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Life, reimagined.

WHITEPAPER

THE GENOME SYNTHESIS REVOLUTION

HOW TO WRITE A GENOME IN 4 STEPS

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> "What I cannot create,
>
> I do not understand."

Richard Feynman

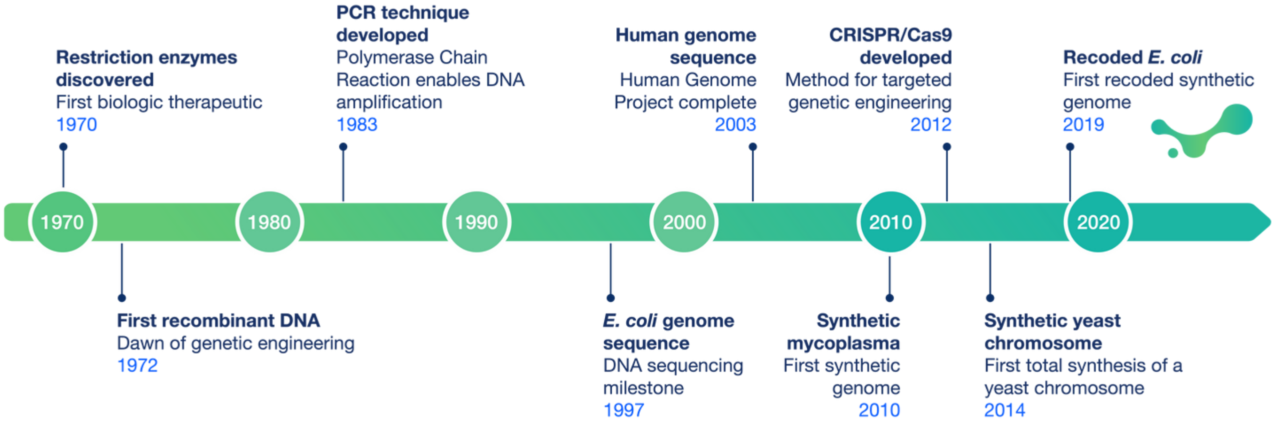
DNA sequencing has allowed us to read and study the code of life, creating a $28 billion dollar industry.

Now, synthetic genomics (DNA writing at genome scale) is an emerging field giving scientists and synthetic biologists unprecedented access to interrogate and explore the central dogma at the core of biology.

Read on to learn how advances in the engineering biology toolkit are enabling new solutions at pace and have potential to transform the bio revolution.

History of genome writing

The genome is the genetic material that carries all the information needed for an organism's growth, development, functioning, and reproduction.



The ability to write genomes has evolved significantly over the last 50 years. Beginning with the advent of recombinant DNA technology in the 1970s, which facilitated the manipulation of DNA sequences, early advances included the development of technologies like Polymerase Chain Reaction (PCR) by Kary Mullis in the 1980s. Subsequent step changes in genome engineering tools revolutionized genetic research by enabling rapid amplification of specific DNA sequences. The emergence of CRISPR-Cas9 in the 2010s allowed precise genome editing, propelling the field further.

A major advancement came in 2010 when the J. Craig Venter Institute created the first synthetic bacterial cell "Synthia". This demonstrated the ability to synthesize and transplant an entire bacterial genome. Advancements in DNA synthesis technology have since led to the synthesis of entire eukaryotic chromosomes, with more than 50% of the yeast genome synthesised by November 2023.

