Engineering Biology for the UK

A Resource to help Build Back Better

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Summary

UK Engineering Biology Leadership Council
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CONTENTS

1. Introduction

2020 marked a period significant dislocation of 'business as usual' operating models in the UK - the combined consequence of the Covid-19 pandemic and planning for Brexit, set within the context of ongoing global climate change and sustainability challenges, as will be addressed at COP26 to be held in the UK in November of this year. This also offers unparalleled opportunities to Build Back New, Build Back Better.

In recent decades, the UK has focussed upon, and benefitted hugely from, the 'knowledge economy', powered by increasingly sustainable energy sources. This now needs to be matched by the manufacturing and supply of sustainable chemicals, materials, food and health products – spanning the bioeconomy and supporting the life-sciences - to generate new job opportunities throughout the country and to increase national resilience to uncertain international supply chains and the impact of increasing global challenges.

Market pull, particularly in response to mounting concerns over global sustainability, and stimulated by the setting of new targets such as net-zero emissions, is already producing clear economic drivers. The challenge is now to harness innovative and emerging technologies such as engineering biology to generate commercially viable solutions, accelerating the growth of new companies and assisting the transformation of existing ones in response to the challenges and opportunities arising. The UK Bioeconomy was worth £220bn GVA in 2016, the aspiration is to double this to £440bn over the next decade, with Engineering Biology at its core. Last year McKinsey ('The Bio Revolution: Innovations transforming economies, societies and our lives', 13 May 2020) estimated the global bioeconomy to be worth in excess of $4 trillion, identifying synthetic/ engineering biology as a key platform technology. Recognising its potential, private investments into synthetic biology start-ups and SMEs globally are rising rapidly this year, already over £3.5bn in the first 3 months alone and set to substantially exceed the £5.7bn raised in the whole of 2020.

The UK is well positioned to benefit from recent and ongoing advances in Engineering Biology, being second only to the US in terms of its research achievements in synthetic biology to date. But it is now necessary to create a more accommodating productivity-oriented 'eco-system' in the UK within which new applications can be rapidly translated and effectively commercialised, combining globally competitive speed with full confidence in the safety and security of innovative developments. One of the best ways to respond effectively to rapidly changing circumstances is to have anticipated the need and to have invested in platform technologies in advance. Engineering biology builds upon the platform of tools and techniques developed throughout more than a decade following the government's decision in 2012 to accelerate the development of synthetic biology and it is already becoming successfully applied and commercialised by numerous specialist start-ups and SMEs. The ground-breaking development of vaccines in the UK in response to the Covid pandemic demonstrates what is now possible, but also highlights the critical role and dependence upon infrastructural and regulatory preparedness, supply chains and the importance of engaging international partners to share knowledge and help set global standards.

Last year the Engineering Biology Leadership Council (EBLC) reviewed the main needs and opportunities to stimulate future economic growth in the UK via engineering biology, clarifying a number of high priority actions that would be most effective in unlocking the economic and societal benefits, increasing productivity and delivering widespread jobs and growth. Three working groups separately addressed in detail the three broad market application segments of agri-food, manufacturing (chemicals and materials) and healthcare, identifying a number of key interventions that could be usefully made to unlock the benefits arising from recent technological advances. Potential first-wave 'trailblazers' were identified as a means to pioneer and 'stress-test' more joined-up systems from feedstock to customer, streamlining routes to market for multiple further innovations to follow. As the new post-Covid 'normal' dawns, so it becomes ever clearer where the greatest needs and opportunities lie. The worked examples and proposals here should provide a valuable resource from which to shape and prioritise the policies and investments required to 'Build Back Better' in the UK with significant help from engineering biology.

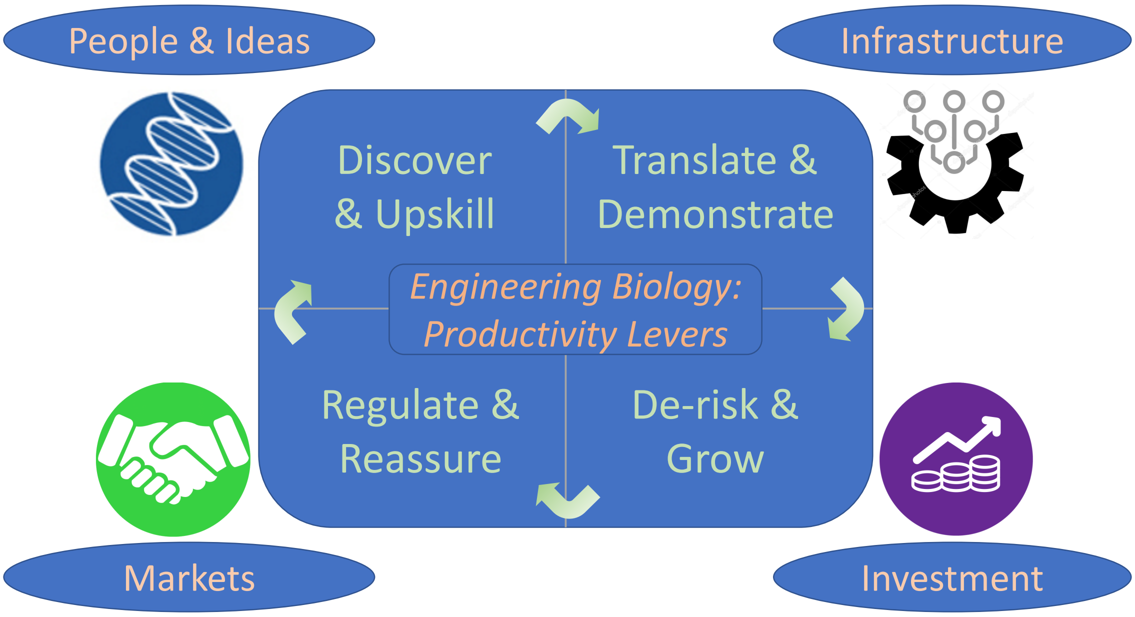
Lionel Clarke OBE
co-Chairman, Engineering Biology Leadership Council, May 2021

2. Four key interventions to help leverage the value of UK Engineering Biology

The many recommendations and 'asks' captured from the three working group studies (see summaries below and Appendices 1 – 3 for details) broadly cluster beneath four key interventions. These four interventions relate directly to the essential prerequisites of a productive system:

(a) a skilled workforce,
(b) ready access to cutting-edge tools and supportive infrastructures,
(c) investments sufficient to accelerate commercially competitive growth, and
(d) a governance system to set standards and reassure the market.

Market Pull generates demand, a flow of de-risked innovative applications supplies the pipeline.



1 DISCOVER and UPSKILL

Continue to invest into cutting-edge synthetic biology research and its translation, underpinning the engineering biology revolution. Develop a skilled multi-disciplinary workforce, technical and entrepreneurial, including guidance and retraining within the existing manufacturing base.

2 TRANSLATE and DEMONSTRATE

Increase available funding and tailor support to the practical needs of start-up and established companies, address constraints and pinch points via affordable, accessible, flexible, infrastructure.

3 DE-RISK and GROW

Stimulate flow of investments into start-ups and SMEs, and nurture them for longer, to help companies demonstrate de-risked propositions, attract private funding and compete globally. Promote the UK's world-leading role in engineering biology and deployment of applications arising.

4 REGULATE and REASSURE

Anticipate market needs. Establish a nimble regulatory system. Support outreach and communication.

3. Goals and Needs underlying the Four Key Interventions

1 Continue to invest into cutting-edge synthetic biology research and its translation, underpinning the engineering biology revolution. Develop a skilled multi-disciplinary workforce, technical and entrepreneurial, including guidance and retraining within the existing manufacturing base.

Ongoing research and doctoral training as an essential front-end to the innovation pipeline is addressed in the UKRI 'Engineering Biology' National Framework CSR submission. The need remains to increase support for translation (including entrepreneurial and business skills) for spin-outs, and training/retraining of staff in SMEs and established companies that wish to pivot towards and assimilate emerging biotechnologies

2 Increase available funding and tailor support to the practical needs of start-up and established companies, addressing constraints and pinch points including affordable, accessible infrastructure.

Current infrastructures are inadequate, obliging some companies to rely upon facilities outside the UK. The need exists to facilitate feasibility and manufacturing scale-up studies by providing demonstration and support facilities that are more affordable and flexible to the breadth of needs and limited resources of growing and adapting companies. Consider a blend of local clustering and national networking options, building around the key hubs and centres of expertise established to date.

3 Stimulate flow of investments into start-ups and SMEs, and nurture them for longer, to help companies attract private funding and compete globally. **Promote the UK's world-leading role in engineering biology.**

Adapt loans and grants such as the Growth Accelerator and IB Catalyst fund to better match needs and limitations of start-ups and SMEs. Assist companies to find and access suitable resources that will help demonstrate and de-risk innovations and attract private investments. Leverage Government 'soft power' to promote UK Engineering Biology as an attractive sector to invest in, and to leverage benefits from international partnerships.

4 Establish a nimble regulatory system. **Support outreach and communication.**

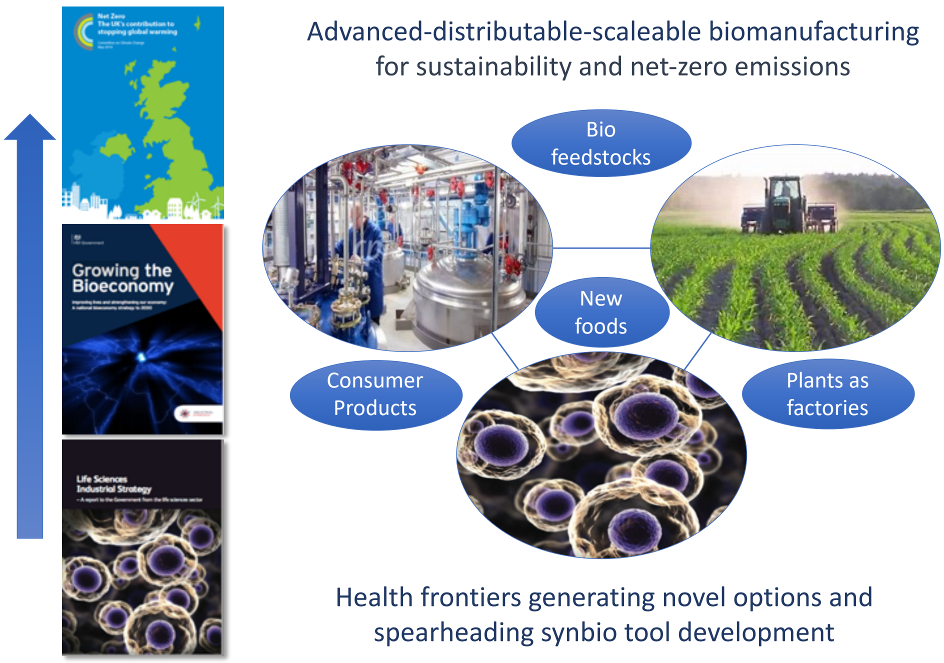
Market demands are rapidly shifting as awareness of global challenges mounts. Develop effective, balanced and streamlined regulations, better adapted to critical current and future global needs and making the UK the partner of choice for the development of world-beating innovative, safe and secure engineering biology technologies and solutions. The Regulatory Horizons Council is currently addressing regulatory frameworks relating to gene editing. Such approaches need to be complemented with the provision of balanced, proportionate information within the public domain, and adequate support for timely, effective, communications and engagement with the wider publics.

4. Market Segmentation of Engineering Biology Applications – Working Groups

The UK EBLC concerns itself primarily with the generation of a more joined-up and overarching 'eco-system' that will support the rapid and effective development and commercialisation of Engineering Biology in the UK, stemming from its world-leading synthetic biology research base developed in recent years, and aligned with the UK Industrial Strategy. Whilst a number of issues that help or hinder translation, commercialisation and productivity are likely to be common to any emerging technology, it is difficult to prioritise the many possible interventions required without first considering the specific issues associated with different market segments and applications within them.

