Bristol BioDesign Institute, University of Bristol – Supplementary written evidence (ENB0043)

This written submission is in addition to the oral evidence provided to the Science and Technology Committee on April-16 2024 by Dr Lucia Marucci and developed by leading researchers in the fields of synthetic and engineering biology at the University of Bristol (Dr Kathleen Sedgley, Dr Lucia Marucci, Prof Claire Grierson, Prof Ross Anderson, Prof Imre Berger, Prof Ash Toye, Prof Dek Woolfson and Dr Kerstin Kinkelin), in collaboration with professional services staff. On request, further information can be provided.

Executive summary:

Academic research institutions, and the fundamental research they produce, are the foundation of synthetic and engineering biology within the UK. The University of Bristol (UoB) is a leader in this field. The Bristol BioDesign Institute (BBI) co-ordinates the University's synthetic and engineering biology research, training, and innovation activity, and oversees the underpinning strategic partnerships. With wide-ranging applications across **healthcare**, the **bioeconomy** and the **environment**, the BBI exploits pioneering approaches to deliver the rational design and engineering of biological systems for useful purposes. This is achieved through multidisciplinary research which brings together postgraduate and postdoctoral researchers, academics, policy makers and industry, whilst also engaging the public with emerging solutions to global challenges.

The economic opportunities afforded by developments in engineering biology are incredibly promising. Bristol has an excellent track record of helping develop **spinout/startup companies** on the back of its research. Aided by the flourishing engineering biology environment within the Southwest, these startups have proved commercially successful. The growth of these small companies, however, requires further support from UK Government.

We have addressed questions 1,2,3,5 and 7 where we make the following recommendations to support engineering biology within the UK:

- There is a pressing need for long-term, 'high risk, high reward' funding for fundamental research without the pressures of immediate translational activities.
- More funding should be made available for startup incubators. If the Government cannot fund fundamental engineering biology research, instead it must work to promote the UK's capabilities internationally to attract further investment from the private sector.
- Though UK research institutions are currently world leading, research staff retention is an issue with the potential to harm our fundamental research capabilities. Efforts should be made to support universities to attract and retain experts.
- The Government must be made/more aware of risks posed by development in engineering biology. Policy and regulatory focus areas include how DNA synthesis companies operate and the kinds of research being conducted at universities.
- There must be better collaboration between academia, industry and government. This should be achieved through academic representation on the UK Biosecurity

Leadership Council, Regulatory Horizons Council and the Engineering Biology Steering Committee.

- The UK's computing power resources must be increased for engineering biology to flourish. This can be addressed with continued funding for the opening of new facilities (such as the new national Isambard-AI facility which will be hosted in Bristol) and the development of existing facilities.
- Engineering biology research must consider public needs and concerns, otherwise public perception of engineering biology research could be a significant barrier to impact.

Q1: What are the UK's key strengths in the area of engineering biology?

The UK's current strengths are in fundamental engineering biology research and a strong research-translation ecosystem, which benefited from the substantial investment via the Government's Synthetic Biology for Growth Programme (2014 – 2022), leading to UK-wide capabilities including six Synthetic Biology Research centres and one Innovation and Knowledge Centre across the country. Of these six, four remain at the forefront of UK's engineering biology research capability: Bristol, Edinburgh, Imperial and Manchester.

Bristol's Engineering Biology Portfolio: The UoB is at the leading edge of advances in synthetic and engineering biology having secured a lifetime grant income in the field of over £180M GBP, including:

- EPSRC/BBSRC Bristol-Oxford Engineering Biology Centre for Doctoral Training (CDT) (2024-2032, £13.9M), predicted >68 students, 29 industrial partners. This builds on the previous Oxford-Bristol-Warwick Synthetic Biology CDT (2014-2023, £6M). The EngBioCDT is the only dedicated engineering biology PhD programme in the UK. The EngBioCDT will work closely with industrial partners to train and prepare the next generation of researchers.
- BrisEngBio Bristol Centre for Engineering Biology (2022-2024, £1.5M), funded by the UKRI National Engineering Biology Programme. BrisEngBio is the evolution of the UKRI-funded Synthetic Biology Research Centre, BrisSynBio (2014-2021, £18.7M), which published more than 600 research papers, enabled the incorporation of nine engineering biology startups (which have collectively raised over £20M and employ > 50 staff) and leveraged additional funding of over £100M.
- Max Planck Bristol Centre for Minimal Biology (2019-2030, £8.7M): Max Planck Society-UoB co-funded international research centre at the interface between the physical and life sciences.
- Partnership with deep-tech incubator, 'Science Creates', to deliver the UKRI-funded Engineering Biology Accelerator.
- A current grant portfolio of ~£60M including: two EPSRC Synthetic Biology Fellows, a Royal Society University Research Fellow, two ERC Advanced Grants, a Wellcome Senior Investigator, a BBSRC-funded European Network in Computational Protein Design and two BBSRC strategic Longer Larger (LoLa) awards, and two EPSRC Programme grants.

