EBNet Response to
Engineering Biology Consultation Questions

1. About you

1.1. If you are happy to do so include your name and organisation here.

Environmental Biotechnology Network (EBNet, www.ebnet.ac.uk)

1.2. What kind of respondent are you? Tick all that apply.

- Other

  If 'other', please explain your answer.

  EBNet is a UKRI-funded Network in Industrial Biotechnology and Bioenergy (NIBB) - see https://www.ukri.org/what-we-do/supporting-collaboration/supporting-collaboration-bbsrc/research-networks/networks-in-industrial-biotechnology-and-bioenergy-bbsrc-nibb/

  Our remit focuses primarily on engineered microbial systems for environmental protection, bioremediation and resource recovery, including both pure cultures and complex microbial communities.

1.3. Please select the nation or region you are headquartered

- South East

1.4. Which application areas do you consider yourselves involved with? Tick all that apply.

- Chemicals and materials
- Renewable fuels
- The environment
- Underpinning technologies

2. Public interest & uptake of engineering biology products

2.1 How do you approach building the public's interest and uptake of innovations and products derived from engineering biology? What are the factors to consider when going about this?

EBNet uses a number of formats and strategies to raise awareness within its own remit, including animations, videoclips, public outreach activities (including Glastonbury, BBC Countryfile Live and various public events), and sponsorship of a short story competition under the Green Stories initiative: see www.ebnet.ac.uk.

A series of short 'explainers' on key technologies is in preparation, to help people understand key technologies within our remit.

2.2 Where and how are government, industry and academia each best placed to build public interest, and more broadly uptake of products? How can we involve the public in this conversation? What can we learn from other countries?

Whilst some early adopters are prepared to pay a premium for new processes or products, broader uptake generally needs a competitive price or regulatory advantage over the status quo. This requires consistent long-term policy, a supportive regulatory regime and a strong investment culture. Government has a key role to play in each of those aspects. Long term policy provides investors with confidence. Both market mechanisms and incentive support are important. As a recent example, market building initiatives such as the Renewable Transport Fuel Obligation (RTFO) encouraged development of a supply chain: however, the RTFO market for biomethane had no floor price and therefore growth was extremely slow, as there was little investor confidence. When the 'new' Green Gas Support Scheme was set up, it allowed investors to switch between schemes and this improved confidence as well. The market (industry) will respond if the conditions for investment are aligned with policy needs.

The regulatory focus on 'waste' and 'end of waste' does not align well in a circular economy model where resources need to be recycled, and the concept of a 'regulator' rather than a 'facilitator' may even suggest discord. With new technologies, public health and safety can be maintained through co-development of collaborative models, coupled with real sanctions for those in breach.

Funding in the UK has historically struggled to take many innovative companies through the 'valley of death', particularly where longer supply chains need to be created. Long term policy helps greatly, but UK lenders are notoriously 'short-termist' and looking at a 2-5 year exit strategy. A tax/investment regime to foster longer-term capital investments would be helpful.

Industry is best placed to build public interest and uptake of new products and technology by cooperating with outside organisations, including regulators and academia, to demonstrate independent validation. In the field of environmental biotechnology it can also showcase successes and demonstrate how investment in R&D has paid off with progress in dealing with environment/product/pollution pathways to help connect these apparently abstract concepts with real life events

Academia can inform progress throughout the technology readiness levels from *deep science through to demonstration, commercialisation and deployment. It is, however, necessary to ensure a degree of alignment between Research Councils and Innovate UK in order to transition research smoothly to commercialisation, particularly as the UK is weak at supporting technology companies through the 'valley of death'.*

Whilst public interest tends to remain largely divorced from much of this work, Citizens' Assemblies have proved useful to inform people, gauge public interest/opinions and spread the word on complex and nuanced issues, particularly where there are ethical considerations. Additionally, there has been relatively little activity (outside the Covid-19 pandemic) in sponsored social media where information and good news stories could be disseminated. Many academics and industry people use social media to promote their work, but their focus is, by definition, elsewhere. The NIBBs, for example, use social media but not sponsored advertisements, as this would likely be outside their funding remit. This applies across all TRLs from fundamental science through to pre-commercialisation and beyond. Public interest generation through such means is arguably less important, however, than the creation of strong markets for products as described above.

