Written evidence from The Rosalind Franklin Institute (ENB0042)

The Rosalind Franklin Institute are a UKRI funded Institute dedicated to creating new technologies to advance human health. Our developments span several areas relevant to Engineering Biology, including imaging tools for atomic scale resolution of tissues and biopsy samples, enabling the imaging of novel reagents and labels in cellular context, new tools for light microscopy, and novel time resolved instrumentation for life sciences. Of most relevance to this call is our theme in Next Generation Chemistry for Medicine, which is dedicated to creating new chemistries relevant to labelling and theragnostic applications, developing techniques and applications for post translational modification of proteins, and peptide or protein engineering via novel means (e.g. light modulated reactions for in vivo chemistry).

We understand that UKRI have provided a full response, so we have only addressed two of the questions where we believe that relatively small investments in the field could yield major returns, or afford the UK a global advantage.

These notes have been prepared by Professor Ben Davis, our Director for Next Generation Chemistry.

2. What are the key applications for engineering biology?

The 2005 European Union commission report on, then, 'New and Emerging Technologies' highlighted presciently a comparison between Synthetic Organic Chemistry and its ability to create small molecule pharmaceuticals and Synthetic Biology's ability to create next-generation 'Synthetic Biologics'. It is striking that whilst we have become used to the idea of unnatural small molecules as drugs, it is still not the case in the large molecule/protein field.
Whilst many current small molecule drugs bear no resemblance to parent natural products, although likely inspired by them in many cases, the field of Biologics (in all of protein, RNA and DNA technologies) makes only small changes from natural counterparts. The vast molecular variation that may be possible in these biomolecules is therefore barely explored. **The creation of such synthetic biologics through synthetic biology therefore remains a powerful opportunity** after two decades.

By combining advances in synthetic biology with advancing in in vivo chemistry, it is possible to extend these methods to allow editing or chemical change of biomolecules in context either on the surface of isolated cells for cellular therapies or inside living organisms.

An enormous opportunity exists in the role of synthetic biology to create a market in sustainable production, potentially based on circular economies in fermentation from biowaste.

It is already widely appreciated that 'cellular factories' might enable the production of certain small molecule chemicals and that fermentation can create some larger 'biologics'.

It is perhaps much less appreciated that **the industrialisation of next-generation medium sized biologics [such as peptides <50 amino acids in length] are reaching an imminent crisis point**. These peptides are of a size that may be accessed through the 'classical' (50-year) methods of synthetic chemistry using non-aqueous solvents and excesses of chemical reagents with a large associated waste stream – despite their great promise, this is unsustainable.

Recent examples of attempted industrialisation of highly powerful anti-obesity peptides and anti-diabetes peptides have highlighted that the global capacity for this type of industrial peptide chemistry is already near-exhausted, despite the coming onto stream of greatly expanded capacity in recent decades. This has been further exacerbated by the restriction of a critical solvent in certain parts of the world (e.g. EU): dimethylformamide (DMF).

An emerging opportunity exists to combine natural methods with synthetic/engineering biology with fermentation of precursors from biological sources i.e. use of natural proteins and then their late stage conversion into the synthetic, unnatural peptides needed as drugs. This form of hybrid 'Synthetic chemo-biology' is an opportunity identified by certain industries but not yet developed or addressed.

7. What are the possible barriers and limitations to good and effective use of engineering biology?

Many in the field of Synthetic Biology would argue that its ongoing growth requires all of the tools of both 'Synthesis' (the craft of molecular assembly / bond-breaking and making) and 'Engineering' (pipe-like modularity / 'Biobricks'). Many synthetic biologists would perhaps consider themselves to

be more akin to architects designing, for example, next generation biologics and biological circuits, using all of the tools of computation, informatics, chemistry, biochemistry, biology and physiology. The field has opportunity to be a ‘broad church’ beyond typical definitions of traditional academic disciplines. This ‘braod church’ requires training which is inclusive and develops interdisicplinary and multi disciplinary skills and teams.

There is a peculiar to the area of synthetic biology that is linked to (semi-historical) factors around legislation and licensing of biologics. The creation of varying categories of biologics (e.g. biosimilars) has in recent years allowed some greater freedom. That said, the unified pathway that is found for small molecules is not found for larger biomolcules.

In seeking to understand ‘synthetic biologics’ there are illustrative examples that have hinged critically on the influence of legislative bodies such as the EMA and the FDA and their distinct approaches to these different classes. One surprising example is the lack of absolute purity required for forms of protein biologics. It is the case that most industrial biologics are made biologically and hence, almost certain to be made as a spectrum of different protein isoforms.

This is despite the fact that the technology exists to create pure proteins and yet is not widely adopted. This is an example of barrier to market entry that, if disrupted, could afford the UK opportunities.

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