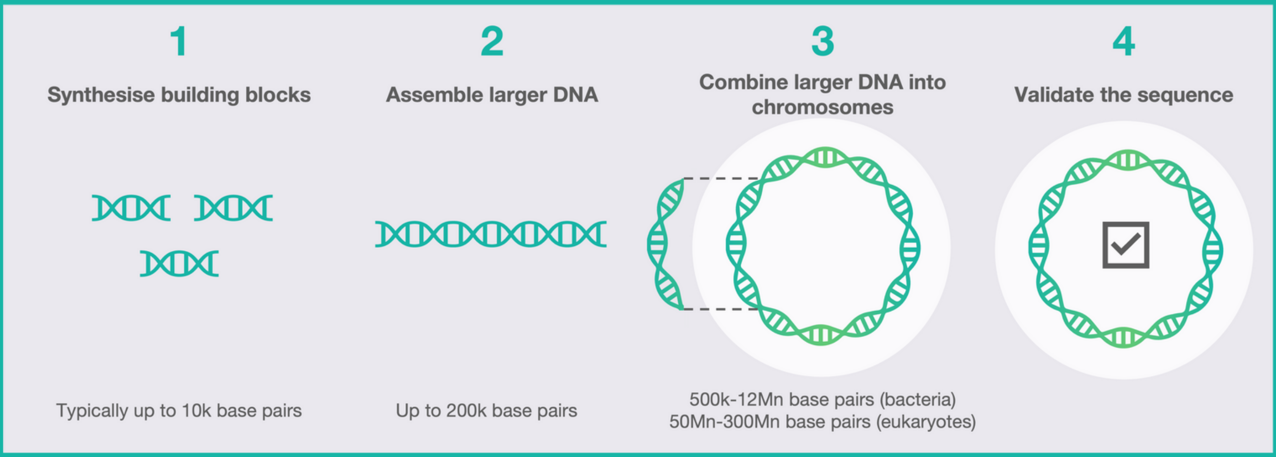
Today, genome writing continues to progress, promising transformative applications in medicine, agriculture, and synthetic biology, while ethical considerations and regulatory frameworks remain crucial considerations for its responsible use.

Enabling technologies

A few fundamental technologies enable genome synthesis:

- **DNA sequencing:** 1 million times cheaper in 20 years
- **Short DNA synthesis:** Rapidly improving with new methods
- **Genetic engineering:** Transformed by targeted approaches such as CRISPR/Cas9

How to build a genome in 4 steps



1 Synthesise building blocks (up to 10,000 base pairs)

Short DNA inputs are generated by chemical or enzymatic synthesis.

2 Assemble larger DNA (up to 100,000 base pairs)

DNA building blocks are assembled into larger sequences, typically within stable vectors such as bacterial artificial chromosomes

3 Combine larger DNA into chromosomes

Assembled larger DNA is combined to form complete chromosomes

4 Validate the sequence

Sequences are confirmed during each assembly step. Once complete, the final assembly is validated for structure, complete sequence and function

Why synthesise genomes at all?

Nature has had billions of years to evolve the genomes of today. So what is the value in trying to recreate that work?

Advancing research

Scientists have made great strides in understanding the sequence and structure of the genome since the dawn of moden genetics in the last century. But many questions remain that can't be answered with current techniques. The human genome, for example, is 3.2 billion base pairs long, but genes make up less than 2% of that sequence. The remaining 98%, previously thought to be "junk", is now known to be critical to regulating how genes are activated and regulated but many questions remain unsolved because researchers have been unable to create new genomes with different "junk" sequences. A better understanding of these regions would help provide treatments for the 90% of disease-associated genetic variations that are found in these regions and not within genes themselves.

Improving traits

Genome synthesis offers a new opportunity to enhance the biological systems we rely on for the production of food, medicines and other products. This includes creating more sustainable agriculture by enabling complete control of the design and development of plants with desired traits. Existing methods are limited to modification of only select regions at a time. By instead precisely modifying entire chromosomes to modulate specific genes or introduce novel genetic elements, scientists can potentially create crops that are optimised for nutritional content, yield and adaptation and more resistant to diseases, pests, or environmental stressors.

Recoding the genome

Recoding genomes holds immense importance in the field of synthetic genomics. By rewriting the genetic code, scientists can create organisms with novel properties, such as increased resistance to viruses and the ability to produce new proteins or materials not found in nature. This approach not only expands our fundamental understanding of life's blueprint but also paves the way for innovative medical treatments, sustainable biomanufacturing processes, and enhanced biosecurity measures. The recent work in genome recoding represents a transformative leap in our ability to harness and direct the very mechanisms of life for diverse applications, marking a new era in biotechnological innovation.

What does the future hold for synthetic genomes?

With transformational research currently underway across a range of different organisms and applications, the next 10 years promises to bring new advancements and opportunities for synthetic genomics.

A new era of biologics therapeutics

With the ability to synthesise entire genomes comes the possibility to reprogram the entire sequence to use a different code and create new valuable therapeutics with enhanced features.

