blood® Editorial

Introduction to a review series on banked allogeneic immune effector cells

Autologous chimeric antigen receptors modified T-cell therapies for CD19-positive lymphoid malignancies and myeloma have had impressive activity in patients with relapsed disease resulting in licensure of 6 products so far in the United States.[1,2] However, despite this success, broader application has been limited by the complex patient-specific manufacturing that limits their scalability, manufacturing failures, and unpredictable potency due to poor T-cell fitness from previous chemotherapy and the cost of goods.[3] An additional limitation is the potential for disease progression during cell product generation in patients who have aggressive lymphoid malignancies.

Although much effort is being devoted to simplifying autologous manufacture and evaluating point of care models,[3] another solution is to develop well-characterized allogeneic banked immune cell therapies manufactured from healthy donors that offer immediate availability and consistent potency and will hopefully also be less costly.[4,5] As these products are of allogeneic origin, potential limitations are the risks of graft-versus-host disease due to recognition of recipient alloantigen by the infused cells and short persistence due to elimination of the infused cells by recipient immune cells.[4,5]

In this review series, the following articles review several types of banked cell therapy including their attributes and how they might overcome these limitations:

- Waseem Qasim, "Genome-edited allogeneic donor "universal" chimeric antigen receptor T cells"
- Frank Cichocki, Sjoukje J. C. van der Stegan, and Jeffrey S. Miller, "Engineered and banked iPSCs for advanced NK- and T-cell immunotherapies"
- Melissa M. Berrien-Elliott, Miriam T. Jacobs, and Todd A. Fehniger, "Allogeneic natural killer cell therapy"
- Amy N. Courtney, Gengwen Tian, and Leonid S. Metelitsa, "Natural killer T cells and other innate-like T lymphocytes as emerging platforms for allogeneic cancer cell therapy"
- David H. Quach, Premal Lulla, and Cliona M. Rooney, "Banking on virus-specific T cells to fulfill the need for off-the-shelf cell therapies"

In the first article Qasim focuses on using gene editing to reduce alloreactivity and enhance function of allogeneic cells. The most widely used strategy being evaluated in several clinical studies is to knockout the T-cell receptor (TCR) in αβ T cells.[6] Multiple editing technologies are now being evaluated, and studies now incorporate multiplexed editing to target HLA molecules, shared antigens, and checkpoint pathways.

It is also possible to genetically engineer induced pluripotent stem cells (iPSCs) into immune cell populations that include T cells and natural killer (NK) cells. iPSC-derived immune effectors are an attractive source of banked allogeneic cells as they have the potential for extensive expansion, allowing repeat dosing of multiple recipients, and they should also have minimal batch-to-batch functional variation. Cichocki and colleagues review the attributes of this source of allogeneic cells and how their characteristics are being exploited to generate genetically modified allogeneic T and NK cells that are being tested in clinical trials.

NK cells lack TCRs and not only have an inherent ability to recognize cancers but lack alloreactivity. Berrien-Elliott et al review different NK cell populations that have been investigated in clinical trials and discuss cellular engineering strategies to broaden target cell recognition and enhance persistence of adoptively transferred cells.

Courtney and colleagues review the use of cell products with restricted or invariant TCRs including NK T cells and other innate-like T lymphocytes. NK T cells are not alloreactive and have other desirable attributes including the ability to traffic to tumor tissues and target tumor-associated macrophages. Both unmodified NK T cells, which specifically recognize CD1d-bound glycolipid antigens expressed by some types of tumors, and CAR-redirected NK T cells are being evaluated in the clinic.

Finally, Quach et al discuss using virus-specific T-cell products (VSTs) such as Epstein-Barr virus (EBV)-specific T cells, which should lack alloreactivity as they have defined TCR specificity. EBV VSTs have recently become the first allogeneic product to be licensed in Europe,[7] and VSTs specific for other viruses are in late-phase trials. In addition to targeting viral infections and virus-induced cancers, allogeneic VSTs can be used as a platform for CARs targeting other tumor antigens. The authors highlight the properties of VSTs that make them attractive off-the-shelf cell therapies and discuss additional genetic modifications to enhance persistence and function.

This series therefore provides an overview the different types of allogeneic cells and genetic modifications being evaluated in this active area of investigation.

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