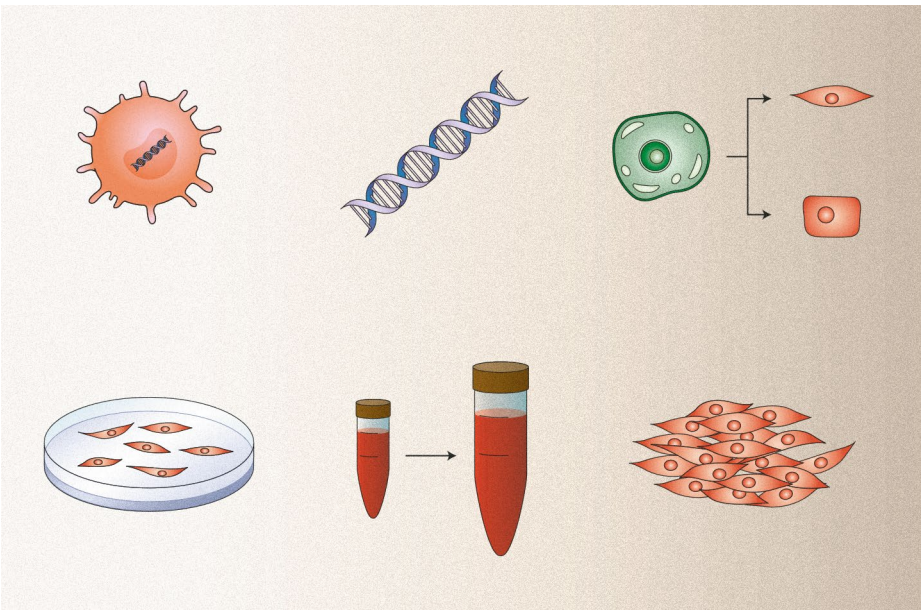
Towards advanced cell therapies

For cell therapies to transition from promises to products, increased efforts need to be put into the identification of the factors and biological mechanisms that affect safety and efficacy, and into the design of cost-effective methods for the harvesting, expansion, manipulation and purification of the cells.



The properties and functions of cells can be harnessed to identify and treat disease. For example, injecting stem cells into diseased tissue — such as cardiac muscle after myocardial infarction — can promote tissue regeneration. Yet despite the promises of cell therapies, very few cell products have been approved for clinical use. One main reason is that cell therapies have failed to provide sufficient safety and efficacy guarantees, in part owing to a lack of understanding of the intracellular factors and biological pathways that determine cell expansion and differentiation. As our understanding of cell phenotype and differentiation deepens, it becomes increasingly possible to manipulate cells for the generation of effective therapeutic products for regenerative medicine and for cell-based immunotherapy, and in the form of cell vaccines.

Although mechanistic understanding is necessary, it is insufficient. To take full advantage of the therapeutic potential of cell products with enhanced or new capabilities, beneficial cellular functions need to be repurposed or reinforced, for instance by re-engineering signalling circuits. Take, for example, T-cell-mediated cancer therapy: the engineering of T cells bearing artificial chimeric antigen receptors (CARs) — each of them a collage of molecular components that links the recognition of a specific tumour antigen to T-cell activation — has led to unprecedented clinical efficacy in patients with haematological cancers (as exemplified by the recent approvals, by the United States Food and Drug Administration, of the two first CAR-T cell products, Kymriah and Yescarta). Yet protein engineering is just one of the many fields contributing to the rise of tailor-made cell constructs for clinical applications. The path towards effective cell therapies also involves mastering the manipulation, expansion, purification and preservation of the cells to establish standardized and robust cell-product manufacturing processes.

