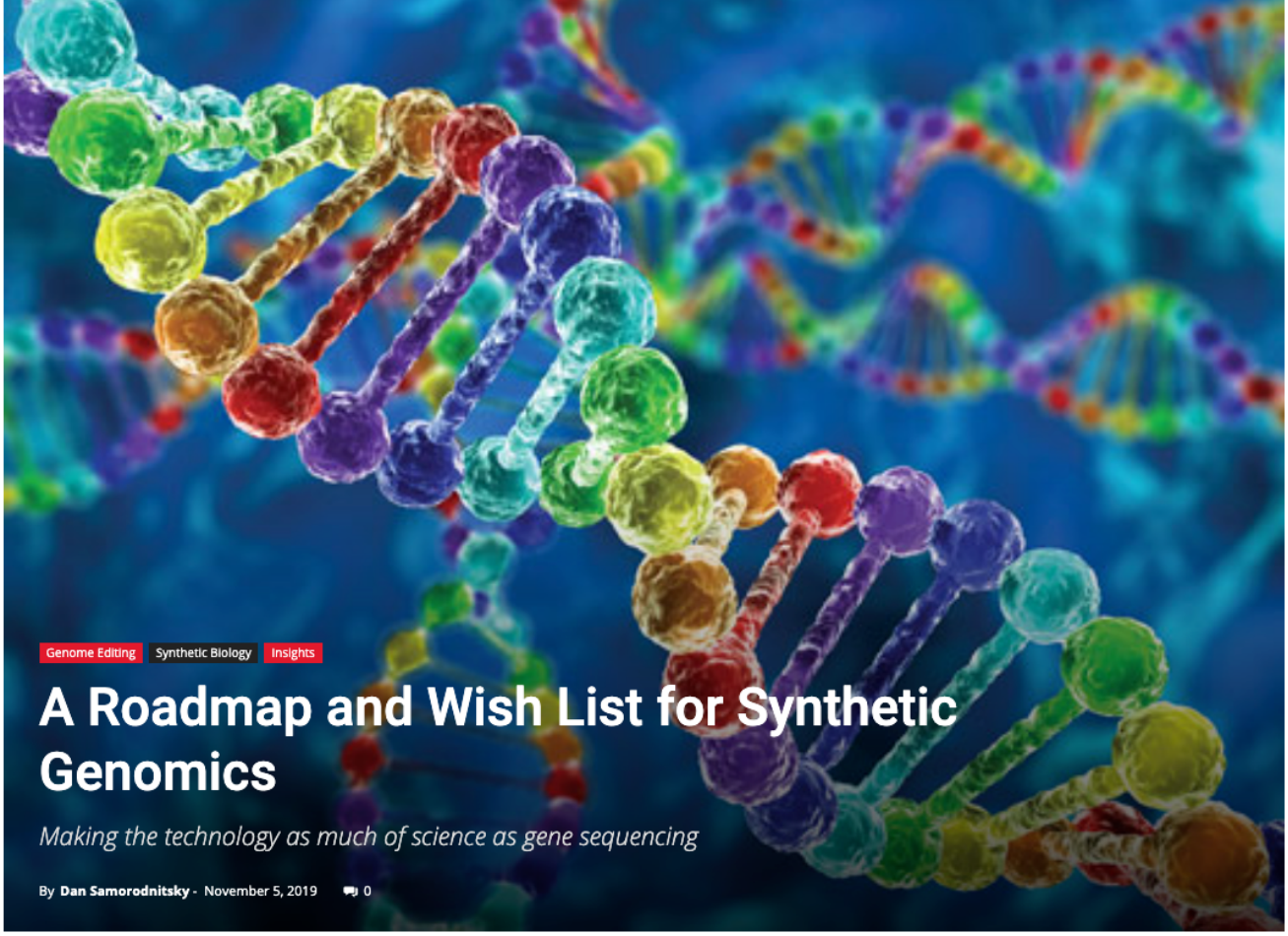

Genome Editing | Synthetic Biology | Insights

A Roadmap and Wish List for Synthetic Genomics

Making the technology as much of science as gene sequencing

By **Dan Samorodnitsky** - November 5, 2019 0

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We are already living in a synthetic biology world. Within that huge world is an enormous variety of ideas and approaches, like custom-made proteins, CAR-T medicines, genetically engineered crops, and more. One sector still in its infancy is synthetic genomics, where instead of one protein or gene, entire genomes are designed, synthesized, and implemented.

To make synthetic genomics bloom, it needs new innovations and support, concludes a new report by a consortium of scientists from academia and industry, published recently in *Science*. Nili Ostrov, PhD, (Harvard Medical School, HMS) and colleagues advocate for advances in four areas they believe are critical for making synthetic genomics as much a part of science as gene sequencing is today.

These are 1) improving the ability to synthesize DNA, 2) the ability to precisely and accurately edit DNA using tools such as CRISPR-Cas9, 3) the design of genomes, and 4) the ability to string together pieces of DNA and construct entire chromosomes.

The manifesto "is focused on what we think are the… major technological challenges and milestones we would like to achieve," said Ostrov, a postdoc in George Church's lab at HMS.

