

## Introduction to a review series on advances in cell-based immune therapeutics in hematology

Cell-based therapy in hematology has a long history. In the 1940s, experiments by Lorenz and Congdon in mice led to the observation that an infusion of spleen cells from a healthy mouse could protect irradiated mice from lethal marrow failure.<sup>1</sup> However, the idea that cell transfer could result in complete marrow was so revolutionary that many preferred the explanation that the protection was mediated by transfer of marrow-stimulating hormones. The hormone theory was only put to rest when Lorenz and others showed that repopulating marrow bore the same unique chromosomal marker of the infused cells.<sup>2-4</sup> This observation established the potential of marrow cells to engraft in a recipient and led to an explosion of laboratory experiments in the 1950s discovering and characterizing all the major phenomena of stem cell transplantation: graft-versus-host disease (GVHD), rejection, and the graft-versus-leukemia effect.<sup>5</sup> Furthermore, physicians were not slow to put the new concept of marrow transplantation to clinical use, in autologous transplantation to mitigate the effect of supralethal total body irradiation for cancer and leukemia, and by the late 1960s, the successful application of HLA typing to perform matched allogeneic marrow transplants for immune deficiencies, aplastic anemia, and leukemia.<sup>6</sup> It is no exaggeration, therefore, that for the last 70 years, clinical and experimental bone marrow transplantation has driven development in our understanding of stem cells and their engraftment and the immunological barriers of engraftment and GVHD.

Today, the field of cell transplantation and cell therapeutics has evolved almost out of recognition of those first pioneering years. Technology has given us the tools to cryopreserve cells indefinitely, select individual cell types for therapy, expand them in vitro, and introduce genes able to confer new properties on them. In step with these advances, a deeper understanding of the behavior of immune cells has grown in the context of stem cell transplantation where it is clear that T cells are key to controlling reactivation of dormant viruses after transplantation. In the field of tumor immunology, the identification of many tumor antigens that are targets of T-cell attack has increased our opportunity to specifically target the malignancy. It is now realized that the interactions between immune cells and malignant cells is dynamic, leading to both immune evasion and active immune suppression by the tumor. Such immune editing can be overcome, for example, by interrupting the programmed death 1/programmed death ligand 1 pathway, unlocking potent antitumor immunity and leading to remissions in advanced cancers and lymphomas.<sup>5</sup> Expertise in new cellular therapies is now being applied to cancer and leukemia immunotherapy, cell-mediated protection against viruses, and correction of genetic diseases. Meanwhile, the therapeutic success of these treatments continues to grow. A dramatic development in the field of cancer therapy has been the engineering of transferred T cells to target cancer. One approach has been to retarget T cells to attack malignant cells by the insertion of leukemia-specific T-cell receptors, with function optimized by molecular modification, described here by Morris and Stauss (University College London). A second strategy has been to direct and arm T cells by insertion of a chimeric antigen receptor (CAR). The clinical demonstration that CAR-T cells specific for a B-cell surface protein can eliminate B-cell malignancies, when all other therapies (including stem cell

transplantation) have failed, is leading to multiple clinical trials which are showing great promise. In this series, 2 reviews address CAR cell therapy: Park, Geyer, and Brentjens (Memorial Sloan Kettering Cancer Center) review clinical outcomes in hematological malignancies and Brudno and Kochenderfer (National Cancer Institute) describe the successful control of the toxicities that accompany these potent cell products. We also highlight here other new and promising cell-based therapies. Bollard (The George Washington University) and Heslop (Baylor College of Medicine) review T-cell therapies for virus-associated diseases after transplant, and Handgretinger and Lang (Tuebingen) with André (Basel) describe recent advances with NK-cell therapies for acute leukemia. Finally, Dotti and Savoldo with Sun (University of North Carolina) describe how gene-modified T cells can overcome immune evasion in hematologic malignancies. We hope our readers will find in this review series a broad picture of the most clinically promising cell therapies in this fast-moving field. Articles in this series include:

- Emma C. Morris and Hans J. Stauss, “Optimizing T-cell receptor gene therapy for hematologic malignancies”
- Jae H. Park, Mark B. Geyer, and Renier J. Brentjens, “CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date”
- Jennifer N. Brudno and James N. Kochenderfer, “Toxicities of chimeric antigen receptor T cells: recognition and management”
- Catherine M. Bollard and Helen E. Heslop, “T cells for viral infections after allogeneic hematopoietic stem cell transplant”
- Rupert Handgretinger, Peter Lang, and Maya C. André, “Exploitation of natural killer cells for the treatment of acute leukemia”
- Chuang Sun, Gianpietro Dotti, and Barbara Savoldo, “Utilizing cell-based therapeutics to overcome immune evasion in hematologic malignancies”

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### References

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