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CAR T cells, immunologic and cellular therapies in hematologic malignancies

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The concept of adoptive cell therapy to treat cancers originated with the advent of high dose chemotherapy followed by allogenic bone marrow transplantation (allo-BMT) for patients with hematologic malignancies. What would become clear over time was that the T cells present in the donor graft could mediate both a deleterious graft versus host disease (GvHD) as well as a beneficial graft versus leukemia (GvL) [1]. In the former, T cells recognize antigens on normal host tissues as foreign and attack, in the latter, donor T cells recognize antigens on host hematopoietic cells including residual leukemia tumor cells eliminating residual tumor and resulting in durable disease remissions. Evidence of a GvL effect include lower relapses in patients with GvHD, re-induction of remission with tapers of immune suppression, increased relapses in patients treated with T cell depleted grafts and whose donors were an identical twin [1]. Recognition that a subset of donor T cells may indeed mediate an immunologic anti-tumor response led to the infusion of donor T cells in relapsed patients after allo-BMT, termed donor leukocyte infusion (DLI) which at times could mediate both a GvHD and GvL [2]. Collectively, this first iteration of adoptive T cell therapy has long served as a proof of principle that T cells may mediate a potent and even quite specific form of anticancer therapy. However, efforts to identify and isolate donor T cells specific to tumors have been met with limited clinical success.

The ability of investigators to harness T cell antitumor efficacy in a more precise manner would require the addition of 2 further technologies: efficient gene transfer techniques primarily through the development of retroviral and lentiviral replication incompetent vectors, and the innovative construction of synthetic receptors targeted to antigens expressed on tumor cells which, when introduced into T cells utilizing viral vectors, can function similarly to native T cell receptors (TCRs) in activating and engaging the cytotoxic functions of the T cell [3]. While efficient gene transfer into T cells has helped the field of TCR modified T cells wherein cloned tumor specific TCRs from tumor specific T cells are introduced into autologous T cells, a large step forward was made possible by the introduction of artificial non-HLA dependent T cell receptors termed chimeric antigen receptors (CARs). CARs are most commonly composed of a single fragment length antibody (scFv) derived from an antibody specific to the desired antigen on the tumor cell surface, fused to a transmembrane domain and cytoplasmic signaling domain, most

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commonly CD3ζ [4]. The gene encoding this chimeric receptor is introduced into a patient's own T cells, minimizing risk of GvHD, and expanded to clinically relevant numbers in a laboratory. In the early preclinical development of CARs investigators found that "first generation" CAR designs containing only the CD3ζ cytoplasmic signaling domain resulted in inefficient T cell activation due to activation induced T cell death as a consequence of missing T cell co-stimulation commonly mediated by costimulatory receptors such as CD28, 4–1BB, or OX-40 [5]. For this reason, "second generation" CARs were introduced wherein the cytoplasmic tail of the CAR contained both a costimulatory signaling domain as well as CD3ζ. Based on studies from multiple centers demonstrating enhanced efficacy of second generation CARs over first generation CARs both in vitro and in vivo, the most prominent subsequent clinical trials utilized patient T cells virally transduced to express second generation CARs [5,6].

The CAR modified T cell platform have several conceptually appealing traits: First, CARs recognize target antigen in an HLA unrestricted manner and are therefore universally applicable; second, CARs are functional in all T cell subsets including CD4 and CD8 T cells; third, in the modern era of human scFv phage display libraries investigators may now readily generate CARs targeted to a wide array of tumor associated antigens; and fourth, CAR modified T cells should be seen as a "living drug" meaning that if suitably generated, only a single infusion of CAR T cells would be required to cure the patient. Obviously there remain multiple inherent limitations with this technology that will require further technological innovations to overcome. First, given the fact that CAR T cells are designed to recognize only a single target antigen there is the risk of antigen escape by the tumor. Second, many tumors, especially solid tumors, exhibit a scaffold of immune suppressive cells (myeloid derived suppressor cells, $CD4^+$ regulatory T cells, tumor associated macrophages), T cell inhibitory ligands (PD-L1), and immune suppressive cytokines (TGF-B, IL-10), just to name a few. Third, infused T cells may have limited in vivo persistence due to terminal differentiation with limited proliferative capacity. Finally, there remains the obstacle of identifying suitable antigens to target with the CAR. An optimal target is an antigen solely expressed by the tumor cell and expressed on all tumor cells. However, there are few ideal targets such as CD19.

CD19 is an early marker of B cell differentiation and is not expressed on hematological stem cells [7]. The antigen is expressed on normal B cells therefore targeting of CD19 with CAR modified T cells may and has resulted in long-term B cell aplasia. What makes CD19 such an attractive target is that it is almost universally expressed on B cell malignancies including B cell acute lymphoblastic leukemias (B-ALL), chronic lymphocytic leukemias (CLL), and B cell non-Hodgkins lymphomas (NHL). Given the favorable profile of CD19, multiple centers began initiating phase I clinical trials targeting CD19 with second generation CAR T cells. Trials conducted at multiple academic centers have reproducibly demonstrated remarkable responses in both adult and pediatric patients with relapsed or refractory B-ALL, relapsed or refractory diffuse large B cell lymphoma (DLBCL), and more modest clinical responses in patients with relapsed or refractory CLL [8–10]. These phase I clinical trials led to industry sponsored phase II registration trials which in turn resulted in the first FDA approved CAR T cell products with Tisagenlecleucel approved for relapsed/refractory B-ALL and Axicabtagene Ciloleucel approved for relapsed/refractory DLBCL [11,12].

FDA approval of these products was the culmination of almost 3 decades of intense research at multiple centers. However, at this current juncture there are many questions which remain in regard to genetically modified T cell adoptive therapy. Simply stated, this is a technology still in its infancy. In reference to the CAR acronym, one could say that at this time we have a Model T Ford, but what we need is a Ford Mustang. In other words, the success seen to date in CD19 targeted T cells may perhaps be viewed as a proof of principle not only with respect to CAR T cell therapies but adoptive T cell therapies in general. There remain many mountains to climb before we can successfully apply this therapy to a broader range of malignancies including solid tumors.

In this edition we have solicited a number of experts in the field to write reviews on various aspects of adoptive therapy of cancer with genetically modified T cells with an understandably strong focus on CAR modified T cells. We acknowledge that a fully comprehensive series of reviews in this rapidly expanding field is well beyond the scope of this issue. For this reason, we selected a series of topics that address some of the critical issues in the field including preclinical development, clinical trial results, clinical production of CAR T cell products, clinical toxicities, universal “off the shelf” CAR T cells, and chapters on the design of novel CAR constructs, which may expand application of this technology to other cancers. We believe that this volume presents to the reader at the very least a comprehensive introduction to the field. This technology has a very high ceiling with profound opportunities for further innovation. We hope that the readers of this volume are equally inspired and perhaps in the future move the field forward.

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