The authors are part of a working group at Genome Project-write (GP-write), a "not for profit organization that seeks to promote the development of technology for genome writing," says Jef Boeke, PhD, professor and founding director of the Institute for Systems Genetics at Langone Medical Center. GP-write "tries to bring together all of the groups that want to make that process easier to deploy, to solve a wide variety of biological challenges and problems both on the academic side as well as on the industrial side."

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Synthesize this

A major priority of the group and the *Science* paper is the current limitations on DNA synthesis. Economical commercial DNA synthesis (used for everything from PCR primers to whole chromosomes) relies on chemical synthesis. For decades this was laborious and prone to mutation until the invention of phosphoramitide chemistry. Despite this breakthrough back in the early 1980s, chemical DNA synthesis is limited to the several hundred-base-pair range–not nearly enough to string together a genome even with modern assembly techniques.

The authors suggest that future technology will boost enzymatic DNA synthesis beyond those lengths, powered by the high-processivity and accuracy of naturally occurring DNA polymerases. Since those polymerases need a template, research has turned towards terminal deoxynucleotidyl transferase (TdT), a DNA end modifying enzyme. TdT has been used since the 1970s to label double-stranded DNA, but turning it into a *bona fide* and economical polymerase has only come into focus in recent years.

"I'm very bullish on the need and opportunity for synthetic genomics… I think [the goals listed in the paper] are achievable," said Emily Leproust, PhD, CEO of Twist Bioscience, one of the largest suppliers of synthetic DNA. However, Leproust expressed confidence that current chemical synthesis technologies were capable of synthesizing entire chromosomes. "In the last 12 months, we've shipped 8 billion bases of DNA — that's almost three entire human genomes… We can do it at scale. If you want us to do the genome for you, we totally can do it today."

Within each overarching goal are various sub-goals. From the base of the "DNA synthesis" target, more specific goals include synthesizing particularly difficult sequences (high GC-content, repetitive sequences, and centromeres) and direct synthesis of long (1000+ base pair) sequences, bypassing the need for assembling multiple shorter sequences. The longest commercially available oligos fall well short of this; Twist Bioscience's longest available is 300 bp, while Integrated DNA Technologies offers 200 bp.

Finally, simply decreasing the cost–aiming for a $1,000 human genome within 10 years, or maybe even for significantly less money. This goal mirrors the long-standing goal in DNA sequencing to get the cost of sequencing a complete genome under $1,000. It currently stands at about $1,300.

Shots on goal

The authors recommend a public/private partnership similar to the Human Genome Project to enable the goals of GP-write. "Since genome construction projects are highly interdisciplinary efforts, a combination of different players will best drive this field forward. Some technologies, for example DNA editing, have been quickly adopted through academia and commercialized by startups. Lowering costs of chemical DNA synthesis has been driven by industry, and startups are pursuing enzymatic approaches" says Ostrov.

Other goals are focused on the design and function of the genomes themselves. As Boeke explained, "function" is key, as synthetic genomics can achieve results on a scale that related fields like protein engineering cannot. "It just enables you to work with a much larger canvas." For example, "design a virus-proof mammalian chromosome" is a goal with a three-year timeframe. Boeke says the goal was to "design" the chromosome, not necessarily implement it. But synthetic genomics has already made strides in this area, such as reassigning the UAG stop codon across the entire *Escherichia coli* genome resulted in strong resistance to T7 bacteriophage.

The final set of goals concerns chromosome construction and delivery. Today the gold standard for cells using synthetic genomes is the yeast *Saccharomyces cerevisiae*. "The efficiency of DNA assembly in *S. cerevisiae* has not been found in other genetically tractable organisms," the authors say. Once a chromosome or genome is constructed, how do you get it into a cell at all? That is one of the primary bottlenecks for biotechnology. Many see plant bioengineering as crucial for addressing climate change and agricultural problems, but it is hindered by relatively crude and labor intensive DNA delivery methods.

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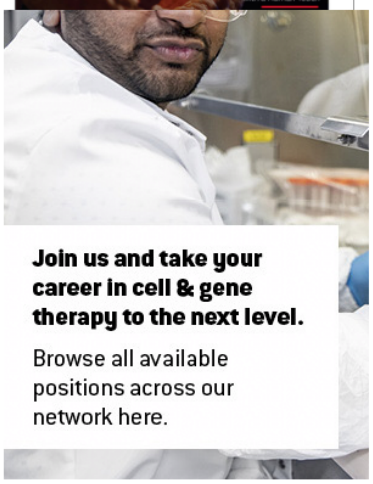

Boeke strikes an optimistic note. Citing research that showed that a DNA sequence on its own can direct its own expression, he said, "What about all the epigenetics and all the modifications of histones and DNA methylation and all that stuff that isn't there on the naked DNA? Does that all really just work when you put it into a stem cell and then differentiate that into a mouse? The answer is apparently, yes, it does work."

GP-Write will hold its next meeting in New York, November 11-14, 2019.

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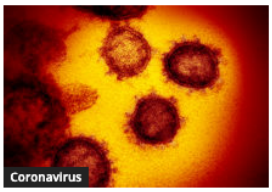

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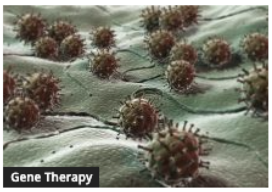

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