'Synthetic Biology' was identified as a 'worked example' within the original 'Eight Greats' policy of 2013, but at the time it was at an early stage of research development and national priorities were different from today. Since then, research output has grown significantly around the globe, private investments increased substantially and the subject has matured into an increasingly commercialisable phase, with many applications already being pursued by start-ups and SMEs and being evaluated by more established companies. Engineering Biology has a clear and potentially significant role to play in responding to ever-shifting market pull, growing the Bioeconomy and ultimately assisting the transition to a future net zero economy. If Synthetic Biology is essentially viewed as a divergent process – an ever-expanding platform of technologies derived from the underpinning research base – then Engineering Biology can be viewed as a more convergent process – helping deliver multiple opportunities through to a wide range of specific, valuable, end markets.

Selecting specific examples helps to communicate what is becoming possible and helps to partition what is common to the sector as whole and what is specific to particular markets and applications. As a first step in separating the commonly shared from the specific issues associated with different market segments, the EBLC partitioned the application space between 'manufacturing/ chemicals', 'sustainable food and agriculture' and 'health' segments and examined these through discussions with the wider stakeholder community, via its working groups. It has also started to map out timeframes – what could be initiated in the near future as a first wave of 'trailblazers' to stress-test the system and generate shorter-term economic recovery options, and what need to be nurtured over the longer-term to help ensure that the Bioeconomy and Net-Zero strategies will be delivered on time.



4.1 Engineering Biology for Materials and Chemicals – Working Group Summary

Scope:
Analysis of current trends and needs in the sustainable materials and chemicals sector and the role that engineering biology can play, incorporating materials drawn from interviews with a cross-section of UK SMEs (80 SMEs analysed, 9 selected for in-depth analysis and interviews with CEOs).

Key conclusions and recommendations:

Government/Public Support
- *Patent box, R&D tax credits and tax incentives are extremely important*
- *Government "soft power" is important:*
- *Include EB in official trade delegations and the "Business Is Great in Britain" Campaign*

Funding Mechanisms
- *Angel Funding, SEIS and EIS are useful*
- *Some Innovate UK Programmes are useful, but stipulations about SME balance sheets or matched funding can be a problem with loans and grants*
- *VC funding difficult in the UK*

UK R&D Base
- *UK R&D base in Science and Engineering is World Class*
- *Long-term R&D collaboration with leading UK universities is important*

Manufacturing
- *A number of companies consider carrying out R&D in the UK but then manufacturing abroad the best option*
- *Need for Government to work on anchoring or re-shoring schemes to retain value*
- *International licensing seen as a good route for many SMEs*

Facilities
- *A great need exists for publicly funded facilities (e.g. Biofoundries and pulp mills)*
- *SMEs cannot afford expensive equipment - they need to get access to equipment and expertise*
- *Consider establishing a National Chemicals Biomanufacturing Institute*

General
- *Engineering biology is seen as very important for the UK BioEconomy*
- *Important to focus on a range of applications/fields rather than just healthcare*

For full details see Full Report Appendices A1a, A1b, A1c:

A1a: Interviews with a Cross-section of UK SMEs in the Materials Area – key points
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A1b: Engineering Biology for Chemicals Production: Basis for a National Chemicals Biomanufacturing Institute to Support UK Net Zero Carbon Targets and Clean Growth.

4.2 Engineering Biology for Sustainable Food and Agriculture – Working Group Summary

Scope:

Analysis of current trends and needs in the UK agri-food sector and the role that engineering biology can play, incorporating materials drawn from interviews with a broad range of stakeholders, comprising 9 start-ups, 1 non-profit, 2 large corporations, 4 research institutes, 1 public funding organisation and 1 venture fund.

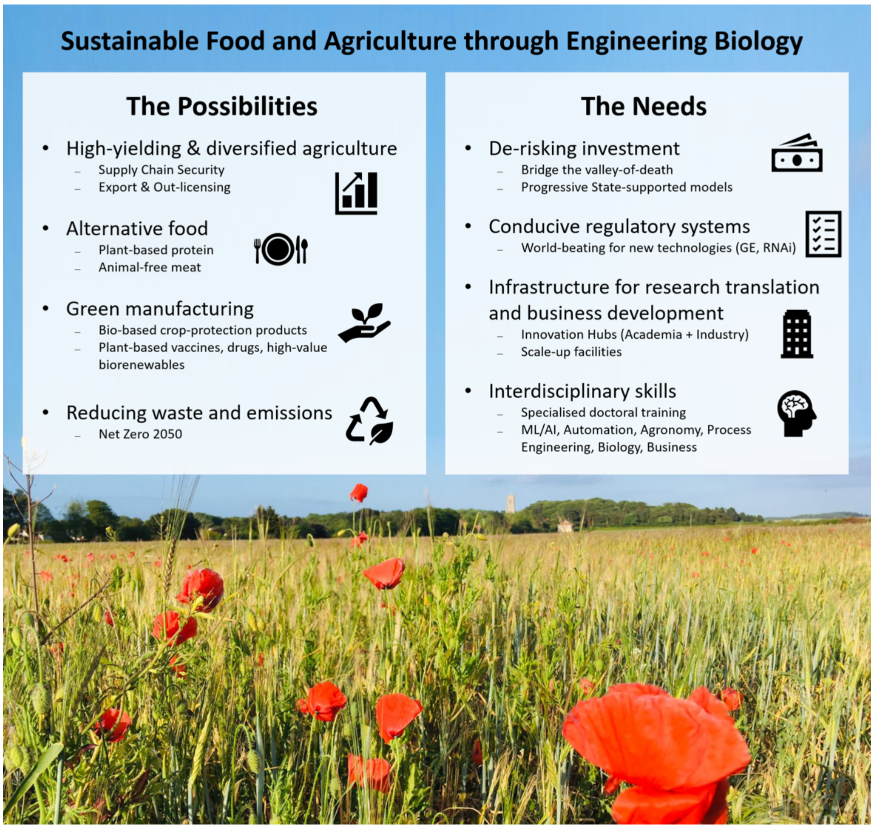
Goals:

To maximize the output of the sector and (i) safe-guard food security and food quality, (ii) reduce carbon emission and waste production, (iii) improve public health, and (iv) stimulate the country's economy and self-sufficiency

Key strategic plan recommendations:

- strategic investment in the agri-food sector,
- strategic investment in green technologies,
- creating a conducive policy and regulatory landscape,
- supporting the translation and innovation pipeline, and
- creating a supportive business infrastructure.

These five recommendations all feed into each other and could have a synergistic impact on the UK bio-economy and its goals to reach net zero by 2050. The recommendations are based on the assessment of the possibilities that Engineering Biology generates for the agri-food sector and the specific needs of the field. A summarizing overview of those possibilities and needs is provided below.



The Agri-Food Engineering Biology Field: a summary of the possibilities and the needs.

For full details see Full Report:

A2: Sustainable Food and Agriculture – Analysis and Recommendations

4.3 Engineering Biology in Healthcare – Working Group Summary

Analysis of current trends and needs in the UK healthcare sector and the role that engineering biology can play, incorporating materials drawn from discussions with academics and industrialists.

Current State: Engineering Biology in Healthcare

- The Healthcare sector had a **global turnover of £70 billion** in 2019 and a CAGR of >3%.
- Sector growth is **driven by "new to the market" products**, making it the UK's most R&D intensive sector.
- **Engineering Biology has been identified as a key driver for growth** in all 3 subsectors of healthcare, Therapeutics, Diagnostics and Public Health.
- The COVID crisis has highlighted significant strengths and weaknesses in each of these subsectors in the UK

Catalysing growth in healthcare sector through Engineering Biology (EB)

5 Key interventions are required to ensure the UK capitalises on its lead in this sector:

1. Establishment of a **nimble regulatory system** that will remove hurdles for the development and adoption of new therapies. Making the UK the destination of choice for global pharma.
2. Investment in an **EB Growth Accelerator program** to ensure our EB businesses have the support to out compete global competitors
3. Investment in **EB for Healthcare catalyst+ fund** that links our cutting-edge research to industry and patient need
4. Development of a **world class EB workforce** through funding for Doctoral training programs
5. Focused funding for a **network of strategic facilities** (e.g. GMP laboratories) that *are currently acknowledge pinch points for EB R&D*

For full details see Full Report:
A3: Engineering Biology in Healthcare – Analysis and Recommendations

Building back better with Engineering Biology - Appendix

A1a: Interviews with a Cross-section of UK SMEs in the Materials Area – key points

This summary document is based on a review of start-ups and SMEs in the Materials Area and their views and requirements. Overall, the activities of 80 start-ups and SMEs were reviewed. In addition, 9 companies were selected as being good examples of companies across the sector with considerable potential for rapid growth. Interviews were carried out with their CEOs. The areas covered below represent specific areas of interest/concern to the companies in the sector. In addition, the material presented also represents the views of a wider cross-section synthetic biology/engineering biology community.

Funding Mechanisms

In the UK, in theory there are substantial amounts of public money available to support start-ups and SMEs. However, the view of many "C Level" executives working in these companies is that, in practice, access to public funds is often difficult or very difficult. The primary reason for this seems to be that a significant number of the public sector funding models are really designed for large companies. Specific examples are some of the current loan schemes, where access by start-ups and SMEs is impossible because of the scheme requirements in relation to company balance sheets. There is, therefore, a clear view that there is a real need for specific funding models in the synthetic biology/engineering biology sector for start-ups and SMEs.

Of the companies that were contacted, some found UKRI funding essential. These companies were principally at a low TRL level. Other companies, which were in the main more developed, found Angel Funding and the SEIS and EIS schemes useful. There are a number of Angel Funds in the UK that will support the development of companies in the sector; for example, the Angel Funds associated with the Universities of Cambridge and Oxford.

VC funding is often difficult to obtain in the UK. By comparison to US West Coast VCs there is a lack of flexibility. Generally, such US funding is difficult to access for UK companies, with one or two exceptions. A number of the companies felt that there were good opportunities for VC funding in Continental Europe. An important problem, identified by many of the companies, is that UK based VCs often do not have domain knowledge and want a return on any investment within three years. An adjunct problem is the need for private investors to have domain knowledge, or at least business support. It is important for organisations, such as SynbiCITE, can act as disinterested advisers. There are a number of examples of High Net Worth (HNW) individuals proving very difficult in relation to their investment in start-ups and SMEs (e.g. requiring a rapid return on their money). What is needed is long-term investment so that the basic R&D can be undertaken, and industrial translation carried out.

Government/Public Support

In relation to the companies interviewed, the Patent Box and R&D tax credits and tax incentives were uniformly seen as extremely important and very useful. The Patent Box scheme was introduced in 2013. It is a scheme for companies to apply a lower rate of corporation tax to profit from patented inventions. If successful a 10% corporation tax is applied rather than the 19% standard tax rate. The R&D Tax Credit Scheme helps innovative new companies undertaking R&D to claim a cash refund from HMRC. Where appropriate, companies can claim on an annual basis. Another area that was seen as being very important for company growth is the exercise of Government "Soft Power" - where the UK Government can have a major influence on the success of a company by promoting its activity. One example of this is in the area of biodegradable plastics. UK companies have developed important IP in this area, which, with Government support, could be effectively licensed abroad. Government help with licensing deals would also be extremely useful. An important aspect of the soft power approach is for UK start-ups and SMEs to be included in official trade delegations and the “Business Is Great in Britain Campaign”. In this context, Government support for international introductions is seen as very important. Additionally, it would be important to launch products with a Best of British Brand. (For example, the US Government buys products that are labelled “Preferred”. This influences other purchasers.)

In specific areas it would be very beneficial to create new technical standards, e.g. working with the BSI, in order to develop standards that would ultimately become ISO standards. The ability to base licensing on a UK Government approved standard could be highly beneficial for the international licensing of products.

Financial support for international patents is also important - to provide adequate protection in countries such as China and Russia. In addition, Government support in relation to protecting “know-how” is another important aspect of IP protection. UK Government-backed very strict NDA’s could be very effective. In addition, Government help in obtaining international approvals (e.g. FDA approval) is seen as very beneficial.

