Making fitter cells and tissues

Better cell sourcing and increasingly fine control over cell differentiation, tissue formation and cell and tissue maturation are pushing forward progress in disease modelling, drug development and regenerative medicine.

The United States Food and Drug Administration (FDA) asserts that "Currently, the only stem cell products that are FDA-approved for use in the United States consist of blood-forming stem cells (also known as hematopoietic progenitor cells) that are derived from umbilical cord blood". Indeed, the cell products included in the list of FDA-approved cellular and gene therapy products are (stem) cells from cord blood (for the treatment of patients with disorders affecting the haematopoietic system), autologous T cells engineered to express a chimeric antigen receptor (for the treatment of blood cancers, in particular multiple myelomas and B-cell lymphomas and leukaemias), autologous peripheral-blood mononuclear cells (for the treatment of metastatic castration-resistant prostate cancer), allogeneic processed thymus tissue (for the reconstitution of immunity in children with congenital athymia, a rare condition), and allogeneic or autologous keratinocytes, fibroblasts or chondrocytes (for the topical treatment of thermal burns, nasolabial fold wrinkles and mucogingival conditions, or for the repair of cartilage defects). The lists of approved or conditionally approved cell therapies in other Western countries are similarly short.

Why have so few cell therapies been approved, despite decades of encouraging preclinical data in animals and the many thousands of clinical trials of cell therapies that have been run across cell types and diseases? There are many reasons, and they can be complex. First, as illustrated by progress in the use of mesenchymal stromal cells, which as a cellular product were first tested in humans in 1995 (ref. [1]), animals and cell-culture systems do not recapitulate the relevant human conditions sufficiently well (and, most often, the reasons for this are unclear). Second, the identification, isolation, manipulation and expansion of the right type of cell are often painstakingly difficult. Third, cells differentiated from patient-specific induced pluripotent stem cell lines can sidestep immune rejection and the need for immunosuppression, but their long-term safety (in particular, a low risk of oncogenic transformation) cannot yet be ensured; and, for allogeneic cells, guaranteeing donor–recipient matching to avoid the long-term use of immunosuppressants is difficult. Fourth, the delivery of cells to the location of disease to aid their engraftment while preserving their viability may require bespoke devices (for implantation or injection). Overall, discordances in the outcomes of animal studies and human trials can be assigned to cell sourcing and the functional fitness of the manufactured therapeutic cells, to their rejection by the human immune system, and to differences in pharmacology, delivery route and dosing. And, unfortunately, exuberant promises and excitement about the possibilities of stem cells have created incentives for the predatory activities of unregulated stem cell clinics.

In addition to the fundamental challenges, the manufacturing of therapeutic cells and tissues for human use requires consistent quality of the cell products (batch-to-batch variabilities can be challenging to avoid), standardized assays for the assurance of their quality, technologies for their preservation and delivery, and the streamlining of the production, testing, preservation and delivery processes[2–5] so that the products can be produced at reasonable cost.

Among the hurdles that limit the clinical success of cellular products, understanding why they fail is arguably the most efficient path to making progress. Do the cells or tissue engraft to the target site? Are their therapeutic benefits mediated by the secretion of soluble factors[6]? Are their phenotypes sufficiently mature? Can the potency of the product be reliably determined by mechanistically informed assays? This issue of *Nature Biomedical Engineering* highlights advances in the production of cells and tissues, primarily for in vitro use, that may help to provide answers to some of these questions.

An example of insufficient mechanistic understanding is the question of how cilia in human cells contribute to disease. In an Article in this issue, Benjamin Freedman and colleagues show that cilia are not necessary for the preservation of pluripotency, and that organoids made from human pluripotent stem cells genetically edited to knock out the expression of kinesin-2 so as to disrupt ciliogenesis (Fig. 1) recapitulate hallmarks of ciliopathies. Microtissues engineered to lack cilia may guide the development of regenerative therapies for these diseases.

Fig. 1 | A flask containing a single organoid grown from genetically modified human pluripotent stem cells lacking cilia. Credit: Benjamin S. Freedman.

In fact, advances in regenerative medicine and in tissue engineering are inextricable. By analysing achievements in cardiac tissue engineering in the past two decades, Gordana Vunjak-Novakovic and colleagues identified three areas of progress: the sourcing and establishment of suitable cell populations, cell and tissue maturation, and the control of tissue structure and function.

The lack of suitable sources of well-differentiated human cells has long constrained the development of in vitro models. This is the case for atrial fibrillation. Antoine de Vries and colleagues now describe how cell lines with the molecular, cellular and electrophysiological properties of atrial myocytes can be produced from fetal atrial myocytes via a conditional cell-immortalization method that relies on lentiviral vectors and the controlled expression of a recombinant viral oncogene. Similarly, scalable sources of many bona fide stem cells for disease modelling, drug discovery and therapy are scarce. Nan Cao and co-authors show, also in this issue, that highly expandable cardiovascular progenitor cells can be chemically derived from fibroblasts by using a set of six small molecules.

The maturity of cells and tissues differentiated from stem cells has also been a major obstacle, preclinically and clinically, in particular for cardiac cells. In a research Article, Kevin Healy and colleagues report that, in cardiomyocytes derived from human induced pluripotent stem cells cultured in a microfluidic chip, cell alignment and suitable metabolic cues in the culture medium synergize to enhance the maturation of the cells. Vunjak-Novakovic and co-authors also show in another Article that, to maintain matured tissues of different types when functionally interconnected in vitro to model complex human physiology, the different media for the individual tissues need to be linked by vascular flow and separated by selectively permeable endothelial barriers.

The ability to control the cellular make-up, structure and function of engineered tissues for disease modelling could benefit from protocols for the simultaneous differentiation of stem cells into different defined cell types. Jennifer Lewis, Mark Skylar-Scott and colleagues show that human pluripotent stem cells can be co-differentiated at the same time into distinct lineages by the forced overexpression of transcription factors (overriding cues from the culture media) in a one-pot system, and that this orthogonally induced differentiation method can be combined with bioprinting technology to produce vascularized and spatially patterned tissues.

Together, reliable and scalable cell sources, matured cell populations, and more physiologically relevant tissue models of disease will also help us to understand whether (and which) genetic or epigenetic modifications can enhance the functionality or viability of injected or transplanted cells or tissues, or favour the suppression of immune responses to them. Manufacturing, preservation and delivery processes can certainly benefit from fitter cellular products. ❐

Published online: 27 April 2022
https://doi.org/10.1038/s41551-022-00892-4

References

1. Lazarus, H. M., Haynesworth, S. E., Gerson, S. L., Rosenthal, N. S. & Caplan, A. I. *Bone Marrow Transplant.* **16**, 557–564 (1995).
2. Aijaz, A. et al. *Nat. Biomed. Eng.* **2**, 362–376 (2018).
3. Yin, J. Q., Zhu, J. & Ankrum, J. A. *Nat. Biomed. Eng.* **3**, 90–104 (2019).
4. Huang, H., He, X. & Yarmush, M. L. *Nat. Biomed. Eng.* **5**, 793–804 (2021).
5. Vargason, A. M., Anselmo, A. C. & Mitragotri, S. *Nat. Biomed. Eng.* **5**, 951–967 (2021).
6. Marbán, E. *Nat. Biomed. Eng.* **2**, 353–361 (2018).