The first synthetic eukaryote

The first synthetic yeast genome is now more than 50% complete. In the next 10 years, the team assembling this expects the project to be complete, revealing new insights into eukaryotic genetics.

Programmable biomolecules of the future

Writing instructions to create complex molecules in life's natural language, DNA, with fidelity, specificity and scalability. Read more in our white paper ***Reprogramming Life: How Genetic Code Expansion Will Redefine The Bioeconomy***.

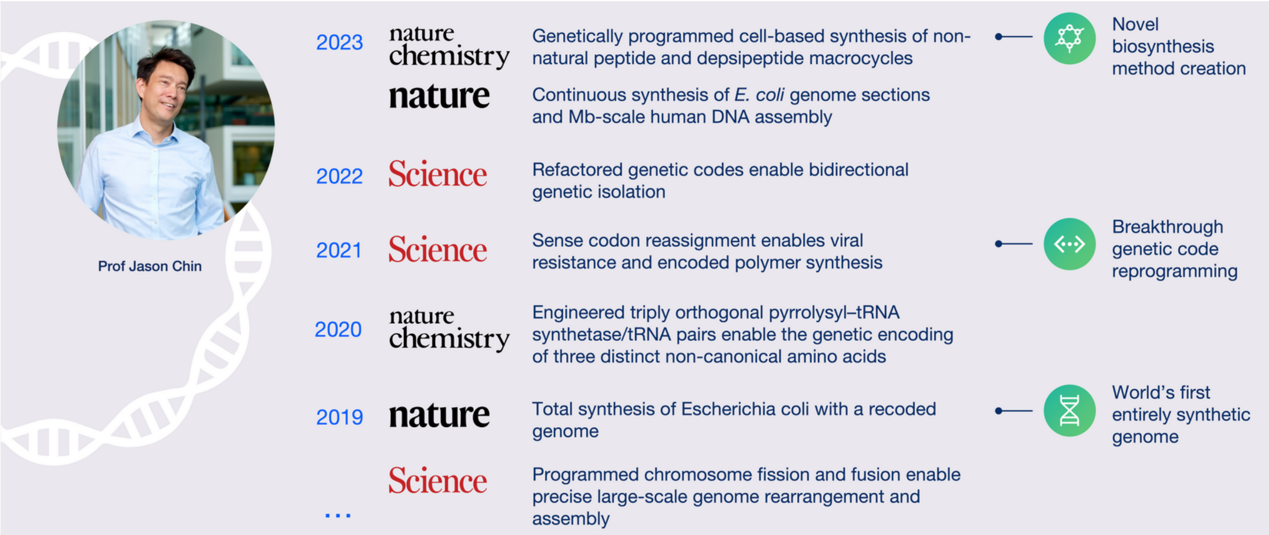
Synthetic mammalian chromosomes

The age of genomic medicine requires the creation and assembly of large therapeutic DNA to develop nucleic acid medications.

About Constructive Bio

Constructive Bio is a biotechnology company that rewrites genomes to create biomolecules that were previously unimaginable. Based on Professor Jason Chin's groundbreaking research at the MRC Laboratory of Molecular Biology in Cambridge and a robust portfolio of proprietary tools and assets, we are creating next-generation therapeutics and industrial solutions while setting the standard for genetic code reprogramming. With a world-class team in synthetic genomics and a passionate commitment to improving global health and bioprocessing, Constructive Bio is reimagining the world of biologic therapies by rewriting the genome itself.

We are built on a series of significant "world-first" technological breakthroughs in synthetic genomics and its applications:



Our technology enables you to:

- Get your hands on large DNA of up to 200kb with 100% accuracy for a range of commercial applications.
- Create megabase-scale custom prokaryotic and eukaryotic DNA in *E. coli.*
- Design and write custom microbial genomes.
- Reprogram genomes to protect against viral infection, prevent horizontal gene transfer and expand the genetic code to incorporate amino acids not found in nature.

Scan the code to start your genome synthesis journey with our expert, Dr Freddie Dudbridge. Together we can advance biotechnology with large DNA writing and unlock new innovative applications.

What will you create?

constructive.bio

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