UK R&D Base

The UK R&D base is generally perceived to be world class. The companies were extremely supportive of the existing major research centres for engineering biology/synthetic biology in the UK, as well as SynbiCITE’s role in industrial translation. There was a strong view that the existing infrastructure should be built upon, not replaced, as it is seen as being highly effective. The synthetic biology/engineering biology research centres, based in major universities, are a very important asset for UK start-ups and SMEs. Access to the centres represents an R&D base that is equivalent to multinational companies, both in terms of expertise and facilities. Consequently, long-term collaboration with leading universities on R&D is seen as being very important for many companies.

Specialist Workforce

The general feeling amongst the companies surveyed is that there is a wealth of research talent in the UK - and it is affordable. But there is a supply/demand imbalance. “In the UK there is a lot of academia and very little industry. What is lacking is a business infrastructure to support academia.” “There’s probably one MBA for every 30 PhDs.” The need for a specially trained workforce for the engineering biology/synthetic biology sector is considered by many in industries as a key pinch point for the industrial development of the area. Another example of a specific quotation in relation to company personnel needs is: “for every engineer, mathematician and computer scientist there are at least 30 PhDs in biology and biochemistry. What is crucial for the development of the U.K.’s engineering biology industry is the training of many more engineers, mathematicians and computer scientists with an understanding of biology”.

Manufacturing

A number of the companies that were interviewed took the view that the best combination, in terms of their operation, is to get the R&D done in the UK (because of the U.K.’s outstanding R&D base) and then to get their manufacturing done in some other area of the world. Continental Europe is considered to be advantageous as a manufacturing base (because of the EU, the size of the EU market and its proximity to the UK for R&D). From a UK standpoint this is of concern, because significant amounts of revenue (and taxation) are derived from manufacturing and not from R&D. It is, therefore, seen as extremely important that the Government develops schemes for anchoring or re-shoring (i.e. the reintroduction of manufacturing into the UK). An alternative model, which is being implemented by a number of companies, is to undertake R&D in the UK and then licence the technology to companies worldwide - thus providing an effective revenue stream back to the UK. An aspect of this model is that certain UK start-ups and SMEs may have very valuable IP, but not the ability to manufacture and market. A number of these companies are using much larger companies (via licensing) to act as OEM suppliers. A variant of this is (and there are examples) to undertake basic R&D in the UK, as well as basic product formulation by UK based manufacturers with high levels of expertise and know-how, and then to licence to large-scale manufacturers throughout the world. (This is essentially the Coca-Cola model, where basic formulation is carried out in the US and then distributed to bottlers around the world.) Some of the markets to which this model could be applied are enormous (e.g. in the toothpaste market, which is worth $23 billion per annum – specifically, new formulations based on bioactive glass could be licensed under the basic formulation model).

Facilities

Many of the start-ups and SMEs in the sector identified a great need for publicly funded facilities, e.g. Biofoundries and pulp mills. By way of example, one specific area is the provision of a network of pulp mills to break down biomass. One area of application is in the use of processed biomass in laminated materials for the building industry. “A key need is for the government to build pulp mills for the use of SMEs - capable of processing different kinds of fibres. Because of the lack of pulp mills and understanding of the technology there is currently a large waste of agricultural materials (e.g. straw). One estimate is that there could be an additional £120 billion of revenue for UK farmers. Farmers are currently selling this waste at around £40 per tonne, as they cannot sell it when it’s wet. Engineering biology/synthetic biology techniques could allow biomass to be processed wet. This would increase its market value to £700 per tonne. Government support for additional biomass processing facilities is critical because such process biomass is the feedstock for a wide range of engineering biology applications in terms of new processes and products.

The basic problem is that SMEs cannot afford to buy expensive equipment but would like access to equipment and expertise at low cost. SynbiCITE is seen as an important source of such support (in terms of its expertise and Biofoundry). It was recognised that there are a number of other Biofoundries around the UK, which can be accessed. Nevertheless, the general feeling amongst the companies in the sector is that there is a need to provide additional facilities and expertise that are affordable and flexible and that of specifically designed to meet the needs of start-ups and SMEs.

The introduction of engineering biology based solutions in the chemicals sector is not only an issue for start-ups and SMEs. The UK Chemical Industry, employing 153,000 people and generating £19.2Bn GVA, is vitally important to the UK economy but is also facing the need to reduce its dependence upon fossil fuel feedstocks, aligning with the UK’s legal commitment to achieve Net Zero emissions by 2050. New alternative biomanufacturing routes will provide the opportunity to convert virtually any carbon containing material into essential pharmaceuticals, chemicals and materials. Three of the four UK’s chemical clusters (Hull, Teeside, Runcorn, Grangemouth) are located in the North of England.

To realise scaled chemicals biomanufacturing prototypes for commercial development, benefiting SMEs and larger more established companies alike, a specific option would be to establish a National Chemicals Biomanufacturing Institute in the region to encompass, but not be limited to, biocatalysis, bio-refining and microbial cell factory platforms. This would provide a clear source of expertise, resources and training as needed to pull lower TRL technologies out of the research base to augment, and ultimately transition from, chemicals manufacturing using petrochemical based feedstocks (see Appendix B).

General

The general feeling amongst the companies surveyed and interviewed was that Engineering Biology/Synthetic Biology is a very important field for the development of the BioEconomy. However, it was also felt that because engineering biology/synthetic biology is platform technology it is important to apply it to a broad range of applications. Specifically, the view of companies in the sector is that at the moment there is a lot of emphasis on healthcare companies and pharma; whereas, the spectrum of application areas and companies is far broader. Of the companies reviewed in depth, the application areas included flavours and fragrances, biodegradable plastics, bioactive glass, smart materials, agriculture, and applications of waste as a feedstock.

A1b: Engineering Biology for Chemicals Production: Basis for a National Chemicals Biomanufacturing Institute to Support UK Net Zero Carbon Targets and Clean Growth.

Objectives:

There is now the potential to engineer nature to sustainably bio-manufacture the chemicals, materials and fuels that underpin global society. Successive investments in the UK's biotechnology research base has led to world-class academic capabilities, creating new approaches that promise to transform chemicals production. However, these developments have not yet transitioned through to large-scale commercial application. This paper sets out a proposal to enable the UK to unlock this transition. The specific objectives are:

- To establish biomanufacturing infrastructure and capabilities at mid-high Technology Readiness Levels (TRL) in the form of a National Chemicals Biomanufacturing Institute (NCBI) to encompass, but not be limited to, biocatalysis, bio-refining and microbial cell factory platforms.
- Use the NCBI to pull lower TRL technologies out of the research base to augment, and ultimately transition from, chemicals manufacturing using petrochemical based feedstocks. Empower the NCBI to work with cross sector stakeholders to realise scaled chemicals biomanufacturing prototypes for commercial development and meet 'head on' identified major bottlenecks in UK chemicals biomanufacturing.
- Through the activities of NCBI, deliver substantial contributions to the UK commitments to Greenhouse Gas (GHG) reduction, the stated ambitions of the bioeconomy strategy, jobs and wealth creation.
- By siting the NCBI in the north of England (where three of the four UK's chemical clusters are located),[1] use the NCBI to drive the UK Government's 'levelling up' strategy by creating wealth and clean growth opportunities in the chemicals manufacturing sector for the benefit of the UK as a whole.

Chemicals Production and the UK Economy

The UK chemical industry is vitally important to the UK economy, with 3608 businesses employing 153,000 people, giving £19.2Bn gross value added on a turnover of £55.5Bn.[2] Since around 15-20% of fossil fuel consumption is used to produce chemicals (including pharmaceuticals), society needs new technologies to manufacture the pharmaceuticals, chemicals and materials essential to modern life, in ways that are decoupled from fossil fuels. New alternative biomanufacturing routes will provide the opportunity to convert virtually any carbon containing material into these modern-day essentials.

The UK also has an obligation under the Paris Agreement on Climate Change to reduce Green House Gas (GHG) emissions by 80% by 2050, with the OECD highlighting industrial biotechnology (IB) as a key enabler to save energy and reduce CO_2 emissions.[3] The UK government understands the importance of IB; the vision outlined in the 2016 paper "Building a High Value Bioeconomy" outlined the UK's potential to become the "*location of choice for global investment in the bioeconomy*" by "*producing high value resource efficient materials, chemicals, and energy*" and thus becoming a "*major exporter of process technologies and business models*".[4]

The UK government has legally committed to delivering a UK Government 2050 Net Zero Carbon target to meet international obligations. Internationally, the UK is recognised as a leading nation in a number of important areas of research and innovation that underpin the bioeconomy, rating near first-in-class in terms of the general policy environment, human capital (e.g. calibre of researchers), IP protection and technology transfer, but falling down on the levels of research and development

[1] UK chemical production is concentrated in four main clusters: Hull, Teesside, Runcorn and Grangemouth.
[2] "UK Chemical Industry Facts", Chemical Industries Association, January 2020.
[3] OECD Directorate for Science, Technology and Industry, "Industrial Biotechnology and Climate Change", 2011.
[4] "Building a high value bioeconomy. Opportunities from waste" UK Government 2016.

spending.[5] The challenge now facing the UK Government and the industrial chemicals manufacturing sector is to implement these frontier technologies at scale for next-generation chemicals biomanufacturing.

Defining the Challenge for UK Chemicals Production

The Committee on Climate Change (CCC) Net Zero Technical Report (2020) notes that industry accounted for 105 Mt CO_2 emissions in 2017 (21% of national emissions which total 507 Mt CO_2 emissions). Of these 40% (42 Mt) are assigned to fossil fuel/emissions sources, segmented across chemicals (13%), rubber/plastic (3%) and textiles (2%), equating to 15-20 Mt CO_2/GHG emissions from these activities alone. This excludes emissions attributed to refining, which contribute a further 15% (15-20 Mt) CO_2/GHG emissions. Assuming that 20% of refining provides chemical feedstocks this also represents a major contribution to CO_2 emissions.

The chemicals manufacturing and fuels production industries are therefore major contributors to UK CO_2/GHG emissions. Current proposals captured in the Net Zero Technical Report for reduction of these emissions are focussed almost exclusively on improving energy efficiency, and carbon capture and storage (CCS). The CCC members have restricted their proposals to those that they consider can be achieved within the UK supply envelope to meet the UK Government 2050 Net Zero Carbon targets. The CCC suggests the establishment of a '*low C market*' and '*tariffs on the import of high C products*', which implies a premium for low C product solutions.

Missing in the CCC report are descriptions of the economic and societal opportunities arising from the development of new bio-manufacturing solutions. This is captured in the UK Government's Bioeconomy Strategy (2018-30) that identifies a pressing need to incentivise industry to stimulate innovative and sustainable biomanufacturing capabilities to meet the UK Government 2050 Net Zero Carbon targets and position the UK at the vanguard of economic Clean Growth.

The market for plastics alone remains globally on a substantial growth curve as noted by the International Energy Agency (IEA) in their report The Future of Petrochemicals (e.g. Figure 1.3 in that report). Of note is the IEA conclusion that *"The manufacture of petrochemicals and their derivatives absorbs an increasing proportion of the world's oil and gas – approximately 14% (13 million barrels per day [mb/d]) for oil and 8% (300 billion cubic metres [bcm]) for gas. Because much of this energy enters the petrochemicals sector as feedstock and does not undergo combustion, the sector achieves the seemingly contradictory feat of being both the largest industrial energy consumer and yet only the third-largest industrial carbon dioxide (CO_2) emitter. Even so, with the market for petrochemical products set to expand further as the global economy develops, the future of the petrochemicals industry is of major significance for both global energy security and the environment."*

Because of the growth in fossil fuel consumption, direct CO_2 emissions from the plastics sector will increase by around 20% by 2030 and 30% by 2050. Similar deleterious rises occur in air pollutants and water demand. Alarmingly, without major improvements in the management of waste stemming from the sector's key material output (i.e. plastics), the quantity of plastic waste, including that entering the oceans, will continue to rise from today's already unacceptable levels.