3. UK value chain for engineering biology

3.1 With regards to the whole sector, what do you think the UK's key strengths are in engineering biology?

The UK is home to concentrated high-level integrated expertise in this area, particularly at the lower TRLs, including fundamental sciences. Engineering biology approaches are inherently complex and are beyond some countries' reach because of the high barriers to entry: skilled and highly-educated people working in interdisciplinary environments within a biotech ecosystem under a strong regulatory framework are needed to exploit the most promising technologies and convert them into solutions that can then be deployed elsewhere.

3.2 With regards to the whole sector, what do you think are the UK's key challenges over the next five years?

Challenge of improving join-up between science and engineering aspects, especially within academia.

Challenge of funding and carrying out scale-up work for TRL progression

Challenge of developing [and gaining acceptance for] agreed principles and methodologies in Life Cycle Sustainability Assessment of new technologies, especially when comparing biologically-based technologies with alternatives

Challenge of ensuring that the policy and regulatory frameworks protect human health and safety, while still facilitating the introduction of new Engineering Biology approaches and products.

Challenge of maintaining a strong international reputation as a go-to location for biotech expertise

3.3 Detail your own personal experiences with the engineering biology value chain outlined below. Where do you source these inputs to your work? What difficulties have you experienced? And what do you think needs to change? Please mention where appropriate any scientific and technical advances required. (Fill in any which apply, 500 word limit)

- **Small scale equipment:** All hardware needed for proof of concept, from pipettes, glassware, benchtop centrifuges, through to autoclaves and automated platforms such as liquid handling robots.

  Apart from cost, no major difficulties reported at TRL 1-5 scale

- **Pilot scale assets:** The equipment and skills needed for running pilots and proof of scalability for engineering biology services and products.

  This is a significant bottleneck: the difficulty of moving from laboratory to pilot scale often blocks progress through the TRL and contributes to the valley-of-death in converting new discoveries into functioning technologies. The issue is especially significant for biotechnologies that show strong interaction between microbial performance and engineering characteristics of the system (mixing, mass transfer etc). Previous support to provide scale-up facilities has not always been as effective as all parties would like, due to cost and other factors.

  It should be noted that companies in the water and waste management sector tend to be cautious in adopting new technologies, being responsible for outcomes at large scale. Pilot-scale testing is a crucial stage in mitigating this, especially if set up in conjunction with the relevant industry partners. But risk aversion in the environmental biotechnology sector needs to be taken seriously at all levels if the UK is to be a forerunner in developing and adopting innovations. In reality, companies may need additional support to try new things before altering an existing process. An open, exploratory attitude on all sides supported by funded opportunities for staff exchange and training is helpful in this respect, to ensure effective transition across this critical stage.

- **Mass Manufacturing assets:** The infrastructure and the skills needed to construct and maintain the equipment required to produce engineering biology services and products at commercial scale (e.g. bioreactors >100 kL)

  The UK has some strong companies in this area, major difficulties are continuity of skills and staffing and attracting young people to work in this area

- **Biological materials and reagents:** Pre-processed intermediate commodities. This includes enzymes, chemicals, biological chassis, strains, and media supplements.

  No major difficulties reported at TRL 1-5 scale

- **Feedstocks:** The largely unprocessed primary commodities and processed primary commodities for media. This includes biomass.

  No major difficulties reported at TRL 1-5 scale

- **DNA sequencing and synthesis capabilities:** The equipment and suppliers for DNA sequencing and synthesis, as well as of other nucleotides.

  Cost can still present some obstacles although this has improved over the past 5-10 years and seems to be moving in the right direction

- **Diagnostics:** The equipment for diagnostics including for quality assurance and control

  There is major scope for further development of online sensors, continuous monitoring and control systems: additional support is needed in this area as companies are often reluctant to invest in products until they are well established

- **Omics and compute:** Both the hardware such as servers, GPUs, and high-performance computer clusters, and the software and data used for bioinformatics, omics, and any other program required for your work from simple scripts through to machine learning platforms.

