Syntax Bio
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Overcoming the cell therapy bottleneck

Biotech firm Syntax Bio aims to transform pluripotent stem cells into clinical therapeutics using its CRISPR-based technology platform called Cellgorithm.

Spurred by the discoveries of human pluripotent stem cell culture by James Thomson in the 1990s and the induction of pluripotency from adult cells by Shinya Yamanaka in the 2000s, therapeutics derived from human stem cells have long been viewed as potential breakthrough medicines. Yet, after more than two decades of hard-won and resource-intensive progress toward improving the differentiation of stem cells into therapeutically useful cell types, that promise remains largely unrealized. Hundreds of clinical trials have been launched or completed for pluripotent stem cell therapeutics targeting conditions such as type 1 diabetes, Parkinson's disease, macular degeneration and heart failure. While some human pluripotent stem cell trials have shown encouraging signs for patients, none have yet achieved regulatory approval[1].

The slow progress stems in part from conventional differentiation methods that are lengthy, costly and difficult to reproduce at scale. Developers of stem cell therapies repeatedly encounter obstacles that delay progress or halt programs altogether. At a time when several established cell therapy developers are signaling fatigue, Syntax Bio has introduced a new approach designed to overcome this bottleneck (Fig. 1). Its platform aims to provide biotechnology and pharmaceutical partners with faster and more reproducible differentiation processes—reducing costs, shortening research timelines, and improving scalability.

Two established strategies dominate the field of pluripotent stem cell differentiation. The first, conventional directed differentiation, involves exposing cells to a sequence of media changes and growth factor combinations. For many cell types, these protocols require one to four months to complete, restricting throughput and limiting iterative discovery. Key inputs such as recombinant growth factors and complex media formulations

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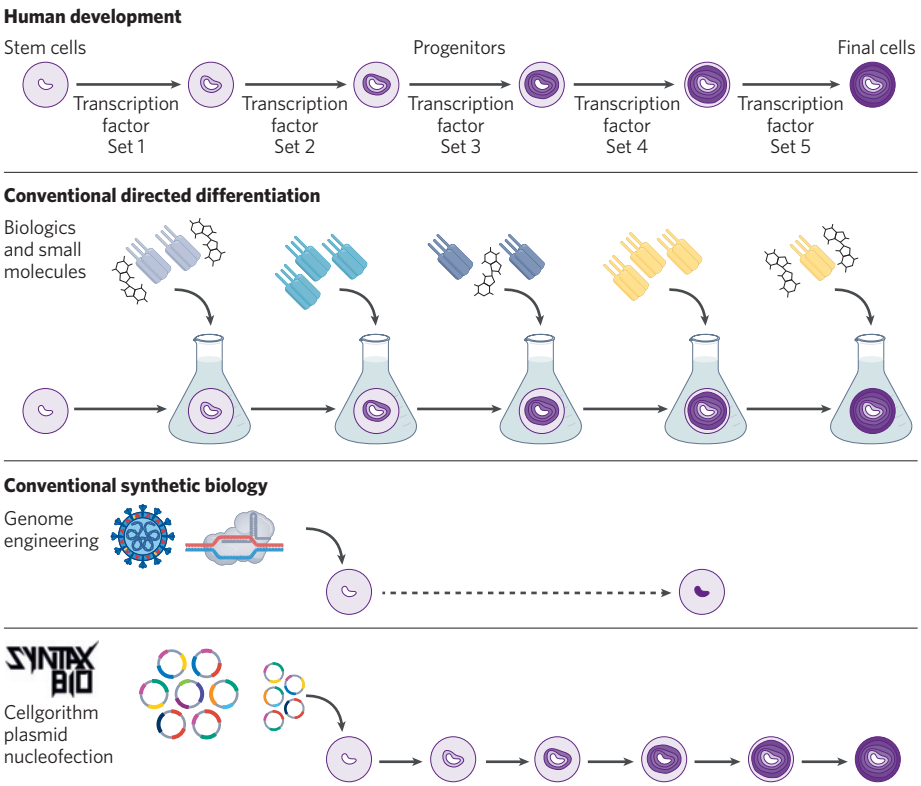

