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Powering the next generation of allogeneic therapies with precision cell reprograming

bit.bio is a synthetic biology company that uses its cell identity coding platform to reprogram induced pluripotent stem cells to create any human cell type.

With its cell identity coding platform, bit.bio can manufacture human cells with unparalleled consistency at an industrial scale. The company believes that this approach will be transformative to human health—from providing relevant models for research and drug discovery to making cell therapies accessible to millions of patients.

Based in Cambridge, UK, bit.bio was founded in 2016 by Mark Kotter, CEO, with a mission to code human cells to provide novel cures for disease. The company seeks to overcome one of the biggest challenges in cell therapies, namely the need for a consistent and scalable source of human cells. Such a source will make cell therapies accessible to millions of patients worldwide. bit.bio was created around opti-ox (optimised inducible overexpression), Kotter's precision cell reprograming technology developed in his laboratory at the University of Cambridge. The company has since developed a cell identity coding platform that utilises opti-ox to generate induced pluripotent stem cells (iPSC)-derived human cells for research, drug discovery, and cell therapies.

Now employing more than 180 people, bit.bio has a growing commercial portfolio of iPSC-derived human cells and disease models for use in research and drug discovery as well as an early-stage pipeline of allogeneic cell therapies. The company is actively seeking partnerships to deliver the next generation of cell therapies.

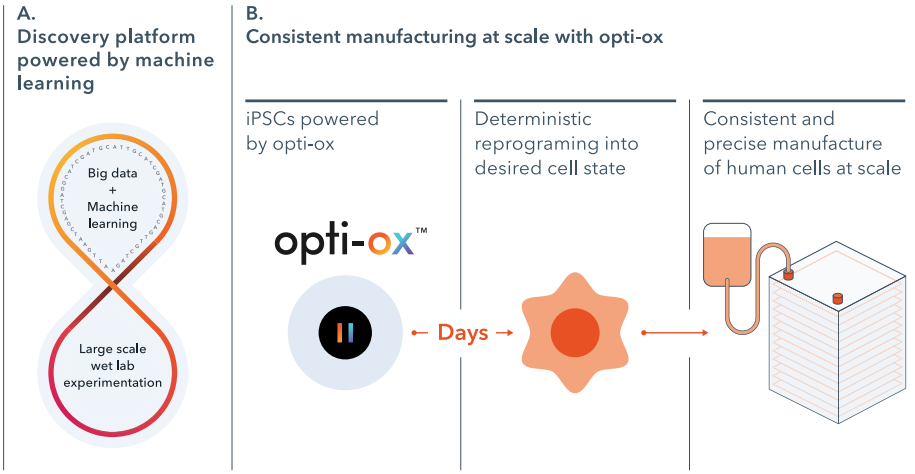

Fig. 1 | Scalable manufacture of human cells through bit.bio's cell identity coding platform powered by opti-ox. A, bit.bio employs a feedback loop between machine learning and big data, and large-scale wet lab experimentation to rapidly discover new transcription factors that define a desired cell state. **B**, opti-ox allows for the deterministic expression of transcription factors ensuring the consistent reprograming of the entire iPSC population into the desired cell type at scale. iPSC, induced pluripotent stem cell.

Overcoming hurdles to realise allogeneic cell therapies

Autologous cell and gene therapies have produced transformative, durable, and, in some cases, curative outcomes for patients with life-threatening disorders. "This class of therapies has answered the unmet therapeutic needs for a specific group of patients who had few other choices," said Kathryn Golden, senior VP of technical operations and cell manufacturing at bit.bio. Golden is a chemical engineer with many years of experience in biologics and cell culture development and manufacturing and joined bit.bio in May 2022.

