there are funding sources available to promote entrepreneurs taking higher level of risks beyond what is generally achievable in the UK's climate, where both the majority of grant funding as well as institutional investors favour pursuing technologies that are more conservative. An example of this can be seen in the relative weight the UK Engineering Biology sector gives to traditional modalities of biologics (e.g. monoclonal antibodies) compared to supporting the next-generation of promising future modalities (e.g. mRNA, microbiome therapies).

Another difference is a trend for much more restrictive licensing arrangements for our talented UK academics to spin-out their technologies from their universities, compared to American universities. Models like the policies employed by Stanford University that give founders greater equity and ownership over their ideas, if brought to the UK, would make founders more likely to overcome the initial red-tape of securing their IP and also make them more attractive to private capital investment because of their improved equity position.

All this said, the UK frequently provides excellent value for money and punches above its weight in basic and applied science e.g. biomedical and engineering biology, plant sciences. The UK is generally more interdisciplinary than many countries. To best capitalise on its strengths, the UK needs to encourage collaboration and support, rather than siloing or creating competition.

Is there a danger that engineering biology advances developed in the UK are exploited overseas?

In several areas where the UK has excellent academic research, there isn't the industry available or accessible to take products to market. For example, as a result of previous EU GM regulation, many UK seed and breeding companies moved their breeding activities to the US, put off by the additional cost and time for product development. The new Genetic Technology (Precision Breeding) Act has the potential to increase innovation across the sector and diversify the global market, helping put the UK at the forefront of crop science. However, this Act does not apply to transgenic (GM) crops, meaning that UK innovations with enormous potential, for example blight-resistant potatoes, are highly likely to be marketed elsewhere.

5. <u>How should engineering biology be regulated?</u>

Is the current regulatory framework adequate? Does it strike the right balance between encouraging innovation and ensuring safety? Where should any reforms be enacted?

There may be an opportunity for the UK to develop its own regulations that could be less restrictive and less cumbersome/ bureaucratic. This is being explored through the Regulatory Horizons Council and the Pro-Innovation Regulation of Technologies Review, with innovative proposals like regulatory sandboxes.

The question of regulation is too often broached only at the end-stage of projects, when commercialisation is envisaged, whereas it should be a two-way street proceeding throughout the research path: where research informs what regulation is needed and regulation responds proactively and in an agile manner.

There is also a lack of space and funding for research that explores the regulatory context as a topic in its own right: it is too often left to be dealt with solely by (often overworked) regulators. A more nimble regulatory system can only be created if it is *co*-created, by regulators, researchers and entrepreneurs working together.

6. <u>What are the possible barriers and limitations to good and effective use of engineering biology?</u>

What is already known about the likely limitations of engineering biology due to limits in our scientific understanding? Are there areas that would benefit from more fundamental research before those limitations might be understood? Are some suggested applications implausible?

One longstanding limitation to the field has been the lack of standardised and quantitative characterisation for the genes and proteins that are discovered through fundamental research. There are effective incentive structures already in place within academic institutions to report novel associations or broad functional roles, but no similar system to reward researchers for characterising to the depth that would be needed to make engineering possible. For example, a fundamental research study may report a new cytokine that is correlated to cancer prognosis, but information that is essential to engineering with that cytokine (such as its kinetic rate constants of binding, degradation rate, and synthesis rate) would not. This means that we lack the input data necessary to truly model and engineer biological systems in a rational way. There should be support for systematic data-gathering initiatives that do not fit in the current incentive structure.

A systems approach has the potential to significantly advance the engineering of synthetic biological systems, ensuring their functions are predictable. Currently, the performance of engineered biological systems varies depending on context, necessitating further investigation. Integrating fundamental principles from control engineering would enhance their robustness and reliability.

Engineering biology and scientific understanding are not mutually exclusive. Engineering Biology encompasses and contributes to scientific understanding via design-build-test-learn cycles. Similarly, synthetic biology approaches are being applied to investigate fundamental scientific questions. Importantly, Engineering Biology is in its infancy. We have not yet made sufficient progress to know what is possible and where the limits might be. Although immense progress has been made, the achievements of the last 20 years are only the beginning of what will be possible in the next 10-30 years. We are a very long way from being able to predict what the limits will be.

What more can the Government do to foster public understanding of engineering biology? Is public acceptability of these technologies a barrier to deployment in the UK?

Framing this as "public understanding" and "public acceptability" risks repeating past errors, as with GM controversies. In those "knowledge deficit" models, the assumption is that the public simply does not understand enough about the science, and the remedy is to explain it at length.

Instead, social science research points towards public *engagement* as a more worthwhile activity. These kinds of bi-directional participatory efforts centre around understanding what publics value and giving them a say in how that value is realised; it gives them a stake. These need to be *conversations* rather than *education*.

There are multiple reasons for involving the public in dialogue around engineering biology – normative, in that wider society will potentially be affected by developments in the science and should thus have a say in their desirability, and substantive, in that listening to patients, consumers and citizens may help focus research on areas of most societal benefit. However, efforts to include the public in the UK also need to acknowledge the long-term legacy of debates about biotech and genetically modified crops. While the continued salience of these debates for the public is not clear (and is a topic worthy of empirical study) it still shapes the discussion around public engagement and involvement in this space.

There are multiple points at which we might include the public in the conversation, from the planning and funding of engineering biology projects, to establishing norms for the forming of public-private consortia, to discussing the value and potential limits of open science approaches.

The Government should also ensure that the UK's regulatory bodies are sufficiently supported to recruit technical experts to conduct horizon scanning exercises and to engage with academia and industry on emerging technologies. Importantly, the Government should ensure that regulatory agencies are transparent, trustworthy and functional, and that they prioritise social and environmental health and welfare. If public trust in the regulation of essential services such as waterways is eroded, for example by the ongoing sewage crisis, this will impact public trust in the regulation of more complex technologies.

Does the UK have a sufficient skills base to harness the potential of engineering biology?

Engineering biology research requires a well-trained and experienced workforce, one that can make the mental leap from discipline to discipline. However, very few engineering students will have heard of engineering biology.

A well-trained workforce will require undergraduates and MSc graduates from biological science, computer science, chemistry, and training in mathematical modelling, machine learning and bioinformatics. However, advanced statistics, computational modelling, machine learning and AI, and biochemical modelling are often lacking from many MSc level courses. Collaborative interdisciplinary student biological lab spaces at the undergraduate level will help students develop skills required for the field, beyond what practicals or short research projects can provide. This provision of project spaces is more common in traditional engineering disciplines in universities, but needs to be extended for engineering biology. Innovative approaches to different kinds of education may also help. When pivoting to commercialisation, an academic/research mindset is not usually the right fit, an apprenticeship model may be more suitable. As an example to remedy this, Cambridge Science Park is building a technical education hub. We also need highly trained technical specialists.

Many of the workflows we use such as routine tissue culture, media prep etc., would be well suited to T-level, apprenticeships, or degree apprenticeships.

Where the UK lacks the skills required for engineering biology, talent from outside the UK must be attracted. Recruitment in this area of science is already globally competitive and the UK offers non-competitive salaries for academics. The short term nature of many postdoctoral contracts and grants generates instability for researchers across fields, but, especially importantly for engineering biology, can mean both that more adventurous projects are not targeted and that skills are lost. Further, immigration policies are adding an unnecessary burden of restrictions and additional cost and bureaucracy. This presents a major disincentive and early career researchers are no longer considering the UK as an attractive career destination. We cannot achieve science superpower ambitions without international collaboration, facilitated by a multinational workforce.

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