Fig. 1 | Comparison of stem cell differentiation strategies. The physiological process involves multiple transcription factor (TF)-mediated steps building upon one another. Conventional directed differentiation uses frequent manipulation of culture systems and conventional synthetic biology uses a direct activation of a set of TF genes. Syntax's platform enables multiple steps of direct activation of TF genes with the simplicity of a single delivery of plasmids encoding entire Cellgorithms.

are expensive and contribute heavily to process costs. Small variations in inputs or handling can alter results, making reproducibility a persistent challenge and leading to costly failures. Moreover, scaling across large two-dimensional cultures or three-dimensional bioreactors introduces additional hurdles, including inefficient mass transfer of growth factors, cytokines and small molecules. These challenges intensify as culture volumes increase, underscoring the need for a more cell-intrinsic, engineering-based solution.

The second major approach, rooted in synthetic biology, attempts to address these shortcomings. By forcing the expression of specific, cell-intrinsic transcription factors, researchers have accelerated differentiation while reducing dependence on external reagents. However, first-generation platforms failed to fully capture the native identity and function of target cells. These systems tended to activate multiple transcription factors simultaneously, disrupting the natural sequence of gene regulation that defines cellular development. The result was faster but incomplete differentiation, with limited applicability across diverse cell types.

Rethinking stem cell differentiation

Syntax Bio, named for the ordered arrangement of words that create meaning in a sentence, has sought to emulate the epigenetic 'syntax' that governs human development. During embryogenesis, cells regulate one set of transcription factors at each stage to prepare for the next, gradually acquiring epigenetic marks that record their lineage. Mimicking this process, Syntax engineers stepwise epigenetic programs that recapitulate developmental timing and logic in culture.

The company's CRISPR-based technology, called Cellgorithm, provides customizable, epigenetic instructions that guide cells through

differentiation. "It's a way of programming cells using their own genes," said Brad Merrill, Syntax's co-founder and head of innovation. "Rather than differentiating cells by changing their environment, we drive changes by acting on a cell's own genetic information. With our system, you can turn any gene on or off in any order using CRISPRa and CRISPRi."

Syntax emerged from stealth in 2024 to commercialize its platform, backed by Astellas Venture Management, Civilization Ventures, DCVC Bio, Draper Associates, EGB Capital, Illumina Ventures, LongGame VC, Mansueto Office, Portal Innovations, and other investors. The company's technology stems from research conducted by co-founders Merrill and Ryan Clarke at the University of Illinois Chicago. Merrill's laboratory, which has studied stem cell development for two decades, sought to overcome a long-standing barrier: tracking cellular lineage over time. Historically, biologists could perturb only one gene at a time, limiting their ability to follow how individual cells changed across generations. Merrill's team developed CRISPR-based lineage tracing tools to integrate temporal control into genetic perturbation.

Their research, described in a paper by Clarke and Merrill, introduced the foundational unit of this system: the proGuide[2] (Fig. 2). Each proGuide consists of an inactive single-guide RNA (sgRNA) that is activated by another sgRNA, enabling successive, preprogrammed CRISPR-Cas9 activities. Although originally envisioned as a method for tracing cell lineage during differentiation, the system evolved into a framework for controlling differentiation itself. A subsequent paper described how proGuides could be used to program multistep activation of endogenous genes via CRISPRa in stem cells[3]. Enhancements to the concept enable five or more sequential regulatory steps using a single plasmid DNA delivery, eliminating the need for genomic integration.

Faster, cheaper, and simpler

Syntax's vision for a new era of cell therapeutics is supported by evidence that its Cellgorithm technology offers clear advantages over conventional approaches. Each Cellgorithm uses a pool of plasmids delivered as a single DNA programming input, replacing the dozens—or even hundreds—of inputs typically required for directed differentiation. The transient plasmid DNA method also avoids permanent genome editing, reducing safety and regulatory concerns.

Across a range of cell types, Syntax has achieved differentiation times averaging about seven days. In every case tested, the process is at least twice as fast as directed differentiation—and for certain cells, such as retinal lineages, up to ten times faster. The system typically requires only one medium formulation for most cell types, or up to three at most, compared with four to seven in traditional protocols. The company estimates that shorter differentiation times and simplified media requirements could reduce manufacturing costs by a factor of four to 20.

