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Rewriting our future

Headlines about a proposal to engineer an entirely synthetic human genome largely missed the point.

Over 30 years after the Human Genome Project was first conceived, a group of 25 researchers is now proposing a complementary effort in whole-genome synthesis. The Human Genome Project–Write (HGP-write) aims to chemically synthesize an artificial human genome from scratch and "reduce the costs of engineering and testing large (0.1 to 100 billion bp) genomes in cell lines by over 1,000-fold within 10 years." The proposal—arising in part from an invitation-only meeting at Harvard Medical School in May and published last month in *Science* (doi:10.1126/science.aaf6850, 2016)—was greeted with alarmist headlines about synthetic life and secret meetings. But the part of the proposal that most coverage focused on—the feat of synthesizing an entire human genome—may be the least interesting and worthwhile aspect of the whole endeavor.

Since Gobind Khorana and colleagues' *tour de force* synthesis of a 77-bp tRNA gene in 1970, researchers have gradually been scaling up DNA synthesis from genes to genomes. It took until the early 2000s before the first whole genomes were synthesized: the 9.6-kb genome of hepatitis C virus in 2000, the 7.5-kb genome of poliovirus in 2002 and the 5.4-kb genome of the bacteriophage ϕX174 shortly thereafter. Researchers at the J. Craig Venter Institute (JCVI) then took construction a step further—building entirely synthetic replicas of prokaryotic genomes—with the synthesis of the 583-kb *Mycoplasma genitalium* genome in 2008 and the synthesis and 'booting' (i.e., to full biological activity) of the 1.08-Mb *Mycoplasma mycoides* genome in 2010. This March, they published a 473-gene reduced version of *M. mycoides* (*Science* doi:10.1126/science.aad6253, 2016), representing the smallest self-replicating organism known.

New York University's Jef Boeke has been heading up the international Synthetic Yeast Genome Project (Sc2.0; http://syntheticyeast.org/sc2-0/), a parallel effort to synthesize a eukaryotic genome. Unlike the prokaryotic and viral genome builds, which were stitched together using a 'build/boot' approach, Sc2.0's approach is to incorporate 10- to 100-kb synthetic DNA segments iteratively into the native *Saccharomyces cerevisiae* genome, with fitness testing at each cycle to ensure the cells' viability as the ratio of synthetic sequence in a chromosome increases. Of the 16 natural yeast chromosomes, an artificial version of chromosome 3 is complete and 1, 2, 4–6, 8, 9, 11 and 12 are now in various stages of synthesis and assembly, with a substantial level of recoding of sequence and an additional entirely new synthetic chromosome planned to encode tRNA machinery.

The HGP-write proposal mentions several intermediate pilot projects that would employ very long synthetic DNA molecules. First, synthetic loci that include intergenic regions of noncoding DNA could be used to investigate the role of noncoding variants in disease and gene regulation. The effects of batteries of synthesized variants/genes shuttled into haploid human stem cells could be systematically tested once the cells differentiated into different cell lineages via organoid formation. Second, one could create artificial chromosomes containing complex combinations of genotypes associated with disease or malignancies for biological study; encode gain-of-function activities, for example endowing human cells with a prototrophic capacity or pig cells with the ability to downregulate human immune and coagulation responses for xenotransplantation; or deliver many genes under control circuits to enable the development of next-generation gene therapy products with exquisite control and galvanize microbial, livestock and plant engineering. An intriguing industrial application is to introduce artificial chromosomes into mammalian cell lines recoded to confer resistance to viral contamination—very handy in situations like the one experienced by Genzyme in 2009 when Vesivirus 2117 contamination of a cell production facility halted production of two biopharmaceuticals.

And there is the rub. All of these compelling applications can be achieved using long synthetic DNA molecules that are much smaller than an entirely synthetic, complete human genome. The huge effort and money spent on creating a full complement of 23 synthetic human chromosomes may be a matter of diminishing returns. Many of the above applications of *de novo* synthesis simply don't require DNA as long or as complex as a human genome. So why bother going all the way?

Take the full synthesis and booting of a prokaryotic genome—an incredible feat. And yet very little new research activity appears to have been stimulated by this breakthrough. This may partly reflect the fact that the mycoplasma project did not prioritize broad sharing of resources and expertise (in contrast to other, more open efforts in synthetic biology). Perhaps there is only a small community working on mycoplasmas. But the upshot was that a lot of money and resources were expended and it remains unclear how much we learned.

A last point is that if, in ten years, the HGP-write does create a complete synthetic human genome, a future that many people fear will then be one giant step closer. That future is one in which someone, somewhere starts putting synthetic human genomes into germ cells and attempts to create live offspring—and the 'ultrasafe' approaches proposed will do almost nothing to prevent that. The HGP-write representatives have made it very clear that this is not their intention. To quote Boeke in *Nature* (**534**, 163, 2016): "We're not trying to make an army of clones or start a new era of eugenics. That is not the plan." But there needs to be an acknowledgment that this project takes us one step closer to that reality.

HGP-write has started a valuable conversation about synthetic human genomes and their implications for future generations. Now is the time to have a debate about the ethical, legal and societal issues relating to synthetic human genomes. But, in all honesty, it is the potential of genome engineering tools to interrogate living systems that will get the hearts of most biologists racing.