



GP-write

1. What is the Genome Project-write?

The Genome Project-write (GP-write) will be an open, international research project led by a multi-disciplinary group of scientific leaders who will oversee a reduction in the costs of engineering and testing large genomes, including a human genome, in cell lines by over 1,000-fold within ten years, while developing new technologies and an ethical framework for genome-scale engineering as well as transformative medical applications. The overarching goal of such an effort is to further our understanding of the blueprint for life provided by the Human Genome Project (HGP-read).

Thus, GP-write will include whole genome engineering of human cell lines and other organisms of agricultural and public health significance. The Human Genome Project-write (HGP-write) will be a critical core activity within GP-write focused on synthesizing human genomes in whole or in part. Because of the special challenges surrounding human genomes, this activity will include an expanded examination of the ethical, legal, and social implications (ELSI) of the project. HGP-write will also be explicitly limited to work in cells, and organoids derived from them only.

2. What knowledge will be gained by GP-write over the Human Genome Project?

The Human Genome Project (HGP-read), biology's first genome-scale project, aimed to "read" a human genome. Successfully completed in 2003, HGP-read is now widely recognized as one of the great feats of exploration, one that sparked a global revolution in science and medicine, particularly in genomic-based diagnostics and therapeutics.

Francis Collins, the leader of HGP-read, described the working draft of the human genome as "the first glimpse of our own instruction book." Despite the significant insights gained from large-scale studies designed to interpret this instruction book, including HapMap, Encyclopedia of DNA Elements (ENCODE), and genome-wide association studies (GWAS), our knowledge of the human genome remains far from complete. Thus, the full benefits of such knowledge have not been attained. Many scientists now believe that the way to truly understand our genetic blueprint is to "write" DNA and build human (and other) genomes from scratch. Such an endeavor will require research and development on a grand scale, but could be used to solve important global challenges facing humanity.

3. Should we synthesize a human genome?

The question of 'whether' to synthesize a human genome implies a yes/no answer and a singular event. It might be more useful to frame the question differently. For example: "Under what circumstances might synthesis of genomes (plural) be a good plan, and what can be done to prevent potentially harmful cases?"

We are in the process of enabling a broad public discourse on HGP-write, and having such conversations well in advance of project implementation will guide emerging capabilities in science and contribute to societal decision-making. It is important to note that if one contemplates banning certain types of scientific work, effective bans do require explicit surveillance methods and consequences.

4. Who will be involved in GP/HGP-write?

Ultimately, this multi-disciplinary effort will include an international group of biologists, chemists, computational biologists, engineers, social scientists, and ethicists. And, as noted in the Commentary first published online in Science on June 2, 2016 and later in print on June 8, 2016, it will also require public involvement and consideration of ELSI from the start, as well as identifying common goals important to scientists and the wider public through timely and detailed consultation among diverse stakeholders.

5. How will GP-write benefit humanity?

The average human lifespan continues to expand as a result of advancements in science, medicine, and public health. The challenge today lies in living extended, *healthy* lives with minimal burden of disease – and the associated costs to society. GP-write is uniquely positioned to address this challenge.

Some potential applications include, but are not limited to:

- Growing transplantable human organs, thus saving the lives of thousands of patients globally who die waiting for donated organs from those who die from disease or accidents
- Engineering immunity to viruses in cell lines
- Engineering cancer resistance into new therapeutic cell lines
- Enabling high-productivity, cost-efficient vaccine and pharmaceutical development using human cells and organoids that makes precision medicine more affordable and universal

6. How will GP-write benefit biomedical research?

Similar to sequencing and computation, DNA synthesis is a foundational technology. GP-write is therefore expected to accelerate research and development across the spectrum of life sciences, supporting basic research and the development of new bio-based therapies, vaccines, materials, energy sources, and foods.

Additionally, the project will develop enabling tools of broad applicability throughout biomedical research, such as:

- Computational tools, which allow the redesign of any genome, followed by compilation and testing of the redesigned code *in silico* before hitting the print button;
- Phenotypic screening platforms such as organoid cultures, which allow characterization of performance of synthetic DNA and variants of unknown significance;
- Cheaper, more accurate and longer DNA synthesis and assembly; and
- Targeted delivery to specific cell types or systemically throughout multiple organ systems

7. Why do whole-genome synthesis from scratch rather than editing?

The proposed project is to improve technology for synthesis and testing and is intentionally open to many ways of achieving these goals, including existing and future editing tools. Indeed, even “de novo synthesis” methods for large genomes such as *E. coli* and yeast pragmatically use combinations of large and small edits. The term “from scratch” is somewhat misleading since all genome synthesis projects present and planned are variations on natural genomes. Nevertheless, there are several examples already in which *de novo* synthesis seems more cost-effective than a large set of small edits.