Strategic Investments to Ramp Up UK Chemicals Biomanufacturing

There is now an opportunity to harness the power of biotechnology and, through the 'engineering of biology', to use renewable biological resources in place of fossil fuel derivatives (e.g. petrochemical, coal and natural gas) in products, processes and services. A transition to a bio-based economy would reduce the UK's dependence on finite fossil resources and would usher in sustainable biomanufacturing routes that will displace incumbent processes centred on petrochemical industries. Such a bioeconomy would have reduced CO_2 emissions and be driven by economic Clean Growth as

[5] "Evidencing the Bioeconomy" A report by Capital Economics, TBR and E4tech for the BBSRC and BIS, 2016.

part of an interconnected strategy for the UK, employing frontier manufacturing to refocus extant manufacturing practises.

Strategic investments made by the UK Government are encouraging a connected ecosystem for translating new technologies for chemicals production, enabled in part through the engineering of biology. Examples include investments in discovery science in the form of 'biofoundry' platforms and associated synthetic biology research centres that have provided new and important UK capabilities for accelerated production of diverse chemicals. These centres are the Synthetic Biology Research Centre for fine and speciality chemicals SYNBIOCHEM at Manchester, BrisSynBio at Bristol, the Centre for Mammalian Synthetic Biology at Edinburgh, and the London BioFoundry based at SynBiCite, the national innovation and knowledge centre based at Imperial College. These UK centres are connected to the Global Biofoundries Alliance[6] to ensure best scientific and ethical practises are shared internationally for the engineering of biology. As an example, SYNBIOCHEM has defined new routes to the production of natural products,[7] precursor chemicals for next generation materials[8] and clean-burning fuels [e.g. bio-ethanol from CO_2; Bio-Liquefied Petroleum Gas (Bio-LPG);[9,10] new precursors for aviation fuels].[11]

These UK Government strategic investments in 'engineering biology' are positioned at low Technology Readiness Levels (TRLs 1-3). They are also supported more broadly by investments in Centres for Doctoral Training (e.g. BioDesign Engineering; Integrated Catalysis) for chemicals production. Allied investments such as the UK Catalysis Hub supports the integration of biocatalysis, homo- and heterogeneous catalysis for more effective use of water and energy, waste minimisation, and material reuse and reduction in gaseous emissions. Pump-priming of academe-industry partnerships is supported through the various Networks in Industrial Biotechnology and Bioenergy (NIBBS). The Henry Royce Institute provides access to national infrastructures for advanced materials evaluation and commercialisation. It provides an exploitation path for new biological engineering materials manufactured using biotechnological approaches.

The EPSRC Future Biomanufacturing Research Hub (Future BRH; established 2019), based at The University of Manchester with Spokes at Imperial (SynBiCite and the London BioFoundry), UCL (Biochemical Engineering), Nottingham (Sustainable Process Engineering), the UK Catalysis Hub, IBioIC (Scottish Industrial Biotechnology Innovation Centre) and CPI (Centre for Process Innovation, Wilton), is pioneering new underpinning technologies across a national network of excellence based on industrial biotechnology (IB) and the engineering of biology. The purpose of the Future BRH is to research sustainable and innovative biomanufacturing in four key sectors – Pharmaceuticals, Value-added Chemicals, Fuels and Engineering Materials. Positioned at low TRLs (1-3), the goal is to research novel biomanufacturing processes through industrial collaboration and co-created science programmes. Future BRH is establishing partnerships with major UK and international companies in the petrochemical, personal care and pharmaceutical sectors, and a number of SMEs with innovative technologies. It has also secured overseas research partnerships for its members (e.g. with the US Navy through its ONRG and SERDP programmes).

Future BRH aims to connect UK strengths in interdisciplinary IB and engineering biology discovery science with industry partners to stimulate innovative biomanufacturing research. It is centred at the Manchester Institute of Biotechnology (MIB), which is one of Europe's leading industry-interfaced academic IB research centres in chemicals production, as recognised by the award of the Queen's Anniversary Prize for Higher and Further Education in 2019.

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[6] Hillson *et al Nature Communs* 10, 2040 (2019)
[7] Carbonell *et al Communs Biol*. 1, 66 (2018)
[8] Robinson *et al Metabolic Engineering* in press
[9] Amer *et al Energy and Environ Sci* in press
[10] Bioethanol production from CO_2 capture, UK patent pending (2019)
[11] Mylemans *et al ChemSusChem* 4, 465 (2011)

Creating a National Innovation Landscape for Chemicals Biomanufacturing

There is a risk to the UK economy of not supporting chemicals biomanufacturing at higher TRLs. The pharmaceutical, chemicals and materials manufacturing sectors are highly competitive and global in scale. Failure to support the move towards sustainable and clean biomanufacturing may have a detrimental effect on the existing sector as other countries leap-frog the UK in their competitiveness and technologies. There is increasing competition from emerging markets, and governments of other developed nations are investing heavily in IB. For instance, France is investing €1.5bn over 10 years on infrastructure and training to support its bioeconomy policies under "the Health and Biotechnologies Programme".[12]

The UK sector cannot do everything and must be strategic. For example, the UK currently does not have the feedstock capacity to be a significant manufacturer of bulk, low value bio-based chemicals, but the UK could for example foster the innovation expertise to develop processes and technologies to then implement manufacturing overseas. Additionally, the UK could position itself to valorise imported feedstocks whilst minimising carbon burden through the implementation of new supply chains and technologies that increase the competitiveness of chemicals manufacture in the UK. The UK could also focus on value added products, and pursue other opportunities though international partnerships, targeting investment *via* mechanisms [e.g. the Global Challenges Research Fund (GCRF)]. Further investment (mid-high TRL) to pull through emerging capabilities in chemicals production from existing engineering biology platforms into frontier manufacturing platforms will help place the UK at the forefront of the global chemicals production sector, promoting progressive, sustainable and clean biomanufacturing.

Proposition

Universities are beginning to build industrial clusters where manufacturing businesses are based (e.g. Advanced Manufacturing Research Centre Sheffield, UK). These provide an attractive offer for technology de-risking close to relevant University Centres of Excellence. Such structures could provide a pull for innovation-intensive manufacturing firms who might otherwise chose to locate elsewhere. The draw for these industries to cluster in such a way would be local access to transformative lower TRL university-based research excellence and technical support, which if made accessible, could underpin new innovation and growth. This could especially enable early, agile manufacturing scale-ups and spin-outs that would benefit from being located close to a university, equipment and a pool of skilled graduates. Such an ecosystem would support seamless working across disciplines, TRL boundaries and academic and commercial sectors, accelerating pathways to market and commercialisation.

A national cluster for advanced biomanufacturing in the chemicals sector, to attract inward investment from companies at this technology frontier, is urgently needed to ramp up productivity in the UK chemicals manufacturing base through increased innovation and skills. It should be a national ambition to commercially establish chemicals biomanufacturing, thus leveraging the exceptional academic base in biotechnology and chemistry already established in the UK. Currently most relevant research in chemicals biomanufacturing is still being carried out in universities, or behind closed doors in big industry (although only to a small extent in the UK). There is now a pressing need to establish a national cluster for advanced biomanufacturing that unites the manufacturing business base with university research and sector relevant training and entrepreneurial activities to pull through the strong science and technology foundations established in the UK towards large scale commercial reality.

[12] Ambassade de France à Londres, Investments for the Future Programme, September 2015

A National Chemicals Biomanufacturing Institute (NCBI) could coalesce crucial infrastructure urgently required to scale chemicals production using biocatalytic and engineering biology approaches. As a National Institute, the NCBI would enable expertise from across the UK, wherever it is based, to contribute to the sustainable manufacturing objectives. This would free the NCBI from the constraints of 'single university dominance' that might accrue if established under the auspices of a single university.

At the heart of the NCBI would be an industrially relevant pilot and scale up capability, connecting industry with bioprocess experts and appropriate technology for the scaling of chemicals bio-production. This would embrace techniques from across the biomanufacturing spectrum, including feedstock pre-treatment, fermentation infrastructure, enzyme engineering and biocatalysis, continuous flow chemistry, downstream processing, and the integration of such technologies to support the implementation of effective bioprocesses at scale. Stage-gated process development, informed from the outset by techno-economic, life-cycle analysis and industry requirements will require multidisciplinary teams to work across traditional sector boundaries. Many of these specialities are currently embedded in multiple UK university departments but are not connected effectively to support higher TRL prototype biomanufacturing programmes.

There are several important challenges that the UK might embrace, for instance feedstock supply (e.g. innovative processes to concentrate feedstocks at source prior to importation to support the UK chemicals biomanufacturing economy); maximising the efficiency and use of available feedstocks through biorefining; efficient production of high value active ingredients for pharmaceuticals with low environmental impact (e.g. flow (bio)chemistry, biocatalytic transformations); development of robust processes with low cost burden for large-scale biomanufacturing (e.g. platform chemicals; next generation fuels; materials precursors etc).

For maximum impact, core activities within the NCBI would need to be coupled with broader commercial skills, for example in knowledge transfer (e.g. an associated Knowledge Transfer Centre), finance and capital raising, IP protection, management and development, sector skills training (e.g. aligned apprenticeship training and continuing professional development), and establishment of real estate (akin to Factory 2050) that can accommodate the multiple requirements of collaborative and industry-led support for prototype development and design. The NCBI would also require spin-in/out space to foster entrepreneurial activities relevant to chemicals biomanufacturing. In its entirety, the NCBI would be a one-stop shop for later stage development of industrial biomanufacturing processes drawing on the excellent academic and industrial foundations in the chemicals production sector. In doing so the NCBI would meet many of the bottlenecks across the UK chemicals biomanufacturing sector that have been identified in multiple roadmaps and strategy documents.

The NCBI would be positioned between the exceptional lower TRL activities available in UK universities and research institutes and the larger scale manufacturing facilities available in the chemicals industry and/or the Centre for Process Innovation, Wilton, and the wider BioPilots UK biorefining network. As such the NCBI would represent the crucial missing capability in connecting chemicals biomanufacturing capabilities within and across the UK research base.

The NCBI would be a multi-stakeholder entity charged with leading a transition to chemicals biomanufacturing. This is a major programme and the journey will occur over many years/decades with early, mid-term and longer-term deliverables for the UK economy. The NCBI would add value to the chemicals manufacturing sector by greening existing manufacturing practices and by ultimately delivering new sustainable biomanufacturing processes.

The impact will be lasting: a transition to biomanufacturing will impact substantially on UK Government targets for reduction of GHG emissions with consequent benefits on the environment; expansion of new jobs; and if sited in the North (which is strong in chemicals manufacturing) 'levelling up' of employment opportunities that will benefit the UK as a whole. Of course, multiple sectors could benefit from the advances in the engineering of biology and allied disciplines, but the UK's chemicals manufacturing sector could be the imminent beneficiary. For this to be realised, the UK needs to act quickly to embed the NCBI into its innovation landscape for chemicals manufacturing.

A2: Sustainable Food and Agriculture – Analysis and Recommendations

1. Market Segment

Food is a prime necessity of life; consequently, the **food and agricultural sector is under any circumstance of key importance to society**. The sector not only feeds the population, but also has the potential to improve human health, generate employment, and make responsible and sustainable use of the planet's natural resources. The sector taps into multi-billion- and trillion-dollar markets globally, and, as mentioned in the BBSRC's Strategic Framework, the agri-food sector employs 3.9M people and contributes to £110Bn gross value added to the UK economy[1].

