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GSK and Elegen Team Up to Develop DNA-Based Medicines and Vaccines

The multi-year collaboration allows GSK to leverage Elegen's cell-free synthetic DNA production technology

By Jonathan D. Grinstein, PhD – January 24, 2024

When Matt Hill, PhD, was in graduate school, the human genome sequence was more or less finished and companies like 454 and Solexa were starting to make waves in next-gen sequencing (NGS).

But Hill became more enamored with synthetic biology—engineering the genetic material of organisms to forge new characteristics. Hill decided to devote his research to generating new genetic material, specifically DNA writing, rather than speed reading. But there's more to synthesizing long stretches of custom DNA than one might think.

"Many of the technologies and processes involved in making longer double-stranded DNA, or gene-length double-stranded DNA, are for reprogramming cells or therapeutics," Hill told GEN Edge. "It's not a straightforward, one-step process. It's a multistep, complex manufacturing process with several procedures involved, many of which are quite antiquated."

Hill set out to understand the pros and cons of the tested DNA writing methods. From this, he developed his own thesis, which became the foundation for Elegen Bio, which Hill founded in San Carlos, California, in 2017.

Six years later, in March 2023, Elegen launched ENFINIA DNA, which claims to deliver high-complexity, clonal-quality, linear DNA up to 7 kilobases (kb) in length—all NGS verified—in as little as seven business days. Researchers can log on and, with a few mouse clicks, order DNA sequences that cover the protein-coding regions of most genes, which are typically shorter than 7 kb (one study calculated that the length of human protein-coding sequences has a median of 2.93 kb and a mean of 3.52 kb).

But Hill always intended Elegen to be more than a DNA writing service—he wants to use synthetic biology to make medicines.

“There is an intention here to focus on the ability to make DNA under a documented quality process, which we think is going to be critical to the pharma customers at large,” Hill said. What’s important, he says, is “the ability to progress from a discovery process to development to the clinical stages with maximum speed and efficiency.”

Today, Elegen announced a collaboration and licensing agreement with GSK to enable the major pharma company to use Elegen’s proprietary cell-free DNA manufacturing technology to develop GSK’s vaccines and medicines.

The terms of the agreement include upfront fees and purchase commitments of Elegen’s ENFINIA DNA to support GSK’s vaccine and medicine development, including RNA vaccines. The agreement provides Elegen up to $35 million in near-term financial and development support and fees, in addition to sales of ENFINIA DNA and a potential equity investment in Elegen by GSK. Elegen is also eligible to receive both near-term milestone payments relating to developing new product features and a potential equity investment in Elegen by GSK.

Hill said the partnership will likely support Elegen in advancing its DNA technology platform to become faster and produce longer DNA sequences with greater complexity for applications such as in vitro transcription (IVT) of mRNAs.

“IVT-ready DNA streamlines the work that many of these types of customers need to do to get to a point where they’ve got an mRNA vaccine or therapeutic program and are exploring a lot of candidates,” said Hill.

Venn diagram of long DNA sequence production

Writing large quantities of long DNA is a complex, multi-step process typically involving oligo synthesis, assembly, and amplification. “DNA production is actually not just synthesis,” said Hill. “Synthesis, properly described, is really the only step going from nucleotides to oligos. Then you take that material, assemble it, and purify it.”

There are a few approaches for the first step, oligonucleotide synthesis. Phosphoramidite chemistry has been the gold standard since the 1980s, with improvements. For example, Twist Bioscience’s core innovation was a semiconductor platform that miniaturized phosphoramidite chemistry to make single-stranded oligomers, which they use to bring down costs.

Phosphoramidite chemistry has also been improved with the introduction of enzymatic oligo synthesis, which can produce longer DNA strands of higher quality while using less toxic chemicals and in the “biological” orientation (with an intact 5’-phosphate group). Molecular Assemblies, founded by one of the developers of enzymatic DNA synthesis, J. William Efcavitch, PhD, developed a technology that employs a template-independent DNA polymerase called terminal deoxynucleotidyl transferase (TdT), which can synthesize longer DNA sequences with fewer errors. Some companies have even developed benchtop instruments for enzymatic DNA synthesis of oligos, such as DNA Script and Evonetix.

But Hill thinks the enzyme-based DNA synthesis approaches are marginally better than phosphoramidite chemistry in terms of error rate and do so at a much higher cost.

It is in the subsequent assembly (or cloning) and amplification steps where Hill see the greatest opportunities because they are cell-based. The conventional method to make long DNA sequences

involves a cell-based process to isolate a small quantity of a perfect sequence, amplified in what Hill views as a cumbersome, complex, and slow process that often introduces variability and complexity. Because some of these sequences are toxic to cells, cell-based methods also have limited sequence types available.

While this is fine for most research purposes, as companies progress from discovery, where they only need small amounts of material, to clinical development, where they require larger quantities, DNA transitions from a research-use-only (RUO) product with no documentation to clinical development, which is a very different ball game.

“To be quantitative about this, the transition from a RUO DNA to a clinical-quality DNA with a documented process typically takes months and hundreds of thousands of dollars,” said Hill. “We want to eliminate those costs and those delays for these companies.”

Ribbon cutting

Hill isn’t alone in seeing the issues with cell-based methods for making large amounts of long, clinical-grade DNA. For the assembly step, companies like OriCiro Genomics have developed cell-free cloning. For the amplification step, Touchlight has developed a DNA vector known as “doggybone DNA” or dbDNA—a minimal, linear, covalently closed structure—that is amplified enzymatically in cell-free conditions.

The innovation behind Elegen’s ENFINIA mostly focuses on using molecular barcodes to facilitate cell-free cloning and DNA amplification (described in the patent US20230399636A1). Research into Elegen’s other patents has to do with the use of microfluidics to facilitate cell-free cloning and DNA amplification.

But Elegen might not be alone when it comes to this approach. Ribbon Biolabs has developed patented technology based on “precise enzymatic synthesis in microfluidic reactions” (described in patent US11352619B2), which was announced nine months before Elegen on July 19, 2022. Ribbon Biolab’s patent describes a method for synthesizing dsDNA using a diverse oligo library, which they claim enables the efficient production of DNA greater than 10 kb with high speed, including a 20-kb sequence for one undisclosed pharma client.

The Elegen advantage may have more to do with their ability to drive commercial-scale mRNA synthesis for vaccine development and production. Elegen’s DNA templates—comprised of an antigen sequence and several recognition sequences, including a capping region, untranslated region (UTR), and a poly-A tail—support the IVT of an mRNA with post-transcriptional stability and translatability.

According to a poster on Elegen’s website, this capability enables a streamlined workflow and may save time and resources spent iteratively cloning, linearizing, and purifying plasmid DNA and generating master cell banks. These innovations, which could power the next generation of mRNA vaccines and cell and gene therapies, are likely a major component of what brought GSK to the table and ultimately sealed its partnership with Elegen. After all, the mRNA vaccine industry shot to great heights with the COVID-19 vaccines and is being expanded into cancer, as highlighted by the recent successes of the melanoma vaccine from Moderna and Merck.

Elegen’s ability to produce “NGS-verified linear DNA” up to 7 kb within a week with error rates as low as 1:70,000 per bp (99.999% per base accuracy) could be an important marker as it tries to establish a leading position in a heated race to deliver what could be the next major medicinal breakthrough.