WHAT HAS SYNTHETIC BIOLOGY EVER DONE FOR US?

The opportunity for the UK to be a leader in "SynBio" for human health

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SYN-WHAT?

Synthetic biology ("SynBio") is a term that is likely unfamiliar. This is understandable, given that even within the SynBio community there are still debates about its exact definition, and many even within the wider biotechnology sector are unfamiliar with it.

Those who are familiar, and on the sceptical end of the spectrum, would likely say SynBio is little more than molecular biology as we already know it "rebranded". I think I occupy a slightly curious centre ground on the topic since I am a huge advocate for the field, but even I can relate to this somewhat cynical idea. To me, there are two types of SynBio. Just as there exists "pure" and "applied" mathematics, I believe there exists the 'purists' discipline, that concerns itself with genetic circuits, modelling, and trying to make biology into, effectively, a branch of engineering; and the 'applied' flavour, which at its core is about building on the capabilities of nature to create new functions and utility - "putting biology to work".

Whatever your perspective, synthetic biology as it exists today is an incredibly broad church, and covers advancements in everything from smart materials and bioremediation, to sustainability and therapeutics[1]. During the Parliamentary and Scientific Committee (P&SC) session on this topic in February, I made an argument in favour of investing in SynBio for this very reason. Not only does it have the potential to impact practically every challenge that we face in the 21st Century (climate change, ageing populations, food equity and so on), in doing so it draws upon the modern scientific pantheon, including AI/computing, chemistry and engineering. Investing in this "confluence" of modern science also means driving advancements and delivering benefits across far reaching areas of our technology base and economy.

SYNTHETIC BIOLOGY IN HUMAN HEALTH

My passion for SynBio has culminated in co-founding my company, NanoSyrinx, specifically to address a real challenge in a particularly difficult area - namely precision drug delivery. This is an area that I firmly believe synthetic biology can make, and already has made, significant waves, with the hope being that our technology is similarly disruptive.

Over the past century science has become exceedingly good at finding and developing new medicines. Though almost paradoxically, the failure rate is still >90-95%, and it takes over a decade and billions of dollars in the process[2]. Much of the reason for that failure rate is that *finding* potential therapeutics is merely the beginning, and is arguably the easiest part of the whole endeavour. Where the rubber really meets the road, and failure skyrockets, is when these candidates are taken through *in vivo* development (animal models and early human trials). Suddenly you are faced with the various systems of the body, evolved over millennia specifically to keep the 'non-self' (i.e. your drug) out. This is where advancements in drug delivery systems, and "precision medicine" more broadly, come in.