Although bit.bio's novel class of cell-based therapies has shown promising results, costs remain high and processes are bespoke to each patient. "Every autologous therapy is personalised to the patient, where one manufacturing run generates one dose at costs between $250,000 and $600,000," Golden explained. "At bit.bio, we are working towards a future where off-the-shelf allogeneic cell therapies are stored at the hospital, ready for the patient. This would mark a paradigm shift from cell therapy to cell medicine—I think everyone working in cell therapy wants to get to this point, and we believe we have the technology to help make this reality happen."

"At bit.bio, we are completely mission-focused on building upon the current successes of cell therapies," said Paul Morrill, CBO of bit.bio. Morrill is a scientist who has worked in the biotech industry for more than 30 years and joined bit.bio in February 2019. "We see that potentially life-changing cell therapies could be deployed to a greater number of patients successfully if they were faster and more affordable to produce while being broadly applicable across a wider range of disease indications. The current reality is that global healthcare systems can fund a certain number of treatments with existing autologous therapies. Any issues in the production process can cause life-threatening delays in delivering the therapeutic to often seriously ill patients. The ideal cell therapy would be off-the-shelf, immune-tolerated, targeted, consistent, and at lower cost point to present therapies. Such advancements will dramatically improve patient access to cell therapies, which is desperately needed as the entire field grows and matures over the next 10 to 20 years."

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Since protocols for the generation of human cells from iPSCs were first published more than two decades ago, iPSCs have been considered a cornerstone technology towards realising allogeneic cell therapies. It is theoretically possible to manufacture infinite numbers of human cells from iPSCs, meaning the production of enough doses to provide an off-the-shelf solution is within reach. However, this promise has yet to be fulfilled. For example, no iPSC-derived cell therapy has been approved for use by the United States Food and Drug Administration (FDA) to date.

The primary reason that the FDA has not yet granted approval for the therapy is that iPSCs are challenging to work with. "Until now, the generation of human cells from iPSCs has required directed differentiation-based protocols, where

cocktails of cytokines and transcription factors are spiked into the culture as a 'guide' from iPSC to the target cell type through a series of intermediate steps," said Golden. "This may work at the proof-of-concept stage, but the complexity of the protocol, combined with the variety of environments within a bioreactor, make moving from a small scale to a larger scale manufacturing process extremely challenging. The pools of differentiated iPSCs can lack homogeneity, necessitating follow-on processing, which uses up expensive GMP [good manufacturing practice] facility time. This lack of consistency is why companies can spend years optimising the scale-up process without success."

"With opti-ox emerging from Kotter's lab at Cambridge University, we saw a technology platform that, for the first time, had the potential to simultaneously solve the consistency and scalability issues faced when using iPSCs for therapeutic development," said Morrill.

bit.bio's cell identity coding platform enables consistent and scalable cell production

bit.bio's cell identity coding platform consists of two key aspects: the first being its transcription factor discovery platform, and the second being the faithful expression of those transcription factors in iPSCs, executed by opti-ox precision cell reprograming.

bit.bio's transcription factor discovery platform combines genetic screening, big data, machine learning, and large-scale experimentation to find the combination of between one and six transcription factor codes that determine the identity, function, and cell state of every human cell type and sub-type (Fig. 1).

"opti-ox carries out the robust conversion of iPSCs directly into a cell type of interest by integrating transcription factors, controlled by an inducible genetic switch, into genomic safe harbour sites of the iPSC genome. This turns on the complex set of genetic pathways that give the cell its identity in a deterministic manner, like flipping a light switch," said Emmanouil Metzakopian, VP of research and development at bit.bio. Metzakopian joined bit.bio in April 2021, following an academic career at the Wellcome Sanger Institute in Hinxton, Cambridgeshire, UK, and the University of Cambridge. "The use of safe harbour sites avoids gene silencing, ensuring that the expression of the transcription factors, and ultimately the composition of the final cell population, is highly consistent between manufacturing lots. Once everything is in place, the journey from iPSC to human cells with the desired identity can take a matter of days."