The world in general, and the agri-food sector specifically, are facing several challenges that need to be addressed urgently. **First, the world population is growing rapidly** and is predicted to reach 9.5Bn by 2050[1]. More food production is needed with ever scarcer land and fresh water. The growing population is putting extreme pressure on the already scarce resources of the planet. **Second**, **we are facing climate change**, which will make large areas of land unsuitable for agriculture. Extreme weather conditions will cause drought in some areas, and flooding in others. The circumstances under which crops need to be grown will thus change drastically. **Third**, **pests and diseases have been a serious problem in agriculture since the moment people started farming**. Plant pathogens currently cost 15% of crop production every year, and the evolution and incidence of resistance to existing crop protection products and varieties is increasing. Likewise, diseases are a big problem in animal husbandry as well. This necessitates the development of new and sustainable solutions to arm farmers with the tools needed to protect their yields and livelihoods. Pest and pathogen pressure are predicted to increase due to changing weather conditions and due to growing pressure on the food chain that will result in more intensive and dense farming practices. **Fourth, we are dealing with waste and emission problems**. Food manufacturing and agriculture generate waste and carbon emission, which will increase with the growth of the population if we do not take action now. **Fifth**, **public health is dependent on nutrition**. Poor and unhealthy nutrition relates to obesity, heart disease, diabetes, developmental abnormalities and cancer. With the availability and comfort of fast-food, several diet-related diseases have been increasing over the past decades. Improving the nutritional content and quality of food is a responsibility we have, to improve the health and well-being of society. **Finally, Brexit** has made certain grant schemes and international trade agreements unavailable and is thus demanding new international ties and a greater national self-sufficiency. Currently, the UK ranks 24th out of 67 countries across the globe on the overall food sustainability scale, and 16th out of 29 countries across Europe (the index takes food loss and waste, sustainable agriculture and nutritional challenges into account)[2]. Thus, although the UK is in the upper half of the index across the globe, there is clearly room for the UK to improve in this area.

A number of recent biological and technological developments have advanced our ability to tackle these challenges. Due to progress in **DNA sequencing technologies**, we have been able to obtain whole genome sequence information of agriculturally important organisms, which provides the information needed to make targeted changes and informed choices. With the speed with which these technologies are developing, access to DNA sequence information becomes ever easier. Moreover, we now also have access to **novel breeding techniques** that allow us to make small and targeted changes in the genomes of these organisms. Third, developments in **AI, machine learning, and bioinformatics** are making discoveries of new genes and complex gene pathways faster than before. Lastly, progress in **engineering and robotics** has advanced phenotyping, which, together with technological improvement in the fields of live cell imaging and metabolic analysis, is feeding into our ability to understand and engineer biology. The combination of these different biological and technological advances in the field of engineering biology provides a remarkable synergy of which we now need to reap the benefits.

To understand current trends and needs in the UK agri-food sector and the role that engineering biology can play, we have interviewed various stakeholders, covering 9 start-ups, 1 non-profit, 2 large corporations, 4 research institutes, 1 public funding organisation and 1 venture fund. Below, the conclusions following from these discussions are captured, culminating in five strategic plan recommendations at the end of the document.

2. Impact from Engineering Biology

Engineering biology can address the above-described challenges in the agri-food sector in numerous ways:

Agriculture:

- **Adaptable crops:** Using DNA sequencing technologies and modern breeding techniques (genome editing and genetic modification) we are able to introduce precise and targeted changes to crops. This cuts down on breeding time compared to classical breeding methods, and moreover, allows us to make improvements that could not have been made in any other way (for example, banana plants are unsuitable for classical breeding due to sterility of the main commercial export variety). Such changes can: **(i)** improve crop yield, **(ii)** enhance resistance to pests and pathogens resulting in less pesticide use, **(iii)** reduce post-harvest crop loss, **(iv)** develop adaptability to changing weather conditions, **(v)** allow crops to be grown in new environments, including vertical farms and hydroponic systems, and **(vi)** unlock neglected or underutilized crops, allowing us to diversify our diet and agriculture. With improved and better-adapted crops, we can address the needs (and opportunities) of national agriculture and leverage the global market whilst supporting agriculture in developing economies.
- **Genetic improvement of farmed animals:** Similar to the situation in crops, genetic engineering can also be applied to farmed animals (poultry, pigs, ruminants and aquatic species) to reduce disease susceptibility and improve production-relevant traits, which will **(i)** improve yield, **(ii)** reduce dependence on antibiotics, **(iii)** improve animal well-fare, and **(iv)** reduce costs of production and inputs required. Like engineered crops, engineered animals will impact national as well as global agriculture.
- **Alternative agrochemicals**: With gene discovery and engineering techniques we are able to identify, characterise and engineer genetically-encoded pathways from plants, animals and microorganisms, which allows the development of new, natural product-based agrochemicals. With these natural and bio-based molecules we can provide new sustainable crop protection solutions to growers and replace existing synthetic petrocarbon-based agrochemicals. Moreover, engineering biology enables us to use natural production systems (i.e. plants or microorganisms), which permits us to synthesize compounds with greater chemical complexity, while producing less waste and greenhouse gas emissions (see also paragraph below on “Alternative manufacturing systems”). In addition, engineering biology has enabled development of alternative pest-control methods including the use of insect pheromones and RNAi.
- **Improving soils:** Engineering biology allows us to discover, monitor and re-engineer soil composition and chemistry. Understanding and optimizing the biotic (microbial) and abiotic (mineral) components in the soil helps us to improve crop resilience, yield and protection against pests and diseases. Moreover, engineered soils have the potential to enhance carbon and nitrogen sequestration, absorb toxins, facilitate waste conversion and decomposition, filter water and produce heat, which helps achieving the sustainability goals.

- **Development of diagnostic tools:** Engineering biology enables the development of molecular diagnostics methods for plant and livestock diseases. For example, this includes: **(i)** detection of the pathogen by making use of host-specific carbohydrates or other cell-surface components that are targeted by the pathogen, or **(ii)** detection of pathogen-specific DNA/RNA with the CRISPR-Cas system. Such advanced molecular diagnostic tools are being developed for animal diseases, including equine influenza and avian influenza. Knowledge obtained in this field can also be applied for detection of human diseases, including COVID-19.
- **Sustainable feed:** Bioengineering of, for example, plant-, fungi-, fish- or insect-based resources allows the development of new feed material and optimal feed composition. As described above for crops, traditional methods to improve feed will take longer, or will not be able to address certain improvements to feed composition at all. Bioengineered feed will help to achieve sustainability goals and improve animal health, thereby contributing to animal well-fare and economic advantage.

Food:

- **Alternative food**: Bioengineering of crops, microorganisms and cell-cultures can unlock novel food sources and increase the nutritional content of food. This includes alternative protein production (plant-based or fungal protein instead of animal protein), increased vitamin, mineral and fibre content, and decreased sugar and saturated fat content. Moreover, as mentioned above, bioengineering can make under-utilized crops more suitable for consumption, whereby we can diversify our food intake. These developments help to improve public health and reduce dependence on animal-based protein, enabling further decrease of our carbon footprint.
- **Alternative food production systems:** Bioengineering does not only allow us to develop alternative foods, but also allows us to develop alternative food production systems. Natural systems (for example of plant or microbial origin) can be engineered to produce food components or food additives, whereby we produce less waste and reduce the carbon footprint (see also paragraph below on "Alternative manufacturing systems").

Manufacturing for the agri-food sector and beyond:

- **Novel/Alternative chemistry:** In addition to production of alternative agrochemicals, modern molecular tools allow us to discover, characterise and engineer genes and gene pathways to generate new food ingredients, drugs, antibiotics, antibodies, vaccines and enzymes. Increased access to genetic information, data analysis and machine learning allows us to discover new natural products, optimize functionality of existing products or create novel products with new functionalities.
- **Alternative manufacturing systems:** Engineering biology presents the opportunity to make use of novel biological production systems for the natural products described above. Natural production systems allow us to address the chirality and complexity of molecules, moreover, they generate a greater degree of bioactive molecules compared to conventional chemical synthesis methods, reduce our dependence on petrochemicals, and produce less waste.
    - **Plant-based systems:** Plants provide a suitable eukaryotic expression system that is environmentally friendly (consuming relatively little power and producing compostable waste) and well fit for scaling up.
    - **Microorganisms and fermentation-based technologies:** Prokaryotic and eukaryotic microbial systems (i.e. yeast, candida) can be engineered to make a range of bio-based high-value chemicals.
    - ***In vitro* (cell-free) systems** are suitable for production of certain molecules that are difficult to produce in living hosts (i.e. complex carbohydrates that are toxic to

production hosts). Moreover, cell free systems are easy to store and transport and may therefore also be beneficial in resource-poor environments.

Using plants and microbes to directly tackle waste and emission problems:

- **Waste processing**: Microbes can be engineered to digest waste (i.e. plastics, toxins). In addition, engineering biology can help to increase accessibility of inedible parts of crops for downstream processing (i.e. the digestibility of cell walls can be modified). Making use of the inedible parts of crops as input material for bio-manufacturing (i.e. through fermentation-based technologies) reduces waste. Moreover, full crop valorisation serves a circular economy and will generate a better return on crops for farmers.
- **Capturing CO_2:** Engineering biology can be used to generate carbon sinks. Plants and microbes can be engineered to fix CO_2 with increased efficiency. In addition, using photosynthetic organisms (plants/microbes) in manufacturing processes (as described in paragraphs above) helps reducing waste and carbon emissions, as these are biodegradable and carbon fixing systems.

3. Innovation ecosystem challenges and requirements

The agri-food sector faces several ecosystem challenges:

Finance

- **Low and distant ROI in the agri-food sector:** The UK agri-food sector faces challenges in attracting venture capital compared to the pharmaceutical sector which gets higher ROI. In addition, agricultural R&D often has a long cycle time (ca. 10 years); returns can therefore be quite distant. However, like the health sector, the agri-food sector is of prime importance to society. Moreover, given the growing world population and climate change, the sector faces major challenges in the decades to come. To safeguard our food supply and establish national self-sufficiency and sustainability, strategic investments in the agri-food sector are essential. Start-ups and SMEs in the sector need between £20-100M investment to demonstrate their potential. To de-risk VC and large multinational company investments, significant injections of public and institutional capital will be required. Funding schemes beyond 5 year-cycles will be needed; the agri-food sector will benefit from patient, long-term investments.
- **High cost of green technologies:** Engineering biology provides green alternatives to manufacturing, whereby waste, emissions and dependence on petrocarbon are massively reduced. However, as these methods are novel, they often require further R&D, as well as costly safety trials and regulatory approval and are thus not price-competitive compared to traditional methods. Moreover, a major inhibitory factor in this equation is the current low price of petrochemicals. Government investments in, and incentives for, sustainable technologies in the agri-food and manufacturing space are needed to generate a level-playing field with traditional petrocarbon-based technologies.
- **Valley of death for starting companies:** There is a funding challenge in the commercialization phase for many starting companies and a need for investment along the entire research translation and production pipeline. New and innovative models for funding should be developed, which will create a diversified ecosystem with increased capital base and investor demographic. In addition, as the major costs for companies in the agri-food sector are related to the regulatory systems, having more proportionate and adaptive regulatory approaches (as discussed further below) will help shrinking the valley of death in a cost-effective way.
- **Daring research is at risk of losing out:** Daring research is at the heart of innovation. However, as it is risky and often far from application, it is under threat of being underfunded. Likewise, interdisciplinary research taps into novel uncharted territories and may therefore miss out on

funding through conventional funding schemes. We need to continue to safeguard this area with public as well as private investments.

Regulation

- **Restrictive regulation of genome engineering techniques:** Engineering biology provides numerous ways to improve agriculture and food production in a sustainable way. Many solutions are ready to be rolled out, however, implementation is held back by regulatory uncertainty over novel breeding techniques (e.g. genome editing). Providing a world-leading regulatory framework for the sector will re-invigorate basic and applied research and remove the barrier to entry for new ventures in the space. The UK will become the go-to destination for agri-food innovation and its translation into commercial success (via the introduction of new crops, or, via development of technology and products for both national and global agri-food markets).
- **Time-consuming and bureaucratic regulation of novel food products**: Bureaucracy and regulatory costs are driving up the expenses and cycle time of R&D in the food and agri-tech sector. A smarter regulatory landscape for novel food products that reduces overall costs and timescales without compromising safety, would stimulate commercial activity in this sector and lower the barrier for venture capitalists (and other investors) to enter this space.