  Many organisations including universities have invested in high-performance computing (HPC) assets; these can still have long wait times, however, leading to significant delays to projects: our members have quoted timings in excess of 62 days. Access to multi-GPU/CPU cloud computing facilities such as those provided by Oracle, Google etc, can make a big difference to the ability of scientists to process this information in a timely fashion. With modern Oxford Nanopore sequencing, terabytes of data can be produced every hour, and this has revolutionised the speed of sequencing and the potential to better understand complex microbial systems. However, with such large amounts of data, cloud computing significantly speeds up the processing time: we believe that scalable cloud-based solutions will be crucial to next-generation gene assembly, characterisation and analysis.

4. Knowledge pipeline

4.1 Within your domain, what are the key scientific and technical opportunities over the next five years for advancing the development of engineering biology, including its foundational technologies?

a. *Biosensors for improved environmental monitoring, and for use in microbially-mediated treatment systems.*

b. *Developing techniques to enhance performance of established treatment technologies, based on manipulation of synthetic, hybrid and natural microbially-mediated communities.*

c. *Developing new treatment processes with improved resource footprint.*

d. *Enhanced ability to predict the resilience or otherwise of new approaches in 'dirty' systems with mixed culture, immigration etc, based on fundamental principles.*

e. *Developing new approaches to tackle emerging and intransigent pollutants.*

4.2 Within your domain, what are the key scientific and technical challenges over the next five years for advancing the development of engineering biology, including its foundational technologies?

EBNet welcomes consideration of a wide range of approaches, including genetic manipulation of micro-organisms, to address environmental challenges: for a round-the-clock industry with 8 billion customers, it is vital to develop robust, effective and affordable technologies. Too narrow a focus on genetic manipulation, however, may risk diverting attention onto a rather limited group of organisms and pathways that are familiar and easy to work with, while missing huge potential in other areas. Excluding complex systems and unfamiliar organisms is an unwise strategy when knowledge is expanding so rapidly. One relevant example is provided by the anammox (anaerobic ammonia oxidation) process: this was only identified in the 1990s, though it is now considered to be responsible for up to 50% of oceanic Nitrogen cycling. Since its discovery, it has been developed into a full-scale commercial treatment technology, while laboratory studies continue to reveal new anammox pathways.

Key scientific and technical challenges for the next 5 years thus include the following:

a. *Broadening the range of tools, techniques and approaches beyond the existing pool. Many microorganisms cannot currently be grown in the laboratory, and others require mixed culture for syntrophy to occur. Tools for genome manipulation do not yet exist in many cases, while those for mixed microbial community metabolomics analyses are less well developed than those for genomics/metagenomics. Without further* *attention and support this lack of breadth is likely to inhibit the range of Engineering Biology outcomes.*

b. *In 'dirty' systems such as those used in environmental biotechnology, factors like immigration and competition are hugely important: this is currently an exciting research area in its own right and needs recognition and support.*

c. *Enhancing our knowledge and understanding of interactions between system biology and its engineering envelope is challenging and depends on support for cross-disciplinary work at appropriate scales*

d. *Handling the vast amounts of data associated with analysis of mixed microbial communities, both alone and in relation to physico-chemical, hydraulic and other aspects of their environment, requires development of advanced multi-scale modelling approaches.*

See also response to section 4.3.

4.3 What works well within the current landscape of UK research institutions? What is missing? Are there examples from other countries we can learn from?

Collaboration between UK research institutions in this sector and between departments with different specialisms is generally good. The main missing item is a ***clear definition of the term Engineering Biology*** *as currently used by funding, policy-making and regulatory bodies. Does it encompass the full range of Engineering Biology tools, including genetic, metabolic, biomolecular and microbial community engineering, or only work involving the use of GM organisms? Members of EBNet report having proposals rejected as out of scope due to an absence of such organisms, even though they were regarded as fully relevant and eligible by others working in this field.*

Uncertainty of definitions is not a trivial point when it can determine which areas have access to funding, and which are ruled out. There is evidence of blurring even within this consultation document ("UK firms using engineering biology received over $3 billion... and UK ranked 4th by number of modern industrial biotechnology companies"). Is Engineering Biology a synonym for industrial biotechnology (of which Environmental Biotechnology is a major subdivision), or a sub-set of this using a group of approaches - or a much narrower discipline, focused only on GM organisms?