Economic Impact: Developments within the field of engineering biology present an economic opportunity for the UK. The outputs of research institutions are already resulting in new startup/spinout companies with potential for growth.

- The UoB is nationally recognised for knowledge exchange, technology transfer and research commercialisation. Bristol's success in translating research to industry comes from a strong regional ecosystem for commercialisation. It is in the UK top 3 by number and value of deals secured by spin out companies (Beauhurst 2022) and top 5 for life science spinouts. (Beauhurst 2021). Regarding engineering biology, 4 of the 8 UKRI exemplar Engineering Biology Impact Case Studies come from members of BrisSynBio. This vibrant environment for engineering biology innovation has also attracted SMEs from outside of Bristol to startup in, or relocate to the region, e.g. Folium Science, Imophoron, and Extracellular. Investment in fundamental research at academic institutions like UoB directly results in industrial innovation.

- In order for startups to scale, they must be supported. This could involve a UK network of local (or at least regional) deep-tech innovation scale up suites that provide space, access to relevant facilities (either in house or in partnership with local industry and/or universities), training and acceleration programmes, investment, and access to industrial networks.
- Large companies are essential to achieve some of the impacts of engineering biology at scale. This includes co-location models between academia, industry and start-ups that can facilitate the creation of a supportive environment to enable the translation or transfer of knowledge.

Q2: What are the key applications for engineering biology?
The UoB is a global leader in fundamental research within engineering biology.

1. **Computational biomolecular and systems design.** The Editorial: Computer-Aided Biodesign Across Scales (2021) describes the opportunities in 3 main areas.

- ***De novo* molecular prediction and design:** At the molecular level, the design of proteins and DNA sequences pose many challenges, but reliable modelling at this level will offer the means to scale-up bio design, moving our focus from single molecules to complex multi-component systems. To make this step, modelling and design tools need to be able to replicate experimental data. This is the biggest challenge at the moment, bridging the gap between computational model and experimental data and more work is required to bring disciplines together to understand each other and work collaboratively.
- **Toward the design of cell-free systems and whole cells:** The potential to describe and build whole-cells *in silico* (i.e. computer simulation), representing and integrating all cellular functions within a unique computational framework, offers an opportunity to develop increasingly automatized, precise and accessible CAD tools and strategies. A proof of concept using genome minimisation (Lucia Marucci, Computer-Aided Whole-Cell Design: Taking a Holistic Approach by Integrating Synthetic With Systems Biology (2020) presents a perspective on how whole-cell, multiscale models could transform design-build-test-learn cycles in engineering biology as well as the technical challenges to achieve this.
- **Computer-aided biodesign beyond single cells:** Most engineering biology efforts to date have focused on the design of individual cells with basic functionalities (e.g., implementing basic logic). However, outside the lab, cells rarely exist in isolation. Their ability to interact through chemical signalling, and the inherent heterogeneity in cellular states across a population due to environmental perturbations, can act as a basis for important collective behaviours. These emergent properties need to be understood even for simple synthetic circuits to function reliably. They can even be exploited to create more robust or scalable distributed biological computations. However, designing individual cells to exhibit desired population-level behaviours is challenging, requiring novel computational and theoretical approaches. A perspective on how some of these challenges could be overcome by using multi-agent modelling as a design framework within engineering biology is presented in the paper Toward Engineering Biosystems With Emergent Collective Functions (2020).

2. Advanced Therapies and Precision Medicine: We anticipate significant advances by 2028 in engineering biology applications in the healthcare sector. Bristol's innovations at pre-clinical stage include:

- **Scarlet Therapeutics** is developing a pioneering platform that generates red blood cell-based therapeutics (tRBCs) to potentially treat a wide range of diseases.
- **Imophoron** is changing the way we make vaccines with a next-generation nanoparticle vaccine platform called ADDomer™.
- **ADDovenom Project** is developing a snakebite therapy platform of unparalleled efficacy, safety and affordability.
- **Puresprings** is leading a revolution in the treatment of kidney diseases by directly targeting the podocyte with Adeno-associated virus (AAV) gene therapy.

3. Development of advanced materials: Bio-based and sustainable composite materials with multiple functions have been developed at UoB using engineering biology. This includes composites of natural fibres (flax, hemp, cactus, wood) with recyclable thermoplastics (PLA, PP) or algae-based hydrogels, silica and diatomaceous reinforcements. Living and self-adaptive adhesive interfaces for natural bio-based and fossil-fibre composites have applications across a number of sectors, including defence, transport, biomedical and robotics. The future will include intelligent and living interfaces that self-repair, exploit bio-hybrid properties, and are reactive with intrinsic computation, for example:

- **3D Printable Memory Matter in Sustainable Engineered Living Composites**: Producing thermo-responsive, self-healing gels that are reinforced with natural fibres to bestow mechanical and memory matter characteristics for industrial use.
- **BioReplication for Optical Coatings and Light Intendance:** Learning from the nano and micro-structure of plant epicuticular waxes to inform applications in solar or light harvesting technologies.

