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Preface

Reprogramming the lymphocyte axis for advanced immunotherapy

Lymphocytes are mainly categorized as T cells, B cells and NK cells, arising from common lymphoid progenitors, which are often defined as $CD34^+$, $CD10^+$, $CD45RA^+$, and $CD24^-$ [1]. T and B cells play crucial roles in the adaptive immune system, which requires antigenic priming and activation. In contrast NK cells are part of the innate immune system and are best-known for killing tumour and virally infected cells, which does not require priming or prior activation. Over the last decade, modulation and manipulation of lymphocyte functions has been at the forefront of immunotherapy. These innovative treatments are predominantly based on chimeric antigen receptor (CAR)-T cell therapy, monoclonal antibodies that neutralize immune checkpoint inhibitors, manipulation of lymphocytes via RNA therapies (e.g. by silencing specific genes with RNA interference (RNAi) or increasing expression of specific proteins using modified mRNA), and the design of fusion proteins that modulate lymphocytic function.

CAR T-cells are lymphocytes that have been genetically engineered to express multicomponent designer receptors, called CARs. These are typically composed of an antigen-binding moiety, a spacer domain, a transmembrane region, and an intracellular signalling domain, that enables T-cells to recognize specific antigens on tumour cells and initiate tumour-cell lysis [2]. Indicating the recent success of this strategy, two CAR T-cell therapies have received approval by the United States Food and Drug Administration. One CAR therapy treats children with acute lymphoblastic leukemia, and another CAR therapy is indicated for adults with advanced lymphomas. These developments push the boundaries of adoptive cell transfer-based treatments to broader malignancies including solid tumours; however, many challenges need to be addressed [3]. In parallel with CAR T-cell developments, the surface of T-cells are an ideal place to identify modulatory molecules that influence T-cell activity. To this end, the discovery of cytotoxic T-lymphocyte antigen 4 (CTLA-4) [4–7] and programmed cell death protein-1 (PD-1) [8] opened a new chapter in cancer immunotherapy through inhibition of negative immune regulation. For example, binding of PD-1 to its ligand on tumour cells prevents T-cells from killing cancer cells [8]. Checkpoint inhibitors (e.g., Ipilimumab, Pembrolizumab, Avelumab) block CTLA-4 and PD-1 functions, thereby allowing T-cells to attack and kill the cancer cells [9,10]. Indeed, checkpoint inhibitors have been credited with saving thousands of lives within the first few years of their approval [10] and in 2018 this secured the Nobel Prize in Physiology or Medicine for James Allison and Tasuku Honjo.

This compendium of state-of-the-art reviews celebrates recent advances in reprogramming lymphocytes for adoptive cell transfer-based treatments. We begin with an overview by Hong & Dobrovolskaia [11], which highlights barriers to effective cancer immunotherapy using nanotechnology. This overview discusses achievements so far, identifies key challenges ahead, and provides a strategic roadmap for generation of the next nano-based immunotherapeutics. We continue with three reviews that critically evaluate and discuss the field of CAR T-cells from different perspectives. First, Eisenberg and colleagues [12] provide an overview of the most recent developments in the field of T-cell genetic engineering, including T-cell receptor (TCR) gene transfer and CAR T-cells strategies. They discuss the development of other types of genetic modifications to enhance their anti-tumour immune response such as the use of co-stimulatory chimeric receptors and unconventional CARs built on non-antibody molecules. To close, they debate recent advances in genome editing and synthetic biology applied to T-cell engineering and elaborate on future challenges. Second, Rahbarizadeh and colleagues [13] focus on unconventional CARs structured on single variable domain of heavy chain antibodies (also known as single-domain antibodies and nanobodies). Indeed, single-domain antibodies not only express a multitude of unique immunological and physicochemical characteristics that makes them as interesting candidates for CAR bioengineering, but also show a high homology with the human VH3 gene family, which could bring new opportunities for safer and more-effective T-cell reprogramming initiatives. Third, Getts and colleagues [14] provide an industrial view of CAR T-cells therapeutics. They further review the current state of TCR development and discuss challenges and solutions for the next generation T-cell therapies.

RNAi has become an indispensible tool to inhibit gene expression or translation, by neutralizing targeted mRNA molecules [15]. However, gene manipulation in lymphocytes is a difficult task due to their hard-to-transfect nature, particularly in vivo. Here, Ramishetti and Peer [16] discuss available strategies for RNAi delivery to lymphocytes and highlight effective approaches for in vivo targeting of lymphocytes subsets within the context of broader leukocyte-implicated diseases. On the other hand, Hutmacher and Neri [17] introduce antibody-cytokine fusion proteins (immunocytokines) as another promising immunotherapeutic approach against cancer and provide realistic pros and cons of emerging immunocytokines, which highlight preclinical and clinical-stage products. The penultimate article [18] focuses on CD40. This is a costimulatory receptor of the tumour necrosis receptor superfamily expressed by B cells, dendritic cells, monocytes, platelets, macrophages and non-haematopoietic cells such as myofibroblasts, fibroblasts, endothelial and epithelial cells [19]. CD40L is the ligand for CD40, which is transiently expressed on T-cells as well as other non-immune cells under inflammatory conditions [19]. CD40-CD40L engagement initiates a multitude of humoral and cellular immunity. Deregulation of CD40

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signalling has been noted in multiple autoimmunity diseases and CD40 targeting has led to novel anti-tumour therapies [19]. Thus, Karnell and colleagues [18] review CD40-CD40L engagement and underscore the essential role this axis plays in adaptive immunity in humans. In the final article, Markel and colleagues [20] critically examine the biology and evaluate clinical progress of reprogramming lymphocytes through a range of immunotherapeutic approaches including checkpoint inhibitors, adoptive T-cell transfer, and personalized melanoma vaccines.

Last, but not least, we express our sincere gratitude to all authors who contributed to this *Special Issue* of *Advanced Drug Delivery Reviews*. We further hope this thematic issue will accelerate integrative engagements in immune cell bioengineering and development of advanced immunotherapies to combat cancer, autoimmune pathologies, and infectious viral diseases.

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