If a broader definition is intended, then much clearer guidelines are needed for those making recommendations and decisions in this area: additional calls to look at specific aspects based on synthetic biology techniques but do not focus exclusively GM organisms could also be beneficial in addressing this. If the use of GM organisms is an essential requirement, and other approaches are not included, much more effort is needed to clarify when such systems are potentially applicable and when they are not or are not the most promising approach for fundamental scientific or technical reasons.

The cross-disciplinary nature of engineering biology means it is helpful to bring together experts from different backgrounds and institutions. The Network or Hub approach provides a focus for this and has proved extremely useful in supporting early career researchers, facilitating interactions between universities, and also creating links between government, regulators, industry and academia. EBNet has more than 1300 members and with its sister networks has enabled access to a vast number of UK and worldwide stakeholders.

5. Talent and skills

Talent refers to influential named individuals and our ability to attract and retain them. Skills refers to the development of scientific or technical capabilities through training for the wider workforce.

5.1 In order for your domain or the domains of those you represent to develop, scale and commercialise products derived from engineering biology, what are the key technical and non-technical skills?

Technical: Expertise in crossover areas between fundamental sciences and engineering. The level and breadth of talent and skills required for innovation in engineering biology is at least on a par with that required for the pharmaceutical industry. We too need chains of people with skills that range from the genetic, biochemical, whole cell, complex system, engineering/chemical engineering though to industry application level.

Non-technical: Entrepreneurship, and expertise in technology transfer, contracts, intellectual property rights; funding; business skills; networking and the development of strong, reciprocal links between industry and academia.

5.2 Please indicate what is working, not working or not to a sufficient scale.

Scale 1= working well, 3= working but not to a sufficient scale/remit, 5 = not working or not happening, 6 = not relevant to me

- Support for early-career researchers [1]
- Support for mid-career researchers [3]
- Support for late-career researchers [1]
- Programmes to support technicians' careers [5]
- Programmes to support regulatory skills [3]
- Programmes to support entrepreneurship [1]

Please explain your answer

Initiatives like the Networks in Industrial Biotechnology (NIBBs) are providing strong support for ECRs: the challenge is to ensure this continues after the end of the current Phase II NIBBs. In general, late-career researchers are fairly well served in terms of funding and other opportunities to ensure their work makes an impact. Mid-career researchers in the UK University sector face difficulties in continuity of funding or, if they switch to an academic pathway, huge pressures which invariably squeeze the time available for research and for profile-building. Technical careers in the academic sector are hindered by lack of opportunities for development, although industry has a little more flexibility.

When technologies start to move up the TRL toward real-world applications, regulatory bodies such as the Environment Agency are often lacking in appropriately skilled staff and/or too resource-constrained to develop appropriate new monitoring and regulatory strategies. Oversight is crucial; and regulators need to develop the institutional expertise needed to match that of the innovators in order to allow them to respond nimbly to initiatives in this sector.

Some entrepreneurship skill training is offered at various levels by a range of organisations, including the NIBBs, but targeted support across the large range of disciplines required (i.e. science, engineering, regulation, funding, policy, etc) is necessary to support such businesses and there is no 'one-stop-shop' or main point of contact to do this.

6. Business ecosystem

6.1 How do we create mechanisms which bring engineering biology small and medium enterprises (SMEs) together with their customers (including larger firms) in a way that promotes a clear understanding of each others' requirements? What are the barriers to this in practice? What can we learn from other countries?

The NIBBs provide a valuable means of bringing together SMEs with larger industrial partners who are potential end users of new technologies. Successful mechanisms used by EBNet include specialist webinars, which can be more popular than face-to-face meetings if they reduce travel time and allow people to dip into the subject or event; and Working Groups which tackle a variety of tasks in different ways. Barriers include identifying relevant or potentially interested individuals in large companies, especially in the water and waste management sectors; this usually requires dedicated messaging i.e. inputs of time, expertise and use of personal contacts.

