Molecular Therapy
Editorial

Showcasing Clinical Development and Production of Cellular Therapies

As interest and investment in cell- and tissue-based therapies has recently exploded, we believe that the science and medicine of the field are converging and, together, will yield a new "golden age" of therapy. It is important to note that current cell- and tissue-based therapies are in a variety of stages of development and are based on a diverse setting of cell or tissue types. The *Molecular Therapy* sibling journal *Molecular Therapy – Methods & Clinical Development* has recently devoted a special issue to work on production and manufacturing of cell types in all stages of differentiation (http://www.cell.com/molecular-therapy-family/methods/collections/development-cell-therapies).

Human pluripotent stem cells (hPSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) are attractive starting material for cell therapies given their inherent self-renewal ability. However, immature cell types often present technical and safety considerations. In the special issue, Wang and Riviere[1] discuss the current hPSC manufacturing platforms and challenges, highlighting obstacles to good manufacturing practice (GMP)-compliant standardization. The therapeutic benefit of engineered hPSCs for the treatment of monogenic disorders is, by now, widely validated. Over the past 20 years, more than 150 subjects with multiple disease indications have received, and most have benefited from, hematopoietic stem cell (HSC) gene therapy. This form of therapy has made significant progress since the seminal studies in patients with SCID-X1, and the disease repertoire for HSC gene therapy is steadily expanding at a fast pace. Up until now, HSC gene therapy has been shown to provide unequivocal therapeutic benefit in primary immunodeficiencies, thalassemia, and leukodystrophies. Strimvelis, the first ex vivo stem cell gene therapy to treat patients with a very rare disease called ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency), received European marketing authorization in May 2016 (Ylä-Herttuala[2]).

While, ESCs and iPSCs are a viable alternative to bone marrow derived hPSCs for some indications, regenerative neural cell therapy has long relied on direct fetal cell transplantation. More recently, iPSCs have been shown to be capable of producing functional neurons, as explained by Irion et al.[3] The manufacturing of iPSCs can be standardized and scaled, making this a desirable GMP-compliant alternative for clinical use. However, to date, iPSC manufacturing cycles remain long and costly. The advent of newer platforms will improve manufacturing efficiency and make this technology more widely accessible. Despite this progress, safety concerns remain regarding gene therapy in pluripotent stem cells. Such cells demonstrate inherent genetic instability, with a selective growth advantage of some transformed cells and, ultimately, the risk of tumorigenesis. Mitsui et al.[4] present novel approaches to enhance the safety profile of genetically manipulated pluripotent stem cells. Techniques such as killing tumor cells by transduction of oncolytic viruses or introduction of suicide genes hold great promise in improving the safety of stem cell gene therapy. Conditionally replicating oncolytic viruses, in particular, could be employed in both ex vivo or in vivo applications. These improved safety mechanisms, along with a number of other advances in hPSC manipulation, are expected to greatly improve the safety and efficacy of hPSCs for cell and gene therapy in the coming years. These improvements include better vector design, a deeper understanding of HSC biology, refinement of existing bioprocessing and manufacturing techniques, incorporation of new gene-editing platforms, and better conditioning regimens prior to bone marrow transplant.

Ex vivo manipulation of more differentiated cell types has also shown great promise in the treatment and cure of human disease. Whereas the therapeutic aim of pluripotent stem cell therapy is regeneration, differentiated cell therapy has largely focused on re-establishing anti-tumor immunity. Attempts have been made to enhance either side of the immune synapse—antigen presentation and T cell response. Weinstock et al.[5] provide a comprehensive overview of the current state of knowledge of the biology of dendritic cell (DC) interactions with tumors and therapeutic use of DCs. DC anti-tumor vaccines are incredibly diverse therapies. In recapitulating a complex, in vivo, immunologic function, ex vivo DC vaccine production employs a wide variety of methods to enhance antigen loading, presentation, and expression of co-stimulatory molecules. While fundamental questions remain regarding the optimal use of DC vaccines, clinical responses and tumor regression in patients with indolent non-Hodgkin's lymphoma and multiple myeloma have encouraged work in this area. Next generation DC vaccines will build on early success by combating tumor-mediated immunosuppression.

On the other side of the immunologic synapse, engineered T cells also have shown enormous clinical potential targeting malignancy. Moving beyond proof-of-principle, Levine et al.[6] highlight the challenges in developing a global manufacturing platform for chimeric antigen receptor (CAR) T cell therapy. Successful transition from a single-institution approach to a large-scale multi-site trial is critical to progression past phase I of clinical development. Therapeutic cell manufacturing from autologous starting material, however, presents a number of unique challenges to manufacturing scale-up. Improvements in vector manufacturing and quality assays have made such scalability possible; however, the international regulatory environment has yet to be harmonized and therefore is challenging for the development of multi-national trials. Nevertheless, multiple companies are conducting registration clinical trials of CAR T cell products, and multiple regulatory authority submissions are expected in 2017.

The paradigm shift of using cells as therapeutic modalities will realize its full potential and further enter the realm of standard-of-care only if suitable cost-effective manufacturing technologies reproducibly yield high-quality cells with defined attributes. Concomitantly, with the establishment of therapeutic proof of principle, the automation and standardization of manufacturing and characterization processes will be critical to practically fulfill these needs and unlock the broader availability of cell therapies.

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