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editorial

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Synthetic biology – reimagine drug discovery

Synthetic biology is a term used to describe an approach by which novel artificial biological pathways, organisms or devices are designed and constructed [1]. Bringing together skills from biology, chemistry, bioinformatics and engineering, it applies engineering-like techniques, at scale, to solve biological problems through a rational process of 'biodesign'.

With the potential to deliver a wide range of new and innovative products to several industries, including the pharmaceutical industry, synthetic biology presents the opportunity to exploit biology as never before, to transform the field of drug discovery. This will lead to the discovery of new medicines, which could potentially result in major improvements in healthcare and patient outcomes. For example, the field of immuno-oncology has yielded chimeric antigen receptor technology (CAR-T), a cancer cell therapy which engineers a patient's own immune cells to fight cancer and has already shown significant benefits for certain patients [2]. CAR's are effectively discovered much in the same way as monoclonal antibodies, an established method to engineer new therapeutic drugs. CARs are not obtainable naturally and have to be engineered. There are currently two CAR-T therapies on the market, which have been available since 2017 (Novartis' Kymriah [3] for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) and Gilead's Yescarta [4] for patients with relapsed or refractory large B-cell lymphoma), and there are many more advancing through the clinic as scientists work to overcome the remaining technical and regulatory challenges.

The momentum building in the application of synthetic biology in industry, including drug discovery, is due to a number of driving factors. The continual decline in costs and increases in the speed of genome sequencing, utilising next-generation sequencing (NGS) technologies, is enabling a greater understanding of disease and uncovering a universe of hitherto-unknown opportunities for biologics. Also, the decreasing cost and greater efficiency of DNA synthesis is providing more access to synthetic genetic material, enabling more powerful genetic engineering capabilities than ever before.

However, the way synthetic genetic material is currently made and supplied is limiting progress and to achieve its full potential, synthetic biology will require the continued development and convergence of its underlying skills and disciplines, to enable the rational and predictable design of biological systems. Fundamental to its success will be the capability to synthesise genes rapidly, at scale and with high accuracy, and to regulate and edit genes to create desirable phenotypes.

Antibody therapeutics

A recent survey of worldwide industry professionals from pharma, biotech, academia, CDMOs, CROs, service providers and consultancies conducted at the Antibody Engineering & Therapeutics conference highlighted that biopharma remains focused on monoclonal antibodies, with 81% of the organisations surveyed focused on developing monoclonal antibody therapeutics [5]. But there are challenges that persist, especially in their discovery and development. For example, respondents agreed that the discovery stage requires a more accurate approach and technologies.

Many of the most fundamental processes in the discovery and development of therapeutic proteins, in particular monoclonal antibodies, rely on synthetic DNA. It is likely that over the coming

https://doi.org/10.1016/j.drudis.2019.10.009

Please cite this article in press as: Brooking, S. Synthetic biology – reimagine drug discovery, Drug Discov Today (2019), https://doi.org/10.1016/j.drudis.2019.10.009

years the marriage of next-generation sequencing, increased bioinformatics power and synthetic biology will establish a new paradigm for biopharmaceutical discovery and the opportunities are significant for emerging technologies that can help to deliver this.

Biopharmaceuticals, and in particular monoclonal antibody drugs, represent the majority of the biggest-selling drugs with Humira [6] (adalimumab) being the clear leader in terms of global revenue. First described in 1975 by Kohler and Milstein [7], monoclonal antibodies have been used clinically since 1985 when the FDA approved Orthoclone OKT3 (muronomab) for acute transplant rejection. When it became apparent that this fully-mouse antibody was rapidly rejected by the recipient's immune system, the field of therapeutic antibody engineering emerged. This has evolved into the current multi-billion-dollar industry that has revolutionised the treatment options available to patients with a multitude of different diseases, although antibody therapies have been particularly prevalent in the treatment of autoimmune and oncology disease indications.

Monoclonal antibodies are developed using different methods and a variety of approaches, but all with a significant requirement for synthetic DNA. The ability to rapidly and rationally generate diversity for *in vitro* antibody discovery allows, for example, the creation of *in silico* designed libraries that harness the power of bioinformatics, allowing for screening guided by protein structural expertise, thereby facilitating the discovery and development of novel therapeutic proteins with desirable properties.