6.2 How is your firm considering overseas production of your products, or exporting to international markets? What are, or would be, the implications of these decisions for your UK-based activities?

Many SMEs are not able to consider the costs and logistics associated with overseas production or international markets if they do not have a stable business at home. We are aware of members who have moved part or all of their operations overseas, citing reasons such as better funding opportunities (consistent, long-term capital investment), as well as more flexible and reactive planning, regulatory and/or permitting regimes. A recent lack of long-term and clear policy in the UK green/circular economy space, as well as political 'churn' has created a lack of investor confidence in this field.

It should be noted that UK universities in general, and organisations like EBNet in particular, host and/or interact with large numbers of international PhD students/academics in this topic. After completing their studies, some PhD students stay and work in the UK, while others return but maintain strong UK contacts for the future.

6.3 At what stage and investment size have your company (or those you represent) found it challenging to raise finance? What were the barriers you faced at each of these stages? How did you solve these barriers?

Difficulty level 1= secured investment with relative ease, 3 = challenging but achievable, 5 = very challenging, 6 = don't know or not relevant

- < £500K [1]
- £500k - £1 million [1]
- £1 million - £2 million [3]
- £2 million - £20 million [5]
- £20 million + [6]

Please explain your responses

This question is not directly applicable to EBNet itself, but the response is a qualitative summary based on members' comments (including those in the academic sector)

7. Regulatory environment

7.1 Do you expect, or have you encountered, any specific regulatory issues when developing, scaling and commercialising products using engineering biology? Please provide as much technical background as needed to fully explain the issue, and an outline of how you navigated the regulatory system.

EBNet members have repeatedly raised regulation and permitting as an issue for new environmental biotechnologies and based on this, we anticipate a number of issues. We are aware of at least one EU funded project where, due to EA resource constraints on creating a permit variation, approximately 24 months passed, and the project lost its opportunity to deploy its demonstrator. The partners were forced to take a different approach in the end, and a lot of time and project value was lost. We are also aware of several small-scale technology providers who have been unable to deploy their systems in the UK, in part because the policy/regulatory framework favoured large installations, but also because there was no low-risk position in place for 'end of waste'. The regulations in this area are complex. For example, a dedicated energy crop may not require Environment Agency permitting or intervention; if some of the crop is used for food and the rest used for bioenergy production, this may increase the permitting level; if the crop is placed in a farm shop but left unsold, an even higher permitting level is required. The higher the permitting level, the higher the cost. Testing associated with achieving quality protocols may also be too expensive for smaller systems.

EBNet Network Managers have advised on several projects that were trying to springboard a technology out of a university environment. We are also aware of difficulties in obtaining advice and support where the market for a product is still nascent.

Oversight is also crucial: regulators need to be as well-equipped as the innovators in terms of skills, and to have or develop the institutional expertise needed to understand and respond nimbly to initiatives in this sector.

7.2 How should government look to influence the development of international regulations, standards, and norms to help grow the UK sector and protect the UK's capabilities?

Regulations, standards and norms in the Engineering Biology sector will need constant revision as applications at scale come to the market. Other regulations will need to be created rather than revised, as entirely new *approaches come into being. As a strong international presence in this sector, the UK should be in a leading position to help shape the ISO regulations and standards for Engineering Biology applications. Government needs to increase its support for participation in appropriate bodies, for example by funding industry and academic input and facilitating secondment of staff from regulatory and policy-making bodies.*

8. Future expectations

8.1 For your own domain or the domains you represent, please select the top three areas from the UK's Science and Technology Framework you would want government to prioritise in any future plans for engineering biology. These are outlined further in The UK Science and Technology Framework linked here.

- **Investment in research and development:** Focus UK R&D investment to match the scale of the Science and Technology Superpower ambition, and have the private sector take a leading role in delivering this.
- **Talent and Skills:** Secure a large, varied base of skilled, technical and entrepreneurial talent which is agile and can quickly respond to the needs of industry, academia and government.
- **Financing innovative science and technology companies:** Improve access to capital at all stages with increased participation from domestic investors, and an environment to grow and scale large globally competitive science and technology companies that drive growth in the economy and high-skilled employment opportunities for citizens.