Biocompare
The Buyer's Guide for Life Scientists

Synthetic Biology Poised for a Big Impact

Synthetic biology, according to the theme of this year's Synthetic Biology: Engineering, Evolution & Design (SEED) conference held in Scottsdale, AZ, is now "at the leading edge of massive DNA synthesis, editing, and decoding." Using engineering principles to design and construct new biological systems—such as manufactured DNA sequences, microbes, enzymes, and standardized biological parts—synthetic biology has the potential to transform medicine and biomedical research, environmental science, agriculture, and information technology.

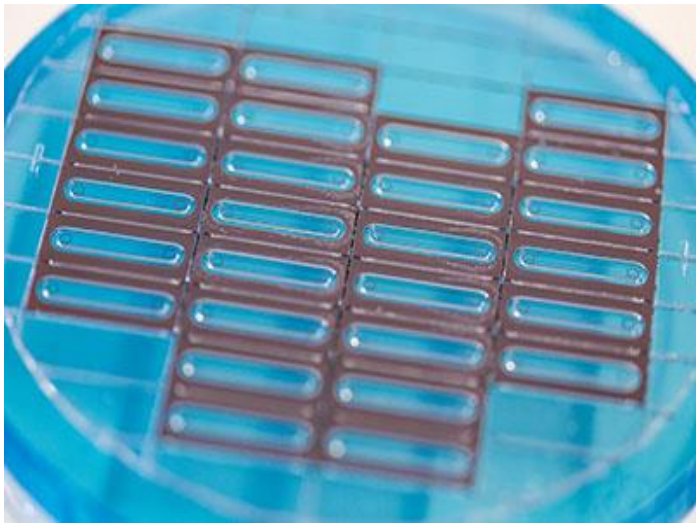
In 2009, synthetic biology companies in the United States raised about $200 million in investment capital, according to the advocacy organization Synbiobeta. By 2017, that figure had grown exponentially, to $1.8 billion, with an anticipated total 2018 investment of $3 billion. Here, we'll talk to some leading players in the field about recent developments in tools and technology, applications, and challenges for synthetic biology.

Making DNA at scale

In July 2018, Evonetix secured $1.75 million in funding from Innovate UK for its novel approach to DNA synthesis aimed at producing DNA at scale for use in synthetic biology applications. The funding will help to develop the company's enzymatic oligonucleotide synthesis, which operates under milder aqueous conditions than phosphoramidite chemistry, the current method of choice for DNA oligonucleotide manufacturing.

"Although there are many applications of synthetic biology across many areas, much of the current attention focuses on the biosynthesis of pharmaceuticals and other small

molecules," explains Evonetix CEO Tim Brears, Ph.D. "The key technological challenges here are largely about understanding and optimizing multistep pathways and being able to make DNA more efficiently," he adds. "Many biologically active substances derived from plants or other organisms are the result of complex pathways." One successful example made the headlines in 2015 when Stanford scientists announced that they had genetically engineered yeast to produce synthetic hydrocodone and launched a startup called Antheia to take their discovery to market, with the hope of designing less addictive opioids—but engineering 23 genes into yeast to produce hydrocodone at scale is a massive task.



And tasks like that, says Dr. Brears, is where Evonetix hopes to come in. "We are looking to make DNA at scale using silicone chips—long DNA, 10 or 20 or 50 kb, or hundreds of copies of a particular gene, at high fidelity," he says. "We're not quite there yet, but this will combine physics with engineering, electronics, software engineering, and the chemistry and biology that goes into DNA synthesis and assembly. There is now so much information out there that provides good starting points for synthetic biology pathways, but there are bottlenecks in the biology and in the DNA synthesis."

From floppy disks to DNA

DNA is more than just "the building block of life." More and more innovators are seeing it as the ultimate storage system, rendering today's storage solutions for big data—such as the exabyte-sized data storage farms planted in the Midwest by companies like Google and Microsoft—as dated as floppy disks.