Public perception

- **Support for genome engineering techniques to deliver public benefits:** It is no longer appropriate to anticipate public scepticism towards genome engineering techniques designed, for example to mitigate climate change, deliver health benefits, reduce the use of pesticides, or improve biodiversity, provided that regulation is effective and does not unnecessarily inhibit innovation. A previous study has indicated that the public is willing to accept genetic engineering techniques as solution to tackle current global challenges, however, public dialogue is key and careful communication of associated risks, benefits and rewards will be needed[3].Scientists and other stakeholders in the field thus need to continue to take a proactive part in the public debate to clearly explain what genome engineering entails, how it relates to traditional breeding methods and why it will benefit society and the environment. We need to communicate successful case studies with special attention for the safety of the generated products.
- **Trust in quality and safety of food:** A challenge is to make sure that novel food products are developed responsibly and do not lead to future public distrust. Sharing information about how foods are made and what they contain, together with safety checks that safeguard food content in a rational way are to be recommended.
- **Attention for the vulnerability of the food and agricultural sector:** The public is becoming more and more aware of the crucial role that the agri-food sector can play in tackling global challenges. Additionally, it is important to note that food security is vulnerable, especially considering the anticipated population growth and climate change in the next few decades to come. On top of that, we have the social responsibility to support food security and agriculture at a global scale, including for the more than 820 million people across the globe for whom food supply is already scarce[4]. Policymakers, scientists, entrepreneurs and investors have the substantial obligation to continue to communicate the necessity of the agri-food sector for society.

Infrastructure

- **Insufficient research translation:** The UK is home to many scientific discoveries, however, there is a gap in research translation. The commercial world needs daring research and new big ideas; the scientific world will benefit from commercialization of innovative scientific discoveries. However, linking up academia and industry is a challenge. Interactive models are needed to support research translation. Entrepreneurship may work well around specific hubs; success is likely to breed success, and public investments are known to pay off more when in proximity to private investment[5]. Hubs for agri-food and associated sectors will enable co-location of industrial R&D with academic and entrepreneurial skillsets (public investment of around £300M can be required for one such hub). This can supercharge the innovation potential for the sector in the UK by establishing a better balance of industrial versus academic expertise in joint projects, making facilities available for co-location of interdisciplinary teams. The ability to house start-ups in an incubator space with access to class-leading industrial R&D facilities will minimise capital costs and accelerate translational science and technology by interaction with experienced industry scientists and leaders. Additionally, research translation is significantly accelerated by grant programmes providing match-funding for joint projects between industry and academia. Current examples of this are the Innovate UK grants and the IB catalyst fund, which have proven very useful.

- **Insufficient opportunities to work to scale:** The UK is not strong in manufacturing at scale; this is however an essential requirement in the production and commercialization process of innovations in engineering biology. Many companies therefore outsource work at scale to CROs and CMOs abroad. To support the UK economy and promote national self-sufficiency and sustainability, public as well as private investments in facilities to work at scale are required (entailing microbial growth facilities, fermenters (bioreactors), and bulk plant growth facilities, including vertical farms and hydroponic systems). Costs of one scale-up facility can be around £50-£75M. The establishment of more accessible and discounted scale-up facilities across the UK will act as a stimulus, encouraging upstream innovation by providing a clear and financially-predictable route to pilot demonstration, technical transfer and manufacture.
- **Inadequate business infrastructure:** The UK is lacking a vibrant start-up culture, as observed in countries like the US and Israel. We should investigate and aim to learn from such successful examples. Investing in business infrastructure is inevitable to facilitate change in this culture. Bringing academia and industry together in hubs (as mentioned above), as well as access to incubator space and accelerator programmes can significantly stimulate the business culture. Moreover, interdisciplinary and international training programmes, in which scientists and business specialists are brought together, can positively contribute to the start-up climate in the UK (see also "Human capital" below).

Human capital

- **Insufficient commercially-minded academics:** There is an evident gap in the availability of skilled professionals that can understand and operate in both the academic and the business world. Investment in business-oriented training programmes, as well as infrastructure for research translation and business development is likely to result in more professionals with such expertise in the UK. Educating academics on assessing and understanding market demand, IP, management, and competitive analysis will be very useful, which could for example be accomplished through connection with MBA programmes. Such programmes can attract international attention and can draw in partners from abroad. In addition to the above, it will be important to change the reward mechanisms for academics to give equal recognition to entrepreneurial activities compared to academic activities.
- **Inadequate connection between different professional disciplines:** The agri-food sector requires a tight collaboration between various professional disciplines. More interdisciplinary initiatives are needed to facilitate growth of the agri-food sector to its full capacity; biologists, (bio)chemists, agronomists, engineers, breeders, data scientists, software developers, regulatory and business specialists need to come together. Part of this integration can start to take place at an educational level and can include structuring education around challenge-

driven assignments for which multiple disciplines need to collaborate. Moreover, grant funding for long-term interdisciplinary initiatives, as well as innovation hubs (as mentioned above) will be necessary.

4. Summary

Following the above described opportunities and ecosystem challenges, we suggest several strategic plan recommendations in the section below. Under pressure of the national and global societal challenges we are facing, these suggested measures are necessary to **(i)** safe-guard food security and food quality, **(ii)** reduce carbon emission and waste production, **(iii)** improve public health, **(iv)** stimulate the country's economy and self-sufficiency, and **(v)** make the UK a world-leading country and go-to place for science innovation and translation.

- **Strategic investment in the agri-food sector:** The agri-food sector is of prime importance to society. The sector **(i)** is necessary to generate sufficient, safe and healthy food, **(ii)** is responsible for a large proportion of the UK economy, and **(iii)** has the potential to mitigate pollution and global warming by smart use of the carbon fixing and biodegradable resources it is using. However, food and agricultural R&D has a long cycle time and generates a lower return on investment compared to the pharmaceutical sector; consequently, private investors are often reluctant to enter the sector. As the agri-food sector is essential for society, public investments are needed to de-risk private investments; this will boost commercialization of agri-food innovations and establish the sector as a vibrant and strong part of the UK economy.
- **Strategic investment in green technologies:** Engineering biology provides numerous ways to develop alternative and environmentally friendly processes, products and practices in the food and agricultural industry, including bio-based products (agrochemicals, food additives, drugs and vaccines), improved crops and farmed animals, and alternative food and feed. Engineering biology can thus help replace current less sustainable food and agricultural production systems and reduce dependence on petrocarbon-based manufacturing. However, some of the conventional agri-food production systems are at present still cheaper than their green alternatives, thus leaving green technology with a competitive disadvantage to reach full potential (or even to get a foothold). To achieve net zero targets, now is the time to give targeted support to green technologies to allow them to enter the commercial market at scale.
- **Creating a conducive policy and regulatory landscape:** Engineering biology has the power to make the agri-food sector bigger, more efficient, less polluting, and produce healthier and higher quality products. However, the current UK regulatory framework for genome engineering and food is inhibiting progress in the sector. Based on the publication of the White Paper on Regulation for the Fourth Industrial Revolution (including the setting up of the Regulatory Horizons Council) and as a result of stepping out of the EU, the UK now has the opportunity to change the regulatory framework to make it more proportionate and adaptive to the needs of innovative technologies. This could have an enormous impact on the country's ability to innovate and become best-in-class in the agri-food sector and beyond. Addition of sustainability measures as a component of regulatory assessments could increase the development of products that will support the UK ambition for clean growth and align with net zero targets.
- **Supporting the translation and innovation pipeline:** The UK is strong in science but needs to improve in research translation. To be able to reap the benefits of the numerous applications engineering biology is bringing to the agri-food space, a better infrastructure is needed to bring academia and industry together. Research translation may work well around hubs, where both academia and industry work side-by-side and can engage in joint projects with

interdisciplinary teams working on daring, innovative, and challenge-driven research. In addition, opportunities to work to scale - which are currently lacking in the UK - will benefit the research translation pipeline in the country and create greater national self-sufficiency. Public investment in such infrastructure will attract private investment and supercharge the sector. Furthermore, grant programmes providing match-funding for joint projects between industry and academia (such as Innovate UK grants and the IB catalyst fund) have proven very useful and should be expanded and diversified. Lastly, training of professionals to achieve both academic and commercial skills is important to support the translation pipeline (as also mentioned below).

- **Creating a supportive business infrastructure:** The UK bio-economy can benefit from a vibrant and stimulating start-up culture. Countries like Israel and the US are frontrunners in this area and we can learn from their approach to create a similar culture in the UK. Focus will be needed on investing in or attracting; **(i)** infrastructure to facilitate a better merge between academia and industry, including incubator space, **(ii)** interdisciplinary and international training programmes, including accelerator programmes, to increase the number of commercially-minded academics, and **(iii)** venture funds that can invest more for longer to overcome the start-up "valley of death". Such initiatives will attract international attention and can help strengthening the UK's ties with partners abroad.

Long-term funding plans:

Importantly, **policy and regulatory changes will enable cost savings** that could bring major financial benefit to the agri-food sector. In addition, to support the above described ecosystem recommendations, we propose a number of **public investments** over the next 10 years, as outlined below. These investments could fit in well with the UK's goal to tackle current global challenges and its commitment to spend 2.4% of GDP in R&D by 2027, as published in the UK Research and Development Roadmap[6]. The proposed public investments are likely to attract further **private investments** into the sector.

Proposed public investments in the agri-food sector over the next 10 years:	**Amount:**
Government support for companies in the agri-food space (Following an anticipated 2:1 ratio of private versus public money[5] this amount could support 60 companies with £20M public funding each)	**£1.2Bn**
Government support for innovation hubs (This amount could support 2-3 hubs)	**£600M**
Government support for scale-up facilities (This amount could support 4-6 facilities)	**£300M**
Expansion of grant schemes to support the innovation pipeline (This amount could support existing grant schemes and/or be used to build new, interdisciplinary grant schemes)	**£250M**
Expansion of investment funds to support the innovation pipeline (Following an anticipated 2:1 ratio of private versus public money[5] this amount could support 2-3 investment funds with £15-£20M public funding each)	**£50M**
Novel interdisciplinary training programmes (With a minimum of 30% industry match-funding, this amount could support a training programme for 6 cohorts of 15 students with a focus on science and business)	**£10M**

The above-described ecosystem recommendations all feed into each other and have the potential to create a positive feedback loop. The proposed measures could therefore have a synergistic effect on the UK bio-economy and its goals to reach net zero by 2050.

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A3: Engineering Biology in Healthcare – Analysis and Recommendations

- **Market Segmentation**

The healthcare technology market can be separated into sectors by function. The major being therapeutics, diagnostics and public health. The UK the healthcare technology sector size is in the top 5 globally and in 2019 had an annual turnover of £70 Billion with a CAGR in excess of 3% of which £30 Billion was as exports. The therapeutics sector is the second largest market sector in the UK measured by GVA and is twice the size of petrochemical and chemical industries combined. The sector is also the most R&D intense in the UK with more than a third of all employees being focused on R&D activities.

However, medicines manufacturing is not as large as it once was with many companies moving their activities abroad., In addition the coming years the continued growth of the sector is threatened by a disconnect between the budgetary growth of healthcare providers and the increased cost of healthcare solutions. This issue is exacerbated by an aging population in developed nations and an increase in prevalence of "lifestyle diseases" e.g. diabetes, obesity. These factors mean that continued growth is reliant on new technological developments aligned with relevant changes in economic, ethical and legal frameworks.
The UK pharmaceutical industry has the potential to be the spiritual home of Engineering Biology in the UK. The adoption of new methods and techniques provided by Engineering biology in the next decade as an inherent part of the industries activities will provide both new therapeutics and new production paradigms. This sort of technology shift has happened before, for example, the second global technology revolution in pharmaceutics, which led to the use of monoclonal antibodies as therapeutics, was only made possible by cellular engineering required to enhance yield and purity of antibody products. Now new modalities of biologic drugs are coming to the market such as bispecific antibodies and TrYbes which require whole new rounds of cell engineering for efficient manufacture. The pharmaceutical industry is also looking to synthetic biology and engineering biology to provide the next therapeutics revolution through cell-based therapies like CART therapy where the aim is to cure and not just treat. The UK Government should be congratulated for investing heavily in this aspect of engineering biology through a number of initiatives including the Cell and Gene therapies catapult (including a recent investment of £70.6 Million)

The global diagnostics sector has annual sales of $41 Bn which focus mainly on customers in large scale healthcare providers (e.g. NHS). There are currently two strong technology development trends in clinical diagnostics towards more point of care testing and tests that provide better patient stratification. There is also a realization that the distinction between therapeutics and diagnostics is diminishing as new therapies require better diagnostics to inform clinical decision making.