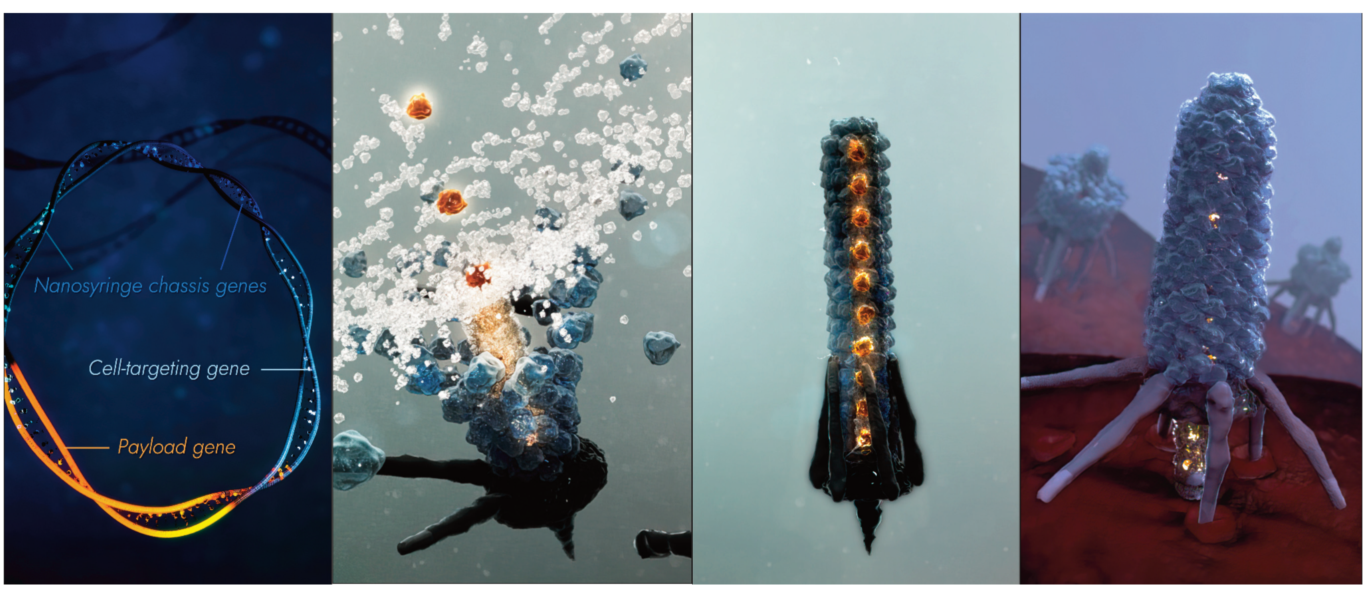
At NanoSyrinx, we are developing a novel delivery system 'powered' by a synthetic biology platform. Originally deriving from a bacterial toxin mechanism, the delivery system resembles a nanometre-scale 'syringe' (referred to as "nanosyringes") that can literally inject protein molecules across the membrane barrier of your cells. Modern SynBio tools give us the capacity to modify practically every single amino acid (~100,000) in each nanoparticle, simply by altering its DNA 'blueprint'.

Advances in gene editing, and the falling costs of DNA synthesis and sequencing are all instrumental parts of SynBio which mean a company like ours could not have feasibly existed even 15 years ago. Drug delivery is just one example of an area which stands to be greatly improved with the power of synthetic biology and a case in point of how investment into synbio - for example DNA synthesis tech - directly impacts wider fields of medicine, industrial biotech and so on.

Part of the reason I am so captivated by our technology, and SynBio generally, is that they are 'manifestations' of what excites me most in science - leveraging nature's existing solutions to solve human problems. Our nanosyringe system is one esoteric example of an evolutionary solution to the problem of "moving molecules across biological membranes", and evolution is a far better molecular biologist than we are.

So the question becomes: what other challenges has nature already solved? During the Parliamentary session I gave several examples of cases from within the healthcare space alone where we're leveraging solutions.

Perhaps the most obvious example to cite here, would be the COVID-19 vaccines developed in the last 3 years (though of course vaccinology as a discipline far pre-dates modern molecular/synthetic biology). Vaccines work *with* the immune system, essentially leveraging nature's solution to keeping us healthy and protected. Our ability to rapidly design, iterate