Molecular Assemblies, founded on the premise of generating DNA through a two-step, aqueous-based enzymatic synthesis process that produces less waste and eliminates a post-synthetic processing phase, is working to reliably, affordably, and sustainably produce long, high-quality DNA for numerous life science applications. It is also one of a number of companies that aims to use the DNA it creates to store the unfathomably epic amounts of data being generated by life science research, government, industry, and, well, everything else.

“We’re generating so much data in the present time that there is some concern that you’d have to basically eliminate historical data to store new data,” says Molecular Assemblies CEO Michael Kamdar. (By 2025, the research firm IDC projects an estimated 163 zettabytes of data will be generated annually. One zettabyte can hold about 167 trillion high-definition movies.)

We often explain DNA to our digital-native children as the equivalent of the computer code: that makes a person who they are, storing vast amounts of data—about 800 megabytes of information, in fact—in each living cell. And indeed, DNA has been compared to a natural hard drive.

“Inside the body, DNA breaks down, but in and of itself, DNA is virtually indestructible,” Kamdar says. “And you can get so much data into DNA. Think about it this way: all the computing and binary code we use now is done using 0s and 1s. DNA is base 4, ACTG. And we have technology that we believe we can use to make it base 8 and base 16. That’s a logarithmic difference in how much data you can store using a very small piece of DNA, and it would scale from there.” (DNA that’s more than base 4? It’s not science fiction; in 2017, a team of synthetic biologists from the Scripps Research Institute, along with protein therapeutic discovery company Synthorx, announced that they had created a semi-synthetic organism with a base 6 nucleotide set.)

In August, Molecular Assemblies announced that it had taken a text message, encoded it using an algorithm, engineered DNA, encoded the message in it, and then successfully

retrieved it—a proof of concept. “The big question was, when you retrieved the data, was it the same message, not garbled like a game of operator,” Kamdar says. “We were able to do that.”

The company, which is funded by groups such as the Agilent, Data Collective, Alexandria Ventures, and Rising Tide, plans to present the data from this experiment at the Synbiobeta 2018 meeting in San Diego next month.

“Different people have different wants” from DNA data storage, says Kamdar. “Some may want a desktop data storage device that can process a million pieces of information a second. Others want data storage that’s not at their fingertips, but stored so that it is retrievable. We’re still in the early days of determining what the final versions will look like.”

RNA and immuno-oncology

Synthetic biology isn’t all about DNA, of course. RNA’s flexibility, along with tremendous advances in the field from the perspective of production and stability, has made it a major tool for synthetic biology—think CRISPR-Cas9, obviously. While the lion’s share of the work to date has been focused on synthesizing the naturally occurring messenger RNA (mRNA), some players in the field are using self-amplifying RNA.

“It looks like messenger RNA, but is able to express proteins at very high levels and allows a much lower dose for effectiveness,” explains Kurt Kamrud, a vice president at Synthetic Genomics who leads the self-amplifying RNA platform development group in the RNA Medicines program. “One of the biggest hurdles in synthetic biology is the innate immune response. The amount of RNA you need to reach a therapeutic threshold for a vaccine or protein-based therapy is higher if you stimulate this innate response—and they all do—and that’s where you get toxicity. The dose of RNA required to produce a therapeutic level is higher with mRNA than self-amplifying RNA.”

A growing movement in oncology focuses on neoantigens, peptides found only on the surface of cancer cells, which could be the target of synthesized immune-oncology vaccines. “Tumors with naturally large burdens of neoantigens are good targets for peptide delivery to let your body recognize those, see them as foreign, and remove the tumor,” says Kamrud. “This is one area where we are applying our system, the self-amplifying RNA sometimes called a replicon, which is capable of expressing essentially any protein you want. Overcoming the innate immune system is critical in a cancer setting, where people already treated with chemotherapy and/or radiation are in an inflamed state and not a good target population for standard vaccines.”

Synthetic Genomics now has data generated in small animal models demonstrating control of tumor growth with a vaccine developed using their system, and is presently completing the necessary primate-model studies to establish dosing for human trials. “We are looking to start IND-enabling studies in the first quarter of 2019, with the aggressive goal of having an IND submitted at the end of 2019 and human studies by the end of 2020,” Kamrud says.

This article was written by Gina Shaw and posted here on the 25th September 2018