The public health sector is focused more on disease prevention than post disease therapy. Conventionally this has been through health messaging and provision of a clean and safe environment. The advent of synthetic biology approaches to eradication of vector bourne disease and population level healthcare interventions (e.g. microbiome engineering) mean that the influence of engineering biology will grow significantly in the future. In addition, new environmental monitoring sensors based on engineering biology approaches will help provide a safe and secure environment for the UK population.

Impact from Engineering Biology

Engineering Biology and Synthetic Biology have already had significant impact on healthcare in all aspects. This is not surprising given the natural link between and inherently biological problem space and the biological nature of solutions produced using synthetic biology approaches. However, it is also clear is that in this sector these solutions have not historically been badged as synthetic biology. The reason for this is two-fold. First, many of these solutions developed parallel to the mainstream synthetic biology movement and so were not classified as synthetic biology by their developers. Secondly, in healthcare (like agriculture) management of customer perception of products is exceptionally important and industry has been very keen to manage the messaging regarding new products. However, given these caveats it is clear engineering biology has revolutionised parts of healthcare and will continue to do so.

Therapeutics: Improved therapies to cell-based cures

The COVID crisis has highlighted the influence Engineering Biology can have on the speed of therapy development. For example, Moderna was able to use Engineering Biology to move from the viral DNA sequence to a potential vaccine in less than a month. A process that would have taken years using non-Engineering Biology approaches. This example highlights that the influence of engineering biology on the future of therapeutics will be significant.

To simplify how Engineering Biology will influence the future of healthcare development the sector can be separated streams. In the first place the integration of engineering approaches in the production of current therapeutics has a potential to drive down cost. For current therapeutics this process is already begun and increases in yield are now being realised, but engineering biology applied to the cells that produce these therapeutics has the potential to increase yield and quality further. New therapies (e.g. Bi-specific antibodies) are also producing new challenges that Engineering Biology will have to solve.

Engineering biology also provides new and improved routes for developing conventional therapies. For example, engineered enzymes provide pharmaceutical chemists with access to new compounds for drug discovery. In many cases these compounds will no longer be created from petrochemical feedstocks reducing the carbon burden of the industry.

The second aspect is the influence of engineering biology approaches on the development of entirely new therapeutics and therapeutic approaches. Those in the industry see this area as potentially the most fruitful and believe that engineering biology could produce the next therapeutic revolution.

There are already signs that the transition to a new paradigm based on cell replacements rather than drug therapies is beginning. The establishment of CART therapy, where cells are removed from a person, “reprogrammed to recognise a cancer” and returned to the body gives a glimpse of such approaches. The approach provides technical challenges that are closely aligned to the capability of EB which has the potential to both provide novel routes for “reprogramming” as well as address the production challenges associated with such an approach (including those of product quality and purity). If the trend, begun by CART, continues then it is likely that ever more complex cell or even tissue replacements will form a central part of healthcare. These could be unmodified replacements of worn or diseased tissue or modified version of tissues with restored or even improved function.

EB will provide the tools reduce the cost barrier to these therapies as well allowing innovation in the therapy space itself. It should also be noted that the use of a cellular-based approach which introduces autonomously sustainable cells to a patient provides a paradigm shift for healthcare by potentially providing a permanent cure rather than a treatment.

Diagnostics Development: towards multimodal embedded bio-diagnostics

The recent COVID-19 crisis has starkly highlighted the capabilities and insufficiencies of modern clinical *in vitro* diagnostics technology (IVDT). With the exception of DNA nanopore sequencing, much of IVDT development has stagnated with only iterative improvements in performance being made, gained through minor changes to existing approaches. This contrasts with the growing need for richer streams of patient data required to compliment new therapies. This is particularly true for stratified medicine approaches which (as detailed in the previous section) have the potential to result in better clinical outcomes and reduced adverse effects. What is required from future generations of IVDT is clear, diagnostics need to be able to monitor a wide range of physical and chemical signals as close to the patient as possible. The COVID pandemic has also highlighted that these tests must be simple and cheap (ideally <£10 per test). Engineering Biology approaches have the potential to provide true, multifunctional point of care testing platforms addressing the clinical need while also reducing cost. These systems will allow GPs and patients to monitor conditions at home. When matched with 5G networks and AI such approaches will provide a complete shift in how we monitor and manage disease. In the next stage we are likely necessitating direct implantation of engineering biology-based sensors into patients with the development of an effective integration into silicon-based technology for data capture, storage, and transmission. The challenges of new sensing modalities and biology-machine integration are perfectly suited to an EB style approach. This could include the development of new nanoscale hybrid silicon-carbon sensors or generation of engineered cells that can measure multiple signals and perform low level signal processing before passing the signal on to a silicon-based instrument. Already work of this kind is occurring at low TRL with groups integrating receptor proteins into cellular chassis linked to metabolic and genetic circuits for data integration. The challenge is going to be to integrate these new modalities into healthcare economics systems based on cost per single test (generally carried out at a central laboratory).

Public Health and Prevention: Population-based healthcare solutions

Since the inception of modern medicine it has been clearly understood that the most cost effective way to keep a population healthy is to prevent disease. For more than 200 years public health efforts have revolutionised our wellbeing, from the development of modern sanitation to campaigns to reduce smoking these have made perhaps the largest effect on global health.

Modern EB approaches are beginning to provide new approaches that could lead a renaissance of public health where prevention comes before treatment. For example it is likely that micro-organisms engineered using Engineering Biology will provide permanent solutions to resistant public health challenges like antimicrobial resistance (AMR). These approaches are not without significant ethical and legal issues that will have to be resolved if they are to be put to larger scale use. In these cases, there are also ethical and legal challenges which would have to be addressed. If these were resolved, then EB also has a place in industrialising these solutions to provide the required material for use. Another area of significant interest in public health is the use of modified gut microbiomes to control disease. All humans have a complex microbiological community resident in the gut which provides numerous benefits to health. It is known that perturbations of this microbiome can cause significant health issues and that these can be resolved by repopulation of the microbiome. It is also possible to modify individual species in the microbiome to produce chemicals that could aid population health. For example, introducing metabolic pathways for vitamin production or production of immunomodulatory molecules for atopic populations. Again these interventions challenge current health economic, ethical and legal frame works but could provide significant step changes in the health of certain populations.

- **Eco-system challenges and requirements**

Structural challenges

The structure of the healthcare technology sector is heavily influenced by strict regulatory structures which means that the research and development environment is more rigidly bounded then many of the other Engineering Biology sector. New products and services not only have to provide a market advantage to a business but they also have to provide patient benefit as measured by external parties and have to align to strict regulations. This does not mean that producing a vibrant and effective R&D environment for Engineering Biology is impossible. Instead it means that interventions must be design that fit into this structure. It is also absolutely key that the regulatory environment in the UK is nimble allowing regulations to change rapidly to incorporate new game changing innovations. The need to develop novel regulatory approaches is detailed in the next section.

To rapidly progress the development of engineering biology solutions for healthcare in the UK there is an urgent need to enhance and coordinate the research community (both academic and commercial). The UK needs to link up healthcare practitioners (the problem setters), academic scientists (the solution finders), commercial scientists (the translators) and social scientists (Regulation innovators) to provide an ecosystem where the time from problem identification to market solution is minimised. This is particularly important in a global environment where are competitors are currently more “fleet of foot” in innovation than the UK. Funding is the key enabler for developing such an ecosystem with previous experience of catalyst funding mechanisms providing a tested exemplar. We propose a catalyst+ fund that provides funding for projects that involve all stakeholders together in problem solving teams that manage a project through from low to high TRL. To ensure that we have a workforce that can execute Engineering Biology approaches in the future we also propose the need for Industry Partnered Doctoral Training Centres focused in the specific training required for this sector. These need to be complemented by some capital investment in UK facilities including GMP laboratories.

It is also important to recognise the crucial importance of innovative SMEs in this space. Our healthcare SMEs have been historically disadvantaged (perhaps more than any other sector) by the lack of venture funding. This is keenly felt in this sector where time to market is crucial and where the cost of the commerciallisation process is perhaps higher than any other sector. To address this issue it is essential that a fund is established to accelerate the growth of our Engineering Biology SMEs.

Ethical Challenges

The UK’s significant investments in research, development and translation for healthcare technologies will fail to deliver the expected benefits unless it is accompanied by the adoption of smarter, more adaptive regulatory systems that are more proportionate to the benefits and risks of todays advanced innovative technologies. This is particularly the case for engineering biology-based technologies, often requiring intimate integration with robotic and data-based innovation. When faced with a new health technology with no clear regulatory precedent we have most often adopted a version of the drug-based regulatory system and application of this approach, for example, to biologics, medical devices and stem cell based therapies, has led to serious delays in the translational process and in many cases failure to commercialise potentially useful innovations.

The more demanding the regulatory system, the more an innovative sector is dominated by the business models of very large scale providers and the more difficult it is for smaller companies to develop disruptive innovations that challenge the strategies and business models of the incumbents. The result is an innovation ecosystem that is dominated by incremental innovation, with a relative dearth of the disruptive innovation that could lead to major health-related breakthroughs, potentially delivering significant national competitive advantage. Rather than adapting new technologies to fit incumbent regulatory systems, we need to adapt our regulatory systems to fit better with the needs of innovative technologies.

UK government departments are aware of this challenge and are taking a leading role in the development of new, more proportionate and adaptive approaches to the governance of innovative technology sectors. This approach is summarised in the June 2019 White Paper on Regulation for the Fourth Industrial Revolution (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807805/regulation-fourth-industrial-strategy-white-paper-print.pdf). As part of the implementation of these commitments, the Regulatory Horizons Council (RHC) is being set up with a remit to identify the implications of technological innovation, and provide government with impartial, expert advice on the regulatory reform required to support its rapid and safe introduction.

Radical change in regulatory systems will require public reassurance that standards of safety, quality and efficacy are still being maintained. With that in mind, Innovate UK has funded the British Standards Institution to produce a standard for responsible innovation (PAS 440; https://pages.bsigroup.com/l/35972/2020-03-17/2cgcnc1?utm_source=pardot&utm_medium=email&utm_campaign=SM-STAN-LAU-PAS-PAS440-2003). This standard guides companies on how to ensure responsible behaviour as they develop an innovative product or process and also on how to demonstrate clearly that they have done so.

Both the 2019 White Paper and the 2020 PAS 440 are designed to apply to any innovative technology and the EBLC would like to draw the Government’s attention to the opportunity to use these two initiatives to support the translation of EB-related technologies to viable, profitable markets, transforming the UK innovation ecosystem for these developments, encouraging inward investment, and supporting development within the UK of innovations emerging from publicly funded research.

- **Summary**

As can be seen from the opportunities outlined in this document there is a real potential for Engineering Biology to revolutionise healthcare approaches in the UK. This includes not only improvements in citizen health but also growth in profitability of our healthcare sector and a reduction in reliance on fossil fuels. To realise this potential critical “pinch-points” in the UK must be resolved. To address these issues, we propose the following interventions.