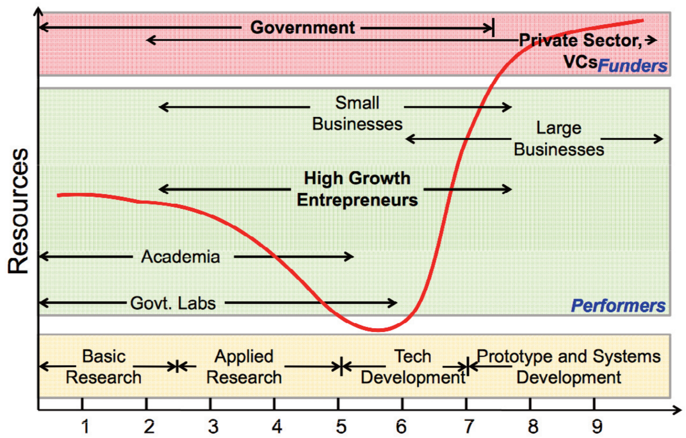


The basis of the NanoSyrinx "nanosyringe" technology. (Left) A genetic construct comprises all of the building blocks for the nanosyringe 'chassis', the therapeutic payloads it contains (orange), and its "cell targeting" protein (blue-black). (Centre-left) The nanosyringes 'self-assemble' when produced using laboratory bacteria, producing a 'loaded' delivery vehicle. (Centre-right) The completed nanosyringe protein complex depicted as a cut-away to reveal the payloads (orange) within. (Right) The nanosyringes bind to the surface of the cell and push a needle-like structure through the cell membrane (maroon) to deliver the drug payload.

and manufacture an mRNA vaccine (for instance), is a prime example of what synthetic biology can do, and is hugely exciting for the future of public health[3]. Much of the same enabling technology for our nanosyringe system applies here too: cheap DNA sequencing and synthesis, advances in expression and purification methods and so on.

Comparatively old hat today, advances in antibody therapy are nevertheless SynBio through and through. These also increased in prominence during the pandemic as we explored monoclonal antibody COVID-19 therapies, but they have been on the front line of new cancer treatments for many years. For example, Keytruda is an antibody therapeutic approved for at least 19 different cancers[4], making it one of the most impactful therapies to date, and best selling medicines of all time.

Another major recent paradigm in biotechnology has been the development of viral-vector based cell and gene therapies. This subsector of modern therapy concerns the engineering and utilisation of naturally occurring human viruses. Viruses are almost uniquely evolved/equipped for the purpose of conveying genetic material into mammalian cells, and we leverage this behaviour to create novel therapies for diseases previously considered intractable if not incurable. These therapies can address a variety of diseases, from repairing/replacing defective genes, to generating cancer-cell killing immune responses and even curing blindness[5]. It bears repeating that what makes these approaches particularly remarkable is that they can not just treat, but cure patients of previously debilitating and incurable diseases in as little as a *single dose*[6]. The list goes on, but I believe these examples more than demonstrate the power of SynBio for human health.



The "Valley of Death" (as seen in the red line) and players involved in translation from early academic and foundational research to commercial prospects. The x-axis numbers are Technology Readiness Levels (TRLs). Image credit: the National Defence Industrial Association.

THE UK'S POTENTIAL

The UK has a real opportunity right now to become not only a science superpower, but a *SynBio superpower.* Many pieces of the puzzle are already in place, with a world-leading research base including top tier Universities & non-profits, a progressive and forward-looking NHS who are already embracing the power of gene therapies[7] (something the US is uncharacteristically slow to do) and a springboard for high-potential ideas in the form of ARIA, UKRI and the excellent VC ecosystem.

To ensure that happens, a number of key themes emerged from the P&SC session. Firstly, SynBio's multidisciplinary nature puts it at risk of 'homelessness' within the UKRI framework, where research is (understandably) siloed. For example, SynBio is nominally within the remit of the BBSRC, but that typically focuses on industrial biotechnology and sustainability - so what becomes of early stage therapeutic projects that are too 'immature' for the MRC? They are left exposed to the second theme: a funding problem. The "Valley of Death" is still a barrier to early stage, high-risk-high-reward, projects progressing through translation/commercialisation. At the other end of the spectrum, there is a dearth of growth capital, and it is considered largely impossible to list a biotech company on UK/EU stock exchanges, making it hard to retain these businesses. Lastly, this funding gap combined with what can, at times, be a 'stifling' academic entrepreneurial environment in the UK (compared with e.g. the US), means translation and commercialisation has roadblocks in its path that need not exist. Programs like InnovateUK's ICURe scheme, which I personally benefited from, are helping enormously here (the secret sauce of which is the shifting of focus to early career researchers-turned-entrepreneurs), but there is work still to be done in improving general academic attitudes to commercialisation which can disincentivise potential entrepreneurs.

I will conclude in much the same way I did during the P&SC session: SynBio is going to happen - we must ensure it happens *here* or risk the UK being left behind.

References

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