8. Does this project propose the creation of so-called ‘parentless babies’?

No. The proposed project explicitly **does not involve ova or embryos** since it is focused on cell culture (from many organisms). This was true from the first time we discussed it as a group. The use of cell culture, rather than whole organisms, can greatly reduce costs of testing ideas (and also reduce animal testing and risks during clinical trials).

9. Why have “human subject consent”, as reported in the media, if the goal is to alter only cells?

The May 10, 2016 meeting on genome synthesis was preceded by one focused on proper consent from OpenHumans.org on April 26. Any research involving data or cells from humans (even so called “exempt” studies) requires the approval of an Institutional Review Board (IRB), a third party organization that reviews research protocols to protect human participants.

10. Does this project focus on a human genome, and would this favor the rich over the poor?

The project is focused on large genomes, including human.

It's important to note that the proposed project is also aimed at bringing down the cost of researching agricultural species and disease vectors that affect the poorest parts of the world. The manufacturing of pharmaceuticals and vaccines in cell culture is plagued by viral contamination -- e.g. the Genzyme -Vesivirus story and so mammalian cell lines resistant to natural viruses could be very useful for global public health. One way to achieve this is via genome-wide recoding -- as has been demonstrated in one organism.

11. Have other genomes been synthesized to date?

Small viral and bacterial genomes written from scratch have already demonstrated the feasibility and utility of synthetic genomes. The largest genome synthesis project currently underway is an international effort to write the 12Mb genome of *Saccharomyces cerevisiae* (baker's yeast) led by Dr. Jef Boeke (NYU) (Synthetic Yeast Project). Dubbed Sc2.0, the project has participation from groups in the US, the UK, Australia, France, Germany, Singapore and China. The synthetic yeast genome is expected to be completed as early as 2017.

12. What are the expected challenges of this project?

In order to complete large-scale design and synthesis of new genomes, many scientific and technical issues must be overcome. While not insurmountable, biological systems, compared to computers, have less predictable processes, evolve over time and evade easy understanding.

Continued breakthroughs in basic science and the development of innumerable tools, assembly methods, and standards will be needed as the project progresses. DNA synthesis methods, while improving in quality and cost effectiveness, are still too limited, slow and costly, and produce DNA fragments that are too small to allow the creation of the large scale projects necessary to create the breakthroughs in applications desired.

A new “Grand Challenge” such as GP-write will galvanize the scientific community, engage a wide network of educational institutions, attract the required resources to successfully conclude the project, and accelerate research and development in order to make the advances engineering biology requires to solve many of the global problems we face.

13. What are the risks of this project, and how will these risks be managed?

Obviously, the highest biosafety standards should guide project work; and safety for lab workers, research participants, and ecosystems should pervade the design process for this project.

It's important to reiterate that genome synthesis is a natural extension of the genetic engineering tools that have been used safely within the biotechnology industry for the past 40 years and have provided significant benefits to society. However, recent technological advancements, such as standardized genomic parts, whole genome synthesis, and CRISPR/Cas9 genome editing technology are revolutionizing the field and creating uncertainty in how these technologies will be applied. For example, society is presently grappling with the ethical implications of CRISPR/Cas9 on human germ-line gene editing.

As human genome-scale synthesis appears increasingly feasible, a coordinated scientific effort to understand, discuss, and apply large genome editing technologies is timely, and public discourse regarding such an endeavor is both expected and encouraged.

However, responsible innovation requires having more than ELSI discussions; it also involves identifying common goals important to scientists and the public through timely and detailed consultation among diverse stakeholders. Having these conversations well in advance of any deliverable will help society better prepare for the emerging capability.

As such, the project infrastructure will be designed to responsibly support and advance GP/HGP-write, with a particular focus on addressing the potential risks and ethical implications of the project as they arise. For example, a percentage of all research funds could be dedicated to these issues. Additionally, there should be equitable distribution of any benefits in view of diverse and pressing needs in different regions across the globe.

14. What was the purpose of the May 10, 2016 meeting in Boston?

The May 10, 2016 meeting, conducted in Boston, was the most recent in a series of meetings held among an international group of biologists, chemists, computational biologists, engineers, social scientists, and ethicists, to discuss a opportunities and challenges with respect to GP-write.

15. Have Ethical, Legal and Social Implications (ELSI) been part of the scientific discussions to date; in particular, the meeting that took place on May 10, 2016?

Yes, all the discussions of this project have included ELSI aspects. At the May 10, 2016 meeting, there were eight members of the ELSI community in attendance (37 were invited) and specific panel sessions where ethicists examined the implications of the project. In fact, overall, the May 10 meeting presentations were 36% ELSI-related.