Q3: How can Government policy support the development of engineering biology?

The Government's "National Vision for Engineering Biology" is a good start point from which to develop a strategic plan for UK Engineering Biology. It builds well on the momentum established via the Synthetic Biology for Growth and National Engineering Biology Programmes. As noted in the Vision, short-termism in funding across the field over the last 5 years has been problematic. Compressed time frames between grant application, award and set up have presented significant challenges in the volume and pace of administration for both funders and applicants. For example, official notification of funding is often not received until after grants are required to start which makes it impossible to negotiate contracts with academic or industrial partner organizations to initiate recruitment processes, all of which results in 'dead-time' whilst the clock is ticking on time-limited grants.

We welcome the aspiration to prioritise longer term funding for underpinning discovery research. UKRI funds for engineering biology over the last few years have either been short term (up to 24 months) or mission-driven. Whilst mission-driven projects are a crucial component of the broader UK engineering biology ecosystem, we believe there is a pressing need for long-term, "high risk, high reward" funding for fundamental research without the pressures of immediate translational activities.

The Government can support long term and impactful development in engineering biology in the following ways:

- **Fundamental research funding.** As reported by Sir Paul Nurse (2023), in order to remain at the forefront of engineering biology, *"There is a pressing need for more complete 'end-to-end' funding of research activities beyond direct research costs, including adequate support for administrative services, sophisticated technical cores and facilities, and for 'well-found' laboratories"*, i.e. we need better appreciation of and funding for the underpinning fundamental research.
  The UK has done well to invest early in engineering biology; however, this should continue for both fundamental research as well as translational activities. Nearly 60% of all funding for engineering biology in the United States has come from DARPA, an agency known for supporting high risk, high reward research. The UK should aim to fund research (and research support functions) in a similar fashion.
- **Translational research funding.** The (lack of) availability of suitable funding to support research translation is not limited to engineering biology, however dedicated engineering biology follow-on funds would address some specific issues. For example, the multi-disciplinary nature of engineering biology which can 'fall between the gaps' across funders, and which feeds into multiple different sectors.
- **Market failure in laboratory space.** The UK is limited by geographically unbalanced access to infrastructure, with high prices driving out start-ups and disconnecting them from their academic communities. Grow-on-space is in particular demand for the scaling up of engineering biology start-ups.
- **Recruitment and retention of research and specialist staff;** this is seen with international, post-doctoral and regulatory specialists in particular.
- **Maturity of the regulatory sector.** Engineering biology creates novel technologies and applications that do not fit easily into current regulatory and legislative frameworks, leading to delays in bringing innovation to market due to confusing and inconsistent regulatory landscapes.

We believe the following Government departments should be particularly engaged in engineering biology and supporting its development: DSIT, Home Office, DEFRA, MoD including Dstl, DHSC, DoE.

Q5: What are the risks posed to society by engineering biology?

The field of engineering biology is developing rapidly; however, regulations are not keeping up with this development and are not/will not be fit for purpose.

Risks: The commercial DNA synthesis industry allows sequences of genetic material to be 'made to order'. At present DNA synthesis companies are voluntarily self-regulatory and monitor the genetic material they are being commissioned to produce. They verify customers' identities and monitor orders to ensure sequences that could cause harm aren't released inappropriately. With developing technologies, however, this model of monitoring is insufficient. Harmful material can be purchased and used in such a way that public health is put in significant danger:

The application of AI to biomolecular design presents significant challenges. The possibility that malicious actors/groups could engineer entirely novel harmful biological material must be acknowledged.

- Although DNA synthesis companies do screen their orders, workarounds do exist. Sequence fragments could be ordered without detection, and it is possible to order parts from different companies that create harmful code when combined. AI could also allow for novel or dangerous genetic material to be developed.
- This is a self-regulated area, and screening is inconsistent across the industry. As the costs of DNA synthesis fall and orders increase it is also possible that companies will be unable to maintain robust and standardised approaches to screening.
- There is additional concern about outsourcing DNA synthesis, particularly where hostile states are involved. Outsourcing makes the UK very vulnerable to disruptions in supply chain, but more importantly this enables these states to accumulate valuable data for free. This is very worrying.