Engineering Biology for the UK – A Resource to help Build Back Better

1) A reboot of the highly-successful Innovate UK "IB Catalyst" as the "engineering biology for healthcare" catalyst+. Like previous catalyst funds the programme must:
    a. address all TRLs to ensure a sustainable development pipeline
    b. involve significant partnership from industry to ensure alignment with industry need
    c. involve funding for significant networking activities to provide a single academic:industry Engineering Biology R&D community for the UK

2) Establishment of a Government commission linking NHS professionals, regulators and researchers to resolve future ethical and regulatory issues that will emerge from the use of engineering biology in healthcare

3) Establishment of an Engineering Biology for Healthcare Growth Accelerator Fund to give our innovative spinouts the investment required for them to out accelerate businesses in other jurisdictions

4) Establishment of Doctoral training programmes that link Engineering Biology researchers with NHS trusts and healthcare businesses with the aim of generating a new Engineering Biology workforce for the future

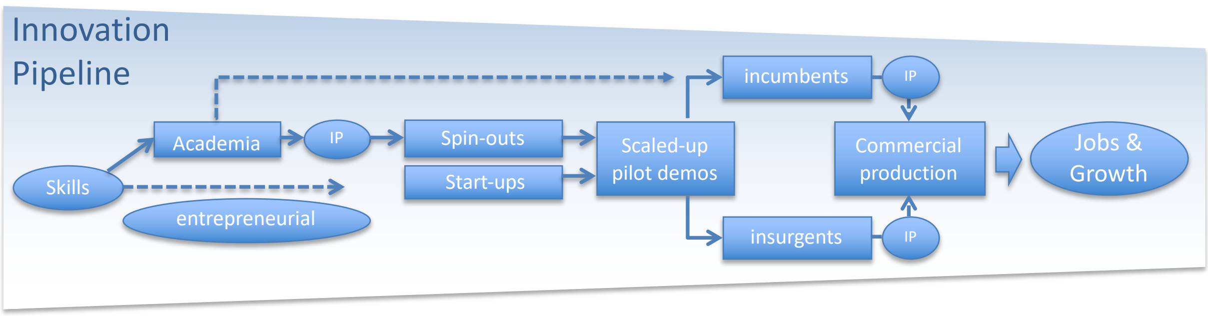
5) Investment in publicly funded GMP production facilities in research institutions and close to primary care for production of new engineering biology-based therapeutics for small scale clinical trials. This step in the development process is currently a significant pinch point in the development process.

A4: 'Trailblazers', Infrastructural Support Requirements and Recommendations

The concept of a 'trailblazer' is to commit to a particular definable concept derived from a clear UK-based research opportunity that is broad enough to permit a wide range of approaches and the engagement of numerous industrial participants, yet is specific enough to address a clear set of market and policy needs.

Commitment to drive it forward should help tease out and drill down into the main blockers and constraints as well as highlight the main forms of incentive and success factors. Importantly, it will serve to 'stress test' the entire UK innovation pipeline, and help shape the innovation 'eco-system' as a whole which has tended to be supported in a rather fragmented and disjointed manner to date and needs to be reviewed for fitness of purpose in the contemporary world.

The objective is certainly not to prioritise a specific application opportunity over any of the many others that can be currently envisaged, but rather to help shape an improved 'eco-system' that will expedite the pathway that others will follow and ultimately accelerate the rate at which multiple options from our research base can be translated, commercialised and grown in future.



Whilst the listing of generic 'asks' is relatively straightforward based on the compilation and summarisation of many inputs, the selection of specific examples to prioritise in the immediate short-term is based on a broad perspective spanning many factors, but also inevitably somewhat subjective.

When using 'specific' examples to illustrate the 'general', the approach must not be misinterpreted as picking the 'best' applications, nor serve to divert attention from the many other valuable applications in the pipeline. The approach adopted here has been to draw upon the many applications emerging from our research base and consider topics that are considered technologically doable in the near future (demonstrators exist either in the UK or elsewhere in the world) and align with current government policy priorities and prevailing market trends, but should also help test the strengths and weakness of the UK innovation support system as a whole. The generation of a rolling programme of 'trailblazers' in future years, as and when they represent a suitable state of market viability could ensure vibrant progress towards meeting longer term national economic and environmental goals.

Summary
Engineering Biology generates potentially significant and innovative opportunities, in response to rapidly increasing and urgent demands for solutions to national and global environmental and health challenges. A high priority is to review prevailing regulatory frameworks to ensure that development of the best solutions spanning the application space will not be needlessly inhibited, whilst at the same time ensuring that public and environmental safety is maintained and recognised

at every level. Effective stakeholder engagement, transparency and communications are key factors that need to be integrated and resourced to this end.

Specific initial 'trailblazer' suggestions discussed within the EBLC include the manufacturing of 'synthetic spider silks' and the effective development and scaling up of gaseous carbon ('C1') emission bioconversion technologies. The former has potentially far-reaching end market applications and job growth opportunities yet is being developed primarily outside the UK despite our extensive research expertise. The latter could play a key role in future CCUS plans which will support the trajectory towards net-zero in the UK, but could also be deployed through international partners committed to climate change solutions.

These initial suggestions fall primarily within the Materials/Chemicals market segment. Within the agri-tech category, trail-blazing options include the generation of 'alternative food' and resilient crops, as follows:

Agriculture is a major contributor to global greenhouse gas (GHG) emissions; it is the fourth biggest GHG emitting sector in the world [Ref 1; Figure 1]. Within the agricultural sector, the largest proportion of emissions currently come from conventional animal farming [Ref 2]. Therefore, **a shift from animal-based products to plant or fungi-based products will significantly reduce GHG emissions.** Within the crop sector, an important contributor to GHG emission is the release of nitrous oxide from the application of fertilizers [Ref 2,3]. The crop sector is also largely dependent on synthetic pesticides (fungicides, insecticides, herbicides) for optimal output. The production of synthetic pesticides requires petrochemical feedstocks and generates GHG emission during production and application. Synthetic pesticide use can present a significant burden on the environment and is becoming increasingly regulated [Ref 4]. **Reduction in the use of synthetic fertilizers and pesticides will have a major beneficial impact on the environmental sustainability of the agriculture sector.**

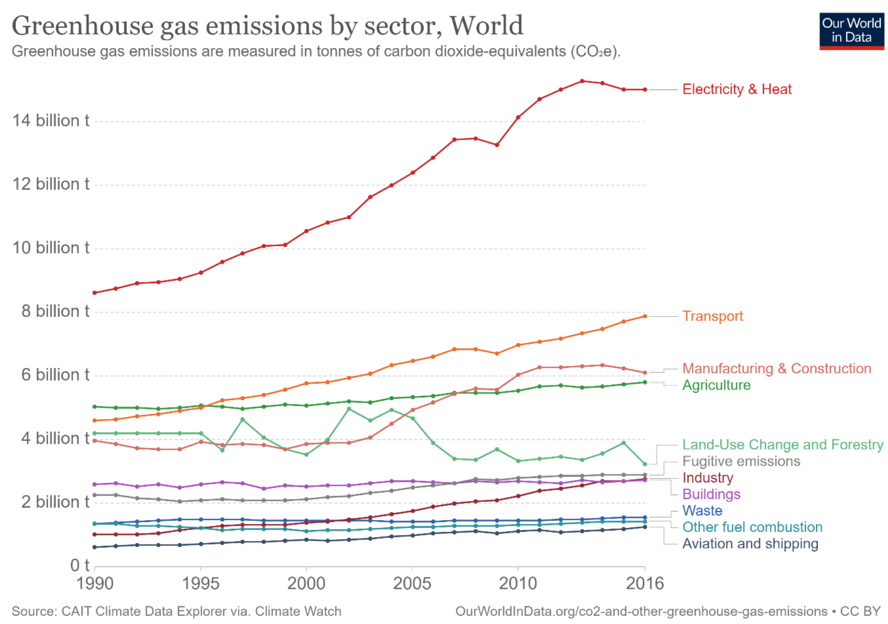


Figure 1: World greenhouse gas emission by sector (https://ourworldindata.org/co2-and-other-greenhouse-gas-emissions).

Engineering biology is a revolutionary enabler to achieve these goals:

- **Alternative food; shifting from animal-based protein to plant/fungi-based protein:** Engineering biology can (i) unlock novel plant/ fungi-based food sources, and (ii) support the development of animal-free protein products. First, through engineering biology, previously underutilized plants and fungi can be modified to accommodate human nutritional needs and crop system requirements. Second, the health benefits of meat (heme-iron and vitamins) can be transferred to plant/fungi-based products, while the health benefits of non-animal products (e.g. low levels of saturated fats) are retained. Moreover, the texture and flavour of meat can be mimicked. "The Impossible Burger" in the US is an example of this; this is the beginning of a global development in which the UK can play a prominent role.

- **Resilient crops; reducing synthetic agricultural inputs (fertilizers and pesticides) and improving crop performance:** Engineering biology can improve crop fertilizer-use efficiency, biotic and abiotic stress resistance and yield through crop genome engineering, bio-based pesticide development and microbiome optimization. Such advances will greatly reduce the agricultural inputs required and lower the environmental burden of the sector. Engineering biology has the potential to create a resilient and strong crop sector that supports the national and the international market in a sustainable manner.

The points listed above are examples of the game-changing potential that engineering biology can have on the agri-food sector. However, they do not do justice to the breadth of the sector, which is captured more extensively in the Agri-food Sector report presented to the EBLC on the 28th of July 2020. For a wider view with further examples and details we refer to the full report.

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Healthcare/Pharma initiatives relating to the 'trailblazer' approach

Healthcare has been a major focus of synthetic biology commercial applications to date, especially in the areas of service provision and specific developments, such as the diagnostics. This has been especially the case recently due to the needs for rapid responses to the Covid-19 pandemic. Recommendations in this segment relate more to the need for investment into supportive infrastructures and regulatory frameworks, as follows:

1) Biomaterials foundries: Working in a similar way to the DNA these would be centres that host the instrumentation to allow novel biomaterials to be produced on small scale and tested. This sort of fits with the Spider web idea, but I would not limit ourselves to just one system. Ideally you would want these to be thematic as, for example, a foundry for clinical materials would need different facilities compared to one for structural materials. These foundries would house state of the art equipment focusing on increasing the throughput of experiments allowing rapid iterative design and testing of new materials. There would also be an element of computational modeling of materials to enhance in silico design.

2) Centres for Advanced Engineered Therapies and Diagnostics would also be very helpful. At the moment we really have a disconnect between the truly innovative stuff coming out from EB and the ability to refine and test under the regulatory requirements required for trials. Solving this issue, perhaps in a partnership with one or more of our pharma, could really accelerate the speed of translation of these new to the market products.

3) A policy commission to develop regulatory frameworks for engineered therapies in the future. This is absolutely essential as in some ways the clarity on regulation (if it is lenient enough) will catalyse a lot of inward investment.

Acknowledgments: EBLC Working Group Leads and Contributors

Materials and Chemicals: Working Group Leads
Richard I. Kitney (Co-Director of the UK National Industrial Translation Centre for Synthetic Biology SynbiCITE)
Nigel Scrutton (Director, UK Future Biomanufacturing Research Hub and SYNBIOCHEM)

Sustainable Food and Agriculture: Working Group Leads
Dieuwertje van Esse-van der Does (Programme Manager, OpenPlant)
Jason Vincent (Vice-President of Technology, Tropic Biosciences, former Head of Synthetic Biology, Syngenta)
Anne Osbourn (Director, Norwich Research Park Industrial Biotechnology and Bioenergy Alliance)
Dale Sanders, (Director, John Innes Centre)

Healthcare: Working Group Lead
Tim Dafforn (Professor of Biotechnology, University of Birmingham)
Susan Rosser (Director, Edinburgh Mammalian Synthetic Biology Research Centre, Co-Director Edinburgh Genome Foundry)
Liz Fletcher (Edinburgh Mammalian Synthetic Biology Research Centre, Centre Manager)

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David Tew (GSK)

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Kirk Malone (Director of Commercialisation, Manchester Institute of Biotechnology and UK Future Biomanufacturing Research Hub)
Joyce Tait (Founding Director, Innogen Centre; University of Edinburgh)