DNA libraries

The design and construction of synthetic DNA libraries has been a major application for synthetic DNA technology within the antibody therapeutics area for many years [8]. Although once made, the libraries can be used indefinitely, most are constantly being refined as the information generated provides feedback about the success of campaigns and the extent to which this can be attributed to factors that may form part of the design process. Using modern synthetic biology approaches, libraries can be constructed using favourable subsets of antibody genes and diversity can be introduced within the antibody sequence with great precision. This fine control ranges from removal of problematic motifs such as stop codons, through to precisely defining the relative proportions of specific amino acids at single positions. As a consequence, the resultant libraries have increased functional content and antibodies derived from them have reduced risk of sequence related liabilities that might impair the development of a compound with drug-like properties. The 'Slonomics' technique (developed by Sloning GmbH, subsequently acquired by Morphosys) was an early example of a synthetic biology approach that accommodated fine-tuned sequences composition control in libraries [9].

These requirements have all contributed to the dramatic increase in both scale and efficiency of synthetic DNA manufacture, together with the rise of new gene synthesis technologies. Both provide the opportunity to significantly improve the rapid and efficient generation of rationally designed synthetic DNA libraries, where controlled diversity at specific positions can be applied to libraries for discovery screening as well as for affinity maturation (the process by which an antibody sequence is reiteratively improved) and the optimisation of candidate antibody sequences (for example, through optimisation of codon usage). The tools that enable these developments are DNA sequence information, metagenomics, bioinformatics and protein structure-activity relationship information, coupled to the ability to synthesise DNA and test many variants, either as proteins in isolation or as libraries. Further benefit can be gained from combining these developments with synthetic biology strategies that also contribute to the exploration, understanding and optimisation of the target and disease biology to streamline the discovery process and develop novel solutions based directly on the underlying biology.

NGS technologies

The rapid development of NGS technologies has created opportunities for re-thinking aspects of the conventional biopharmaceutical drug discovery process, by using data processing power as a substitute for intensive screening of physical molecules. This approach is still relatively unproven and has both advantages and disadvantages; however due to the potential for this to develop significantly in the coming years it is important to consider its potential impact.

Conventional antibody drug discovery is based on a process that has not fundamentally changed over ~30 years; different methods have been used to create diversity and the ability to perform screening at ever higher throughput continues to evolve, but the selection of antibody-expressing clones, production of the antibody and assessment of binding/functionality remain the principal mode of operation. The ability to sequence at massive scale has shown that there are potentially alternative ways to identify lead antibodies for therapeutic development [10]. By combining the power of NGS with synthetic biology, this approach could effectively double the output diversity and content from a single selection experiment. In addition to the clones obtained using traditional screening methods, the sequences of clones found in abundance in an NGS output can now be synthesised in an optimised form and introduced into secondary screening assays.

The future of synthetic biology

It is clear that synthetic biology has the potential to impact many aspects of drug discovery, but the scale of the impact will depend on the further development of its underlying technologies. These include DNA synthesis, powerful bioinformatics, suitable chassis organisms and the ability to build/engineer pathways and organisms in a predictable fashion. In the same way that DNA sequencing underwent a revolution in the mid-2000s resulting in massive parallelisation and reduction in cost, a comparable breakthrough in DNA synthesis would catalyse many opportunities in this area, especially for optimising the drug discovery process.

Synthetic biology has the potential to become, at least in part, the solution to many of our present and future needs in medicine. Through global research efforts, synthetic biology is providing insights into pathways and processes that underpin all living systems; in turn, we can take this insight and design and use it to build a ''better biology''. Beyond the examples discussed above, the impact of synthetic biology on drug discovery will be broad, including the development of novel vaccines (e.g. antigen genes or nucleic acid vaccines), gene therapy (with its requirement for

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synthetic DNA), CRISPR-Cas9, and other cellular engineering techniques.

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Please cite this article in press as: Brooking, S. Synthetic biology – reimagine drug discovery, Drug Discov Today (2019), https://doi.org/10.1016/j.drudis.2019.10.009