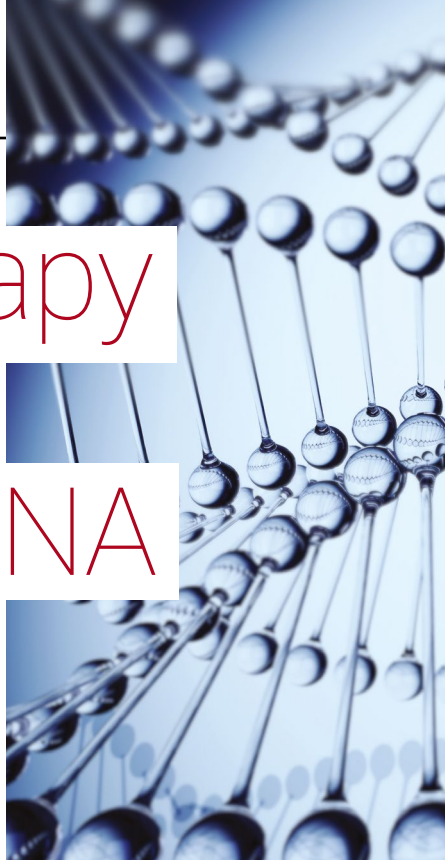


Accelerating biotherapy and personalised medicine with long DNA

Matt Hill, Founder and CEO of Elegen writes about the importance of innovation in DNA synthesis to address critical bottlenecks in biotherapy development.

With advanced technology and a growing understanding of the underlying biology, biotherapy development has evolved. Since 2010, investments in the field have grown and the number of therapies launched globally has tripled. According to McKinsey & Company, from 2019 to 2021, venture capitalists invested over $52 billion in therapeutic-based biotech companies, with investments more than doubling between 2019 and 2020[1]. However, there are challenges to manufacturing patient-specific biotherapies in a timely manner; fast, reliable access to high-quality DNA remains a critical bottleneck that limits further progress.

The expansion of nucleic acid-based therapies

One factor contributing to increased investment during this time was the success of the mRNA-based Covid-19 vaccine. While concern swirled around its rapid development, mRNA-based programmes for infectious disease and cancer had been in place in biopharmaceutical companies for over a decade. The pandemic, and the development of its nucleic acid-based vaccines, brought attention to the need for faster healthcare innovations to meet medical challenges.

Because of the Covid-19 vaccine success, many drug programmes pivoted to mRNA-based strategies for other diseases, including influenza, shingles, multiple sclerosis, or heart conditions, with several therapies having regulatory approval or in clinical. Cancer vaccine programmes also gained interest, targeting tumour antigens that are often unique to the individual patient. Personalised medicine therapies, such as immunotherapies for cancers that are challenging to treat, are designed to elicit a patient's own immune response to identify and destroy cancer cells and prevent recurrence.

Regardless of the type of disease targeted, at the core of biotherapy development is synthetic biology and the use of synthetic DNA to programme specific behaviours within living cells. Waiting four-six months to test a new synthetic DNA design, in a series of design iterations, can delay the development of a biotherapeutic candidate by months. Further, scaling up to the amounts of a particular DNA sequence at the quality required for clinical use can add additional critical months of delay and hundreds of thousands of dollars of cost, greatly limiting our ability to deliver these life-saving treatments to patients. The speed, accuracy, and cost of DNA manufacturing need to be addressed to enable personalised medicine.

Synthetic DNA in personalised biotherapy development

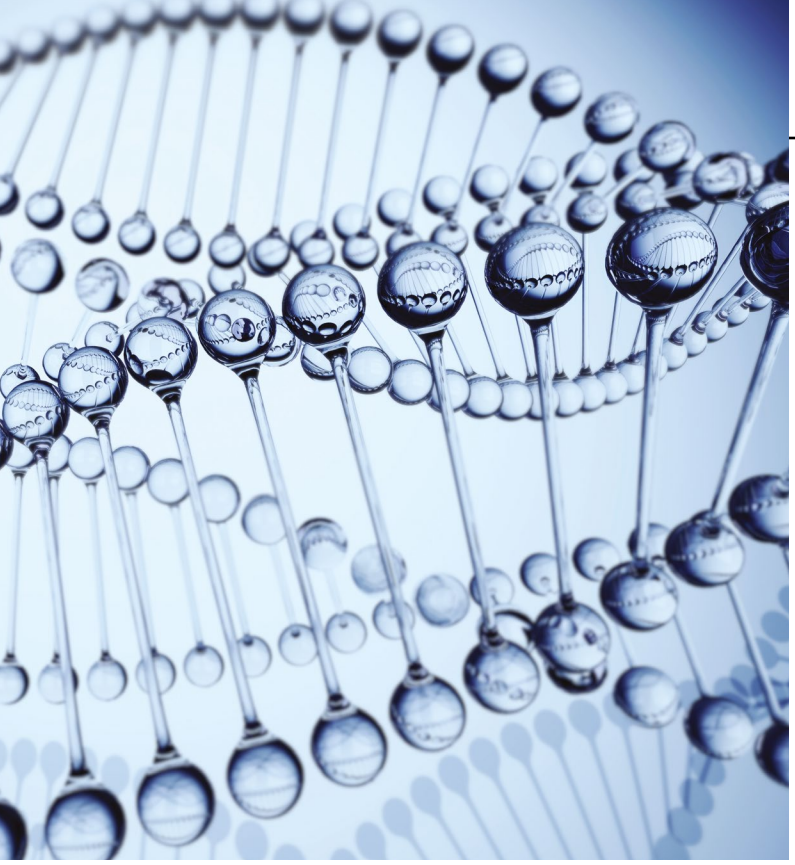
For decades, industry thought leaders have viewed the transition to personalised medicine as necessary for the future of patient care. As technology and our understanding of disease advance, so too do personalised treatments, which use a patient's unique genetic profile to develop targeted and effective therapies.