"You're not having to change the media formulation every other day or every couple of weeks," Clarke said. "It's one delivery—you keep the cells in the same media the entire time. It's a much more standardized approach than the onerous process that stem cell differentiation historically required."

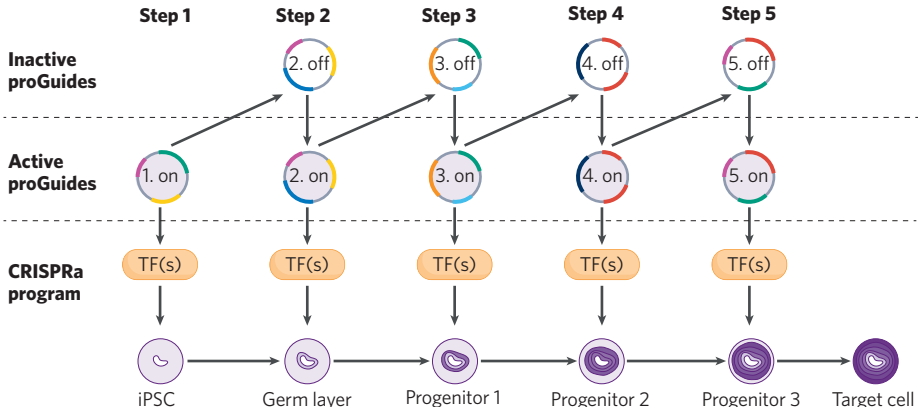

Fig. 2 | Multistep Cellgorithm cell differentiation program. Schematic illustrating proGuide-mediated stepwise activation of transcription factor (TF) genes that direct progression to the target cell state.

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Syntax's platform also enables differentiation processes that have long eluded researchers. Traditional efforts to identify small molecules that activate a desired transcription factor at the right moment can take years and often fail. With Cellgorithms, those transcription factors can be switched on and off directly. "You can test many different recipes in an arrayed format, and the turnaround time is rapid," Clarke said. "You get your answer quickly, then mix and match plasmids to optimize conditions."

The platform functions as a screening system, allowing large-scale, parallel testing of differentiation pathways. Cellgorithm DNA pools are easy to construct, enabling libraries in which each pool represents a distinct sequence of endogenous gene activations. Hundreds to thousands of conditions can be screened in parallel with a single DNA delivery and a simple culturing protocol, often using one medium formulation. The turnaround for these screens is measured in weeks rather than months.

The cell-autonomous nature of the process also reduces batch-to-batch variability that often plagues directed differentiation, improving reproducibility and facilitating scale-up from two-dimensional to three-dimensional formats. That scalability has been demonstrated through Syntax's successful transition from screening assays to suspension culture. Researchers using the platform to revive stalled projects or accelerate active programs have reported rapid progress; in one case, Syntax delivered a novel cell therapy differentiation program to a biopharma partner within one year of contract signing.

A cell therapy force multiplier

Syntax serves as a 'force multiplier' for other developers while also selectively advancing its own therapeutic pipeline. By enabling faster, more reliable differentiation, the company allows partners to benefit from using the Cellgorithm platform and expand their cell therapy pipelines efficiently. Cellgorithms have performed consistently across diverse cell types while preserving native cellular functions, suggesting broad applicability across therapeutic areas.

To maximize impact, Syntax has built a comprehensive technical support infrastructure to help partners address specific challenges and train their teams to use the platform effectively. By pairing its technology with collaborative expertise, Syntax aims to help cell therapy developers, organoid researchers and manufacturers of therapeutic-grade cells accelerate discovery and manufacturing.

After decades of incremental progress and unrealized promise, the stem cell field may finally possess a technology capable of unlocking its full therapeutic potential. Syntax Bio's Cellgorithm platform represents a pivotal step toward realizing the long-envisioned goal of transforming pluripotent cells into consistent, scalable, and clinically meaningful regenerative medicines.

1. Kirkeby, A., Main, H. & Carpenter, M. *Cell Stem Cell* **32**, 10–37 (2025).
2. Clarke, R. et al. *Mol. Cell* **81**, 226 (2021).
3. Puppala, A. K. et al. *Sci. Adv.* **11**, eadt1532 (2025).

CONTACT
Ryan Clarke, Co-founder & CTO
Syntax Bio
Chicago, IL, USA
Email: contact@syntax-bio.com