GENOME ENGINEERING

The Genome Project–Write
We need technology and an ethical framework for genome-scale engineering

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T he Human Genome Project (“HGP-read”), nominally completed in 2004, aimed to sequence the human genome and to improve the technology, cost, and quality of DNA sequencing (1, 2). It was biology’s first genome-scale project and at the time was considered controversial by some. Now, it is recognized as one of the great feats of exploration, one that has revolutionized science and medicine.

Although sequencing, analyzing, and editing DNA continue to advance at a breakneck pace, the capability for constructing DNA sequences in cells is mostly limited to a small number of short segments, which restricts the ability to manipulate and understand biological systems. Further understanding of genetic blueprints could come from construction of large, gigabase (Gb)–sized animal and plant genomes, including the human genome, which would, in turn, drive development of tools and methods to facilitate large-scale synthesis and editing of genomes. To this end, we propose the Human Genome Project–Write (HGP-write), named to honor HGP-read but embracing synthesis of all large genomes.

RESPONSIBLE INNOVATION
Genome synthesis is a logical extension of the genetic engineering tools that have been used safely within the biotech industry for ~40 years and have provided important societal benefits. However, recent technological advancements—e.g., standardized gene parts, whole-genome synthesis, and clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 genome editing technology (3, 4)—are revolutionizing the field (5). Some applications are controversial; human germline editing in particular has raised intense moral debate (6). As human genome-scale synthesis appears increasingly feasible, a coordinated scientific effort to understand, discuss, and apply large-genome engineering technologies is timely. HGP-write will require public involvement and consideration of ethical, legal, and social implications (ELSI) from the start. Responsible innovation requires more than ELSI, though, and involves identifying common goals important to scientists and the wider public through timely and detailed consultation among diverse stakeholders.

We will enable broad public discourse on HGP-write; having such conversations well in advance of project implementation will guide emerging capabilities in science and contribute to societal decision-making.

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push current conceptual and technical limits by orders of magnitude and deliver important scientific advances.

HGP-write will aim to address a number of human health challenges. Potential applications include growing transplantable human organs; engineering immunity to viruses in cell lines via genome-wide recoding (12); engineering cancer resistance into new therapeutic cell lines; and accelerating high-productivity, cost-efficient vaccine and pharmaceutical development by using human cells and organoids. The project could encourage broad intellectual property access via patent pooling. Extreme cost-reduction is feasible, as demonstrated by the $1000 genome grant program (2), as well as making whole- or partial-genome synthesis an efficient route to these goals.

**PROJECT LAUNCH AND ADMINISTRATION**

The goal is to launch HGP-write in 2016 with $100 million in committed support, from public, private, philanthropic, industry, and academic sources from around the world. The costs of the project lie not only in obtaining de novo synthesized DNA but in the assembly, integration, and functional assays required to evaluate and understand the modified genomes. Total project costs are difficult to estimate but would likely be less than the $3 billion cost of HGP-read.

HGP-write could be implemented through one or more centers [similar to Centers of Excellence in Genomic Science (CEGS) and the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative centers] that will coordinate and support formation and work of multi-institutional and interdisciplinary research teams working in a highly integrated fashion responsive to and engaged with a broad public outreach.

We celebrate 2016—the 25th anniversary of HGP-read—as a major step forward for human knowledge and health. In this spirit, we look forward to the launch of HGP-write.

**REFERENCES AND NOTES**


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**SUPPLEMENTARY MATERIALS**

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This PDF file includes:

Fig. S1
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Fig. 1. Synthesizing synthetic or semisynthetic genomes. A. Efficiency trends in DNA sequencing (green) and synthesis of double-stranded DNA (dsDNA, blue) and single-stranded DNA (ssDNA, red) over the past ~35 years. Double-stranded DNA, or gene synthesis, has improved noticeably over the past ~10 years, but still lags behind sequencing and ssDNA synthesis. The disruptive improvement in sequencing and ssDNA (oligonucleotides) synthesis technologies has improved from multiplex and miniaturization technologies in high-throughput DNA sequencing and oligo microarray technologies, respectively. Commercial gene synthesis technologies relies on both oligo synthesis (building blocks) and sequencing (validation of synthesis) technologies. B. Graphical representation of four representative genomes benchmarked to the size of the 3,000 MB human chromosomes: 9.5 kb hepatitis C virus (HCV) enlarged ~380,000-fold, 1.1 MB Mycoplasma mycoides enlarged ~1,000-fold, 12 MB yeast enlarged 100-fold.
Bibliography
As further support for the arguments in our paper, this is a (non-comprehensive) sampling of precedents for projects that could take advantage of radical reduction in cost of genome-scale synthesis and high-throughput cellular/organismal testing of consequences. As with HGP-read, this effort need not be restricted to human but could and should include mouse, pig, Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana, Saccharomyces cerevisiae, etc. The bibliography, along with proposals for pilot projects, maybe found online at the project web site www.hgpwrite.org

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