This focus issue dedicated to the prospects of cell therapies provides an overview of the current state of the art, with emphasis on cardiac regenerative medicine and immunotherapy, and explores the challenges that lie ahead. It highlights the need for interdisciplinarity, from developmental biology to materials engineering to cell-product manufacturing, in order to overcome the hurdles that prevent many advanced therapies from reaching the clinic. Indeed, despite decades of advances in cell therapies for cardiac regeneration, evidence of efficacy from clinical trials has been underwhelming. In a Perspective, Eduardo Marbán highlights the importance of designing therapies that are deeply rooted in understood biological mechanisms, and posits that cell-secreted exosomes could become next-generation therapeutics for cardiac regeneration, with advantageous efficacy and safety profiles. In cardiovascular regenerative medicine, research on the biology of stem cells has largely focused on the characterization of stemness and on differentiation factors that enable the differentiation of stem cells into functional cardiomyocytes and other cell types found in diseased cardiac tissue. In a Review Article, Joseph Wu and colleagues discuss the critical factors limiting the therapeutic efficacy of stem cells transplanted to the heart, delineate how non-myocyte cells may be reprogrammed for cardiovascular regenerative applications, and emphasize the importance of cell-delivery strategies that do not impair the survival and therapeutic efficacy of the transplanted cells.

Cell therapies are transforming oncology. From cell-based vaccines to engineered T cells, encouraging results from multiple clinical trials in patients with haematological cancers are setting new efficacy goals. In a Review Article, Crystal Mackall and colleagues provide an overview of the many CAR-design strategies used in clinical trials and reported in preclinical studies, including the use of new genetic modules, co-stimulatory domains and suicide switches that improve the specificity, efficacy and safety of these engineered T cells. They also discuss the design of CAR-T cells for treating solid tumours — which are harder to tackle owing to their immunosuppressive microenvironment and to the paucity of targetable tumour-specific antigens — and outline what would be needed for the development of off-the-shelf CAR-T cells.

Cells can also provide a source of tumour antigens for immunization. Similarly to the use of traditional vaccines for preventing infectious diseases, dead tumour cells can be injected to kick-start an immune response against tumours; alternatively, the antigen-presentation functionality of dendritic cells

can be hijacked to present specific tumour antigens to the immune system for the activation of tumour-killing T cells. In a Comment, Nina Bhardwaj and colleagues posit that dendritic cells can make highly efficacious tumour vaccines. Multiple antigen compositions, dendritic-cell formulations and delivery methods are currently being tested in clinical trials, including some in which vaccine efficacy is being assessed in combination with potent antitumour immunotherapies such as checkpoint-blockade inhibition.

As biotechnologies evolve at an ever faster pace, the toolkit for manipulating mammalian cells for therapeutic applications keeps expanding. The ability to modify a cell's DNA with precision, enabled by methods based on clustered regularly interspaced short palindromic repeats (CRISPR), has paved the way for a degree of cell customization that is without precedent in biomedicine. Today, it is possible to create synthetic gene circuits in cells that, via intracellular computational modules and effector agents, 'upgrade' the cells to make them fully autonomous therapeutic machines. The repurposing of endogenous proteins or the de novo design of protein building blocks controlled by tailored genetic networks allows for cell customization, with exquisite targeting specificity, controlled timing and therapeutic activity. Martin Fussenegger and colleagues provide in a Review Article an overview of developments in synthetic biology that enable the programming of cells to sense environmental triggers and identify, eliminate or prevent the development of pathologies.

Irrespective of disease type, the production of cell-based therapeutics needs standardized, safe and cost-effective scale-up production processes. In a Review Article, Biju Parekkadan and colleagues discuss the need for robust infrastructure that enables all the necessary steps to manufacture clinical-grade cell products. Biomanufacturing and commercialization challenges can be daunting, yet need dedicated efforts if next-generation cell-based therapies are to see widespread application.

The rise of powerful and easy-to-use tools for the molecular manipulation of cells is opening up wide prospects for cell therapy. Yet one should not forget that the route to clinical success is paved by the acquisition of deep biological knowledge and by thorough preclinical and clinical testing, and facilitated by the painstaking optimization of production protocols and processes. ❐

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