Policy: Government has the ability to influence how DNA synthesis companies operate and the kinds of research being conducted at universities. It is important that industry, government and academia are coordinated and well informed:

- Government should insist on strict monitoring by DNA synthesis companies, which is regularly reviewed and updated.
- The UK must also pay attention to developments internationally. As the UK can only regulate our own engineering biology industry, we must coordinate efforts our efforts internationally. Government should also ensure that regulations around the import/export of genetic material is tightened.
- The UK should support funding into biosecurity research, to stay ahead of the emerging risks and develop solutions. We have the potential to be world-leading in this area.
- There must be better collaboration between academia, industry and government. Academic institutions should be well represented on the UK Biosecurity Leadership Council, Regulatory Horizons Council and the Engineering Biology Steering Committee. Collaborative bodies, such as these, should be better informed of key discussion and developments in the field and our research institutions are a valuable resource in helping to understand and address these biosecurity risks.

University of Bristol risk mitigation activities: The UoB, being aware of the risks associated with developments in the field of engineering biology, has taken steps to mitigate these risks (or explore the ways in which these risks could be mitigated):

- Bristol will host an international conference in late 2024 exploring risks in engineering biology, specifically at the interface of computational protein design and AI.
- The management committee of AIBio-UK network (of which UoB is a partner) is organising workshops focusing on issues pertinent to engineering biology security.
- UK-Swiss Synthetic and Engineering Biology Summit, hosted by the UoB, the UK Bioindustry Association (BIA) and the UK-Swiss Business Hub will cover risks and opportunities in engineering biology for healthcare and environment.
- Bristol's Engineering Biology CDT will provide bespoke training on risks, ethics and responsible innovation to prepare the next generation of engineering biology researchers.

Q7: What are the possible barriers and limitations to good and effective use of engineering biology?

The UK is currently among the forerunners in engineering biology; however, we are at risk of falling behind without coordinated and strategic efforts. Engineering biology is applicable in an international market, and part of the role of the government is to ensure that UK developments are in line with (if not ahead of) those of e.g. the US, China, Australia, opening a global competitive market. The following barriers/limitations should be considered and addressed:

Financial Barriers: Lack of adequate research and development funding will see the UK unable to remain globally competitive in engineering biology.

- There must be a greater appreciation of the value of fundamental research, even where there is no immediate route to commercial benefit. If the Government cannot fund fundamental engineering biology research, instead it must work to promote the UK's capabilities internationally to attract further investment.
- More funding should be made available for startup incubators. UoB and partners Science Creates, a deep tech incubator, investor and accelerator, will open their third incubator in 2024. Investment in the £8.5M OMX incubator has been enabled by a £4.75M award from Research England Development. OMX will provide space for approximately 275 new companies, significantly increasing capacity in the region. There is a need for facilities of this type across the UK. The size, ambition and number of such incubators will help research translate impactful commercial organisations.

Industrial Barriers: Government should encourage investment from the private sector into engineering biology and encourage collaboration in research. UoB currently works very closely with industrial collaborators on engineering biology research. The UK Government should explore incentivising private sector to work with academia.

Technological Barriers: Computing power has been a limited factor for research. Certain research questions (e.g. biomolecular prediction and design) require significant computing power. The pressure on existing high power computing facilities will increase in the coming years. In response to this, the UoB will open the Isambard-AI supercomputer later this year. It will be 10 times more powerful than the UK's current fastest supercomputer and among the most powerful in the world. This will offer a significant boost to the UK's engineering biology research capabilities. The issue of computing power resourcing can be further addressed with continued funding for the opening of new facilities, maintenance and development.

Public Engagement: In order to maintain the pace of development within engineering biology, it is vital that the public are engaging with, and approve of, the UK's innovation activities. As seen with the development of genetically modified organisms (GMOs), poor communication of technological development can inhibit its impact. Public outreach is an integral part of research at the UoB (as recognised in our Vision and Strategy for 2030). Public engagement and responsible research and innovation are also integral to our CDT programmes. By embedding public engagement and responsible research and innovation into our training programmes, we can ensure that the next generation of academic and industrial researchers are comfortable and confident in building public interest and support for socially relevant engineering biology products.

Industrial Engagement: We work closely with companies to understand their research and development needs and have built long-term relationships with industry in a range of sectors. These include: healthcare (Astra Zeneca, GE Healthcare, GSK, Medimmune, NHS Blood and Transplant, Vabiotech), materials (Dstl, Lucideon, Qinetiq), chemicals (Hypha Discovery), agri-tech (Syngenta) and advanced computing (Microsoft, NVIDIA, Oracle). Where academia can bring value is in drawing on public engagement expertise and accessing the funding to develop meaningful research-public-industry collaborations.

Workforce Barriers: Academic research institutions are suffering from recruitment and staff retention issues. Though UK research institutions are currently world leading, experts are being lost to the industrial sector. This harms our fundamental research capabilities. It has also become increasingly difficult to bring in/attract experts from abroad, and short research contracts are primarily to blame.

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