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Accelerating the Pace of Drug R&D with Synthetic Biology

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The slow pace of drug discovery and development continues to be a significant obstacle for bringing potentially life-saving therapies to patients. Critical bottlenecks include an inefficient manufacturing process hindered by the intrinsic characteristics of the drug itself, technical limitations spanning vendors, instruments, and infrastructure, as well as difficulties accessing materials (i.e., DNA fragments, viral, or other vectors, etc.) required to design and test therapeutics.

Synthetic biology is a powerful solution for addressing these bottlenecks. By deepening our understanding of biological systems, widening the genetic design space, and enabling rapid iteration of new designs, synthetic biology can accelerate the discovery and development of novel treatments. We recently spoke with several companies that have developed critical enabling technologies for drug discovery and development with synthetic biology, gaining valuable insight into its current achievements, what the future looks like, and key areas that need to be addressed for us to get there.

Synthetic medicines for a healthier future

Synthetic biology in drug discovery and development isn't new: it was nearly 50 years ago, in 1978, when Genentech developed and licensed the first biosynthetic human insulin molecule, produced in *E. coli*. Microbes not only will continue to be used to produce biologics like insulin, but we are likely to see an increase in engineered microbes that can produce complex biologics and small molecules, says Adam Clore, Technical Director of Synthetic Biology at Integrated DNA Technologies (IDT), which provides a range of services, from custom oligos to CRISPR gene editing.

But how else does synthetic biology support drug discovery and development? The better question may be, how doesn't it? We've seen important successes, such as the development of CAR T cells used to cure certain cancers and lipid nanoparticle and exosome alternatives to viral vectors for delivery of payloads. Lipid nanopores and exosomes "demonstrated significant utility during the recent COVID pandemic, proving crucial to enabling mass vaccination," according to Dr. Brian Burke, Chief Commercial Officer at Tozaro, which develops synthetic affinity reagents to improve the analysis and purification of viral vectors used in cell and gene therapies.

Synthetic biology also promises to deliver important improvements to current technologies, such as improved accuracy and reliability of CRISPR/Cas9, decreased reliance on in vitro systems, more effective and versatile payload delivery systems, the generation of specific cell lines and animal models of disease, more precise control over the expression of engineered therapies, and automated screening of drug compounds. All of these advances will ultimately shorten the time between discovery and clinical testing, says Clore.

We've already seen the impact through the rapid development and manufacture of new therapeutic modalities and COVID-19 mRNA vaccines, which are pure synbio products, says Thomas Ybert, Ph.D., co-founder and CEO of DNA Script, which has developed the SYNTAX® benchtop enzymatic DNA synthesis platform.

"Rapid DNA synthesis, mRNA production by in vitro transcription, and other synthetic biology best practices were critical for developing these new therapeutics faster than we've ever seen before," he explains. "This is a template we can use for many other areas of drug discovery and development moving forward.

Beyond speed, synthetic biology approaches to drug discovery and development can also contribute to a higher likelihood of success with regulatory bodies—particularly for complex therapeutics with little regulatory precedent, such as cell and gene therapies.

"By enabling precise genetic edits and control over biological systems, applied synthetic biology can standardize production methods, reduce batch-to-batch variability, and ensure higher-quality outcomes," remarks Cillian McGorman, Commercial Operations Manager of ERS Genomics. "This level of control is crucial in meeting the safety and efficacy benchmarks set by regulatory bodies, streamlining the approval process for new drugs."

All of this lays the foundation for precision and personalized medicine, which pose unique quality, safety, and regulatory standards because they are targeted to individuals or small groups of people with unique characteristics. All of the experts we talked to unanimously agree that synthetic biology will underpin the major therapeutic breakthroughs enabling personalized medicine, from vaccines to treat cancer to gene therapies for neurodegenerative diseases.

Better writing of better DNA

Clore believes that the “continual advances in artificial intelligence and computing power that allow researchers to rationally design experiments with greater chances of success” have and will continue to drive the success of synthetic biology-based approaches to drug discovery and development. However, there is one significant deficiency that remains. Although we’ve made incredible advances in reading and editing DNA, our ability to efficiently, reliably, and quickly write (i.e., synthesize) DNA lags behind, seriously hamstringing the development of innovative new bio-based therapies.