16. Was the May 10th meeting “secret”, as some media have reported?

No, it was not ‘secret’. 325 participants were invited from all over the world on a first come, first serve basis, without any requirement that the meeting could not be spoken about. The meeting room could only accommodate 135.

The original intent of the May 10th meeting was to be highly open and transparent in order to catalyze broad community discussion, including media presence on-site, a live video feed, a web site, and real-time social media dialogue. These plans had to be put on hold because the publication of the Commentary in the journal Science was undergoing peer review at the time, and the authors had to respect the journal’s guidelines for pre-publication publicity. Those guidelines permit free exchange of ideas at scientific conferences, but not public announcements about the contents of the pending paper, or even a mention that a paper was about to be published.

Now that the Commentary has been published online in Science on June 2, 2016 and later in print on June 8 2016, we have disseminated all the materials online, including the GP-write website, a Meeting Summary, White Paper and videos of the actual May 10 sessions. In the coming weeks, we will begin to engage with the community through social media.

17. What is the range of openness in scientific conferences?

There are many different approaches for scientific conferences.

For example, some meetings are held in rooms with no electronics permitted; but most meetings have limited space for both cost considerations and encouraging participation. So options include: a) open signup, first-come-first serve, b) a larger, less intimate meeting, c) web cam and twitter extensions, d) entirely via internet without face-to-face, e) a series of smaller meetings. Each of these has its place, but none is inherently superior, compulsory or dominant. Some of the organizers are known for openness: for example, founding world’s only sources of fully open medical genomics data (PersonalGenomes.org and OpenHumans.org) and the world’s only open sequencing hardware. Nevertheless, we respect colleagues who choose to hold private meetings, or in this case, wanted a slight delay in order to prepare materials for public engagement.

18. Do you agree with the statement made in the media: “Such an enormous moral gesture should not be discussed behind closed doors.”

The May 10, 2016 meeting in Boston was not held in secret. 325 participants were invited from all over the world on a first come, first serve basis, without any requirement that the meeting could not be spoken about. The meeting room could only accommodate 135.

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19. How will this project be rolled out?

Similar to other large-scale genomic projects, including HGP-read, Encyclopedia of DNA Elements (ENCODE), and the Synthetic Yeast Project (Sc2.0), GP-write will be conducted in phases with explicit milestones, metrics, and assessments. Each of these earlier projects began with pilot projects.

For GP-write, the pilot projects chosen will provide resources valuable for advanced biomedical research and/or biotechnology development. For example, using induced pluripotent stem cells (iPSCs) to create a more stable biomanufacturing human cell resistant to any virus could help reduce costly incidents of virus contamination of vaccines seen in the past, including SV40 contamination of the Sabin oral polio vaccine, and Vesivirus in the Genzyme orphan drug production fermenters in both the EU and USA.

In addition, these projects will also be expected to address the social, ethical, and public perception issues likely to arise as a reaction to this proposal.

20. How much is GP-write expected to cost?

Total projects costs are difficult to estimate but will likely be less than the \$3 billion cost of HGP-read. Indeed, recent and continued improvements in enabling technologies are not only improving the cost, quality and time period necessary to complete this project, but also most other fields of biomedicine. The return on investment is expected to be swift and large.

21. How will HGP-write be funded?

Andrew Hessel, Distinguished Research Scientist at Autodesk and one of the leaders of this project, has obtained a leadership gift of \$250,000 from Autodesk to seed the planning and launch of HGP-write. The project will require four matching gifts to cover the planning and launch effort.

The goal is to launch HGP-write this year with \$100 million in committed support. Initial funding is expected to come from public, private, philanthropic, industry and academic sources from around the world.

22. Is there a specific organization that will implement HGP-write?

GP/HGP-write will be implemented through a Center of Excellence for Engineering Biology, a new, independent nonprofit organization that will manage initial planning and coordination efforts. These efforts include supporting the 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.

The Center will create a neutral environment for international participants and will accept funding from the public, private, philanthropic and academic sectors, including international funding agencies. However, this will in no way preclude direct grants and sponsored research agreements by government agencies and others to academic and industrial laboratories through more traditional mechanisms.

The Center will add capacity to accommodate the design of the technology and infrastructure that may be required to support the project.

23. When will GP-write be launched?

GP-write will be launched in 2016. This year is a significant milestone since it falls during the 25th anniversary year of the original HGP-read, and marks another big leap forward. This is a chance to inspire a new generation of scientists and engage the public in sustained discourse.

24. How can I become involved in this project?

For all project-related matters, please contact Nancy J Kelley at: info@engineeringbiologycenter.org.

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