> **Most biopharmaceutical companies—and patients—however, cannot wait weeks or months for a supplier to generate a full-length, sequence-perfect gene.**

Central to realising this vision is fast and scalable synthetic DNA manufacturing that delivers full-length, sequence-perfect DNA in a short time to rapidly screen, validate and scale the production of biotherapies. Despite decades of development, DNA manufacturing technologies have evolved slowly to produce single-stranded oligonucleotides in the low hundreds of bases in length—a far cry from the high-quality, multi-kilobase, double-stranded DNA required to produce personalised cell and gene therapies at scale. Even with a fast turnaround of oligonucleotides, the time and effort required to build full-length, double-stranded DNA at the scale needed for clinical treatment are unworkable.

DNA engineering

A look at the workflow necessary to obtain accurate DNA at the length required biotherapy reveals the bottleneck. Once scientists identify a target sequence, they design, produce and test DNA molecules repeatedly. Each cycle takes a month or more to



complete. Scientists can spend several months producing and testing therapeutic candidates and even longer for more complex DNA sequences.

Currently, the production of long double-stranded DNA starts by assembling short single-stranded oligonucleotides of 80-200 bases into short double-stranded DNA fragments, typically up to 2,000 base pairs (bp) long. Due to errors inherent in the synthesis methods used, the short fragments must be purified by a cumbersome cell-based cloning process, where several copies of each fragment are produced and sequenced to identify a sequence-perfect copy. These sequence-perfect fragments are then assembled into longer strands of DNA, exceeding 20,000 bp in some applications, using several cycles of assembly, cloning, and sequencing. Sometimes it can take over six weeks to produce a sequence-perfect copy of the final therapeutic construct.

The DNA supply conundrum

To save time, many scientists are forced to deal with the conundrum: Outsource the DNA manufacturing process and risk unpredictable delays or purchase short fragments and invest time and effort to manufacture DNA internally. Both options take weeks to produce DNA used to develop therapeutic candidates, which then must be produced at a larger scale to treat patients. Clinical production can take months and typically involves an expensive process to produce a master cell bank from which a large amount of plasmid DNA is isolated and purified under GMP compliance.

Most biopharmaceutical companies—and patients—however, cannot wait weeks or months for a supplier to generate a full-length, sequence-perfect gene.

The conventional DNA synthesis workflow is a bottleneck for therapy development and is almost unattainable in terms of achieving the scale and turnaround time needed to treat patients. Eliminating the DNA supply bottleneck requires suppliers with innovative methods, strategies and technologies for producing long, highly accurate and complex double-stranded DNA on a fast and predictable delivery schedule on which biopharmaceutical companies can rely.

Next-generation synthetic DNA

It is estimated that over 5,000 biopharmaceuticals currently invest in biotherapies. These companies realise that enabling rapid and scalable production requires them to revisit their supply strategies and tap into innovative DNA synthesis solutions. As a result, their demand for high-throughput, cost-effective and production-ready synthetic DNA has put pressure on DNA manufacturers to rapidly deliver DNA that requires far less processing for biotherapy production.

Recently, several biotech startups have emerged that use enzymatic DNA synthesis technology to deliver synthetic DNA to scientists faster. However, most have yet to commercially launch products and are far from producing gene-length DNA at scale. While enzymatic synthesis has the potential to produce single-stranded DNA that is longer than chemical (phosphoramidite) synthesis, several rounds of assembly and cloning are still required to achieve full-length DNA.

More recently, new suppliers have emerged with a focus on producing long double-stranded DNA. These companies use innovative cell-free synthesis, assembly, and cloning strategies to accelerate and scale full-length DNA production. The result is highly accurate, multi-kilobase, double-stranded DNA that can be manufactured in days and used in therapeutic workflows with minimal or no additional cloning. Some biopharmaceutical companies have received high-quality, complex DNA as long as 7,000 bp in less than a week and full DNA constructs as long as 20,000 bp within two weeks, both ready for immediate use downstream.

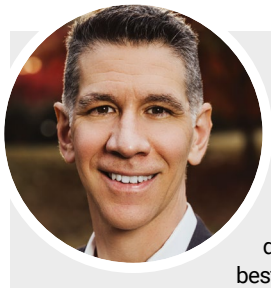
Driving down biotherapy development

Reliable access to accurate multi-kilobase DNA means biopharmaceutical companies don't need to invest in internal resources or external biofoundries for sequence assembly and cloning. Access to long, accurate DNA, delivered in as little as a week, has the potential to double or even triple production pace to bring products to market faster. Rather than spend resources in the mundane and labour-intensive process of assembling DNA, biopharmaceuticals can re-direct resources to testing, learning and designing therapeutics.

Through innovating the DNA and gene synthesis process, a new class of synthetic DNA supplier is ushering in a new era where faster access to high-quality, long DNA is the norm. It promises opportunities to develop new technologies and engineering paradigms that produce even longer, more complex DNA that reshapes the life sciences landscape.

REFERENCES:

1 Leclerc, O., Suhendra, M., and The, L. (2022, June 10). What are the biotech investment themes that will shape the industry? McKinsey & Company. https://www.mckinsey.com/industries/life-sciences/our-insights/what-are-the-biotech-investment-themes-that-will-shape-the-industry



About the author:

Matt Hill is the founder and CEO of Elegen. Dr. Hill earned his PhD from Stanford and was formerly Vice President of Research and Development at Natera where he co-invented and deployed their core technology in Natera's best-in-class non-invasive prenatal test used by millions to ensure healthy pregnancies, a product that enabled Natera's 2015 IPO.