“Therapeutic discovery relies on the iterative design-build-test-learn cycle, where DNA synthesis (the build phase) remains a major bottleneck,” explains Randy Dyer, VP of Marketing at Elegen, which is “laser-focused on bringing long-overdue innovation to ‘DNA write.’”

“A lack of innovation in DNA manufacturing has limited the ability of gene synthesis providers to reliably meet customer timelines, especially as the length and complexity of designs have increased,” Dyer adds.

This is precisely why Daniel Lin-Arlow and his colleague Sebastian Palluk founded Ansa Biotechnologies, a company currently specializing in the synthesis of complex DNA sequences such as sequences with variation in CG content, repeats, or hairpins—sequences that are necessary to improve both viral and mammalian vector delivery systems, CRISPR/Cas9 cassettes, cancer vaccines, and many other components of advanced, precision therapeutics.

“If you take a random 5-kilobase chunk of the human genome and submit it to the leading U.S.-based vendors, they’ll only accept it for synthesis about 10% of the time—that really shows you how much opportunity to engineer biology is off the table right now,” laments Lin-Arlow. He says that in order to fully realize the potential of synthetic biology for advancing novel therapeutics, scientists need more—much more. “There are vendors that will try to synthesize 5 kilobase or even 10 kilobase complex sequences, but it’s not a routine service,” he says. “Five kilobases will barely fit a Cas enzyme and some additional machinery. Imagine you want to develop a CAR T cell with three receptors, a logic gate, and a transcriptional circuit: you’re going to easily blow past that 5-kilobase limit and you’ll almost certainly require some complex sequences.”

Leveling up

Putting longer, more complex DNA sequences into the hands of researchers is going to make a huge difference in the pace of drug discovery and development. Lin-Arlow says that Ansa has customers using their DNA to create cancer vaccines and complex cell and gene therapies. In fact, the company’s very first paid order was for a panel of promoters for precisely dialing in the expression level of the receptor transgene in a cell therapy—and he said such orders continue to be a theme as researchers increasingly aim for precise control over expression levels and, in the case of gene therapies, tissue-specific activation in the body. Elegen is working closely with biopharmaceutical organizations,

including global pharma giant GSK, to accelerate the development of genetic medicines and vaccines through the use of cell-free production of synthetic DNA.

And while DNA may be at the crux of it all, without groundbreaking technologies such as CRISPR editing systems or novel delivery systems, the therapeutic potential of DNA will remain unrealized. That's exactly why ERS Genomics takes their role in empowering researchers so seriously.

"By providing access to CRISPR, we facilitate the creation of disease models, the identification of drug targets, and the development of new gene therapies. Our work enables our partners and licensees to push the boundaries of what is possible in synbio, ultimately contributing to more efficient and precise drug development," says McGorman.

And, as we saw with the use of lipid nanoparticles for the COVID-19 vaccines, improved and alternative vector delivery systems for vaccines and cell and gene therapies are a crucial means for developing better therapeutics faster. This is an area that IDT works in, and they've introduced expression vectors that will accelerate research timelines for their customers.

"In the past, customers would order genes and then have to sub-clone them into an expression vector or onboard their custom expression vectors. Now they can get genes delivered directly in an expression vector," explains Clore. These vectors include mammalian vectors for gene expression and protein production, allowing customers to see the effects of those genes or proteins in cellular systems similar to the target patient population.

Looking ahead

Synthetic biology has already enabled the development of lifesaving therapies that were unattainable in the not-so-distant past. With advances in DNA synthesis, expression and delivery vector design and analysis, CRISPR, and other enabling technologies, the pace of innovation will only accelerate.

Not only will synthetic biology help make precision and personalized medicine routine, but it will also contribute to organ regeneration or "living medicines" that dynamically respond to changes in a patient's condition, says McGorman. Importantly, synthetic biology will also ensure that the medicines of the future are produced sustainably, further contributing to our health, as well as that of our planet, adds Lin-Arlow. Clore agrees: "Many products, including medicines, rely on rare plant species, and there are opportunities there to convert the synthesis of those products into bacterial expression systems. Scientists will no longer have to go into the rainforest to find rare species—they can just make ingredients in the lab."

There are countless opportunities for synthetic biology in the drug discovery and development space, and we're only just scratching the surface. As Dyer says, "we can't even fathom the capabilities synthetic biology will unlock at this point." But I'm confident that, given what we've already achieved, we won't have to wait long to see those capabilities delivered.