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> Emmanouil Metzakopian, VP R&D, bit.bio

"As opti-ox gives us deterministic control of transcription factors in the cell genome, we can simultaneously convert all the iPSCs in culture directly into the desired cell type. This is a step change over traditional technologies that coax and guide cells through a series of developmental stages," continued Metzakopian. "We consistently see that opti-ox can be used to program cells with up to 99.9% efficiency, every time creating a consistent cell culture. Hands-on, it is also a straightforward process to manage. Together, these properties mean opti-ox powered cells can be manufactured at scale—both easily and reproducibly."

"We have also invested heavily in our people. The team behind the cell identity coding platform have decades of shared expertise, and they are integral to our ability to precisely develop desired human cells," said Golden. "These opti-ox powered cells have the potential to reduce the time required in costly GMP facilities, cut the number of specialist chemicals required, and reduce the hands-on time from staff, ultimately cutting the cost of goods per manufacturing run by one to two orders of magnitude. Access to more consistent and scalable iPSC-derived cell types ultimately broadens the scope of allogeneic cell therapies, allowing for the potential treatment of a greater number of diseases and patients," said Golden.

Driving allogeneic cell therapies forward

As the company develops its offerings and its technologies, it plans to create a variety of partnerships. Collaborating with bit.bio provides partners with the opportunity to utilise its cell identity coding platform to create inherently consistent and scalable human cell types that have the potential to form the foundation of a next generation of cell therapies.

"Our cells are scalable by their very nature. This means we can shift the focus for our partners from 'How are we going to make enough cells to treat one patient?' to 'How can we ensure our therapy can treat every patient?'," said Morrill.

Using its platform, bit.bio has created ioCells, which are mature, functional human cells that are precision reprogramed from iPSCs for research use. ioCells can be produced at scale within days and allow scientists access to standardised, consistent, and easy-to-use human cells for fundamental disease research, drug discovery, and clinical translation.

"We have taken everything that we have learned or developed to date, and used this to create ioCells," said Morrill. "The success of our platform means our commercial portfolio has grown rapidly over the last year, including cell types that haven't been readily accessible on the market before, like microglia and oligodendrocyte-like cells. We currently offer extensively characterised neuronal and muscle cell types, including variants of these cells engineered to contain disease-relevant mutations, and versions that allow users to generate their own mutations with CRISPR [clustered regularly interspaced short palindromic repeats]. To our knowledge, there are no other companies able to run the end-to-end process from transcription factor discovery to manufacturing and then deliver billions of cells reproducibly and consistently, to relevant industry partners."

"Working on ioCells has helped us to develop our cell identity coding platform further, and has provided validation for our technology and the company," said Metzakopian. "The production of our ioCells is not just faster, cheaper, with greater scalability—the data and feedback we get from the market on these research products are directly helping us to improve our platforms."

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Partnerships and beyond

bit.bio already has several platform partnerships in place. Most recently, in August 2023, Bayer subsidiary BlueRock Therapeutics and bit.bio announced a collaboration to discover and manufacture iPSC-derived regulatory T cells (T_{reg}s) for use in cell therapies. BlueRock has options to license transcription factor combinations emerging from the partnership and to license opti-ox technology for the manufacture and subsequent development of iPSC-derived T_{reg} cell therapies.

bit.bio is also developing an in-house pipeline of therapies within key focus areas including liver, immunology, and metabolic disorders; the team plans to move into human clinical trials in 2025.

"We are building the capabilities to develop our own therapies, but we also realise we can't do everything, therefore we have created a partnership strategy to leverage our platform and seek development and commercialisation partners for the next generation of allogeneic cell therapies," said Morrill.

Several other companies are developing iPSC-derived cells, but what differentiates bit.bio is that its cell identity coding platform has the potential to solve the key challenges of scalability and reproducibility in the manufacture of allogeneic cell therapies. With its platform, bit.bio is looking not just to improve this generation of cell therapies, but to create the next generation of cell medicines.

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