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SYNTHEGO

Transforming the writing of DNA

Genome engineering company Synthego pioneers agile genome 'writing' with a high-throughput CRISPR-based platform to provide innovative solutions for next-generation therapeutics.

Scientific advances have often depended on tinkerers: curious, ambitious souls who invent new tools to expand knowledge. In the modern era, high-throughput screening and next-generation sequencing (NGS) have driven advances in medicine and begun to transform scientific research from a near-artisanal pursuit to an industrial one. The promise of genome editing has been evident from the start, yet has mostly been done on a small scale, gene by gene, without standardization, and with limited predictability and reproducibility. Synthego has created a large-scale genome engineering platform, leveraging its origins as a bioengineering company and top-notch scientific advisors, including CRISPR luminary Jennifer Doudna.

The company's 'full-stack' gene-editing platform combines high-throughput automation and machine learning to make CRISPR rapid, reliable and accessible. The Synthego platform supports a wide range of applications, and users include many top biopharma companies and research universities. According to Jason Steiner, Chief Strategy Officer at Synthego, "We are part of building a new paradigm for R&D of programmable discovery across the genome, accelerating discovery and increasing impact on patients with next-generation therapies." Much as NGS transformed genomic research by standardizing and scaling up workflows and processes, Synthego aims to accomplish a similar feat in genome editing, transforming 'writing' of DNA.

Synthego's facility in Redwood City, California.

Genome-editing approaches

Synthego supports diverse applications of genome editing across 120,000 genomes and 9,000 species. The company's offering includes automated bioinformatics design pipelines and optimization of CRISPR–Cas editing and cell engineering. For each optimization, a range of candidate single-guide RNAs (sgRNAs) are tested in high-throughput screens to define sequences and conditions that yield robust results. Engineered cell line production also leverages automated optimization protocols that allow testing of hundreds of parameters currently implemented across more than 300 cell lines, including induced pluripotent stem cells (iPSCs), primary cells and immortalized cell lines. Instead of plasmid DNA delivery of CRISPR–Cas, which requires that cells manufacture the required gene-editing proteins, Synthego uses fully synthetic ribonucleoprotein (RNP)-based editing complexes, which offer higher efficiency—often an order of magnitude better. In THP1 cells, for example, DNA plasmid-based knockout (KO) efficiency is ~5%, while Synthego's optimized reagents achieve KO in 72% of cells. Synthego guarantees a >50% KO rate in its custom-engineered cell products and services.

Validating an edited cell line requires not only sequencing the targeted gene, but also screening for off-target edits. To achieve high-quality gene editing, Synthego developed ICE, an industry-leading and much-cited CRISPR analysis tool that monitors DNA repair activity to produce the NGS-quality determination of the editing efficiency and accuracy.

Just as NGS has moved quickly from the research lab to clinical diagnostics, Synthego anticipates its platform will similarly accelerate translational medicine. In traditional drug discovery, Synthego's CRISPR-based strategies can be used in target identification and validation, pathway analysis and development of engineered cells for high-throughput screening. Synthego also manufactures good manufacturing practice (GMP) grade sgRNA, allowing customers to rapidly move their genome-editing therapeutic strategies into clinical trials. Similarly, in cell and gene therapy, the programmable components of Synthego's platform have the potential to speed translation from concept to first-in-human testing.

> **"We are part of building a new paradigm for R&D of programmable discovery across the genome**
>
> Jason Steiner, Chief Strategy Officer, Synthego

Targeting rare diseases

For rare diseases, Synthego's technologies can be used to expand iPSC-based models to include more variants and genetic backgrounds. The ability to 'write' genomic variants into any cell background can also accelerate genome-wide association studies, helping to answer questions of causality and provide insight into genomic variations of unknown significance. In addition, high-throughput screening of CRISPR-engineered cell lines representing 10,000 different rare diseases could potentially reveal new targets and indications for approved or failed drugs. The unique advantages of its high-throughput CRISPR-based cell engineering technology recently won the company a competitive NIH grant as the primary vendor of more than 150 IPSC-based model cell lines of neurodegenerative diseases.

In a recent example of how the convergence of multi-dimensional technologies can inspire novel research, Synthego is collaborating with University of California, San Francisco (UCSF) to develop CRISPR-based screening tools to probe the biology of the SARS-CoV-2–human protein interactome. Within a few weeks of publication of the interactome, Synthego produced tools and products, including CRISPR KO screening libraries and KO cell panels that researchers are using to probe the biology of the virus in human cells and develop or repurpose drugs.

The Synthego team believes the unprecedented scale and speed of discovery now possible will alter the R&D landscape, shortening timelines from discovery to clinical trials, and ultimately improving patient outcomes and access.

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