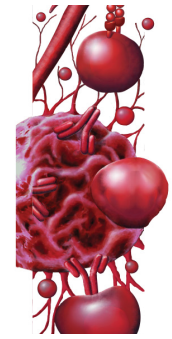
Foreword
Special Focus Issue: Adoptive cell immunotherapy for cancer
For reprint orders, please contact: reprints@futuremedicine.com

Immunotherapy



Adoptive immunotherapy: a new era for the treatment of cancer

Phillip K Darcy
Author for correspondence:
Cancer Immunology Program, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia
and
Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia
and
Department of Pathology, University of Melbourne, Parkville, Australia
and
Department of Immunology, Monash University, Clayton, Australia
Tel.: +61 396 563 769
Fax: +61 396 561 411
phil.darcy@petermac.org

Paul J Neeson
Author for correspondence:
Cancer Immunology Program, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia
and
Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia
and
Department of Pathology, University of Melbourne, Parkville, Australia
Tel.: +61 396 563 769
Fax: +61 396 561 411
paul.neeson@petermac.org

"...for application of adoptive cellular therapy to a wider range of solid and hematological cancers, several challenges remain. In this special focus issue, we have invited several experts in the adoptive immunotherapy field to discuss these issues and propose potential strategies for enhancing the current success of this approach."

Keywords: adoptive immunotherapy • cancer • chimeric antigen receptor • cytokines • immunosuppression • T cells • toxicity

The early promise of adoptive immunotherapy is now coming to fruition with exciting clinical responses being reported against various cancers. This has particularly been the case with adoptive transfer of tumor-infiltrating lymphocytes in patients with advanced malignant melanoma [1–3], transfer of chimeric antigen receptor (CAR) T cells targeting CD19 in patients with B-cell malignancies such as chronic lymphoid leukemia and acute lymphoblastic leukemia [4–7] and transfer of Epstein–Barr virus (EBV)-specific T cells against viral-induced malignancies such as post-transplant lymphoproliferative disorder (PTLD) [8,9]. However, for application of adoptive cellular therapy to a wider range of solid and hematological cancers, several challenges remain. In this special focus issue, we have invited several experts in the adoptive immunotherapy field to discuss these issues and propose potential strategies for enhancing the current success of this approach.

Smith and Khanna discuss the use of adoptive T-cell therapy for EBV-induced cancers. This therapy has been very successful for PTLD, however, this is currently not the case for other EBV-induced cancers including lymphoma and nasopharyngeal cancer. This review discusses various new strategies for altering the tumor microenvironment and increasing tumor immunogenicity. This includes adjunct-based approaches involving chemotherapy in combination with adoptive T-cell therapy which has shown some promising signs against nasopharyngeal cancer. Alternatively, targeted approaches for preferentially expanding T cells recognizing EBV-associated antigens LMP-1, LMP-2 or EBNA1 have showed some promising results in lymphoma patients.

Beavis *et al.* discuss the negative effect of immune suppression pathways on the efficacy of adoptive T-cell therapy. The recent success of immune checkpoint inhibitors blocking PD-1 and CTLA-4 pathways in patients with advanced cancer such as melanoma, renal cancer and non-small-cell lung carcinoma suggests that immunosuppression can be effectively overcome resulting in increased antitumor immunity in some patients. This has raised the possibility that combining these drugs with other immunotherapies including adoptive T-cell immunotherapy may lead to further enhancing antitumor effects in patients particularly for less immunogenic cancers. This review discusses several nongenetic and genetic strategies that may be employed to overcome tumor-induced immune suppression for enhancing the efficacy of adoptive

Future Medicine part of fsg

immunotherapy against both solid and hematological cancers.

In parallel with this review, Hinrich Abken raises other specific challenges for utilizing CAR-T-cell therapy for solid cancers. These include 'on-target, off-tumor' toxicity, cytokine release syndrome and immunogenicity of the CAR, leading to low persistence of adoptively transferred T cells. Furthermore, low frequency of CAR-T cells trafficking to the tumor site and immune suppression within the tumor microenvironment are factors that restrict the efficacy of CAR-T-cell therapy. This review covers several strategies that may be employed to overcome these challenges including the use of fourth generation CAR-T cells, designated TRUCKs (T cells for redirecting universal cytokine killing) that enable delivery of an inflammatory cytokine such as IL-12 to the tumor stroma thereby altering the protumoral environment.

CAR-T-cell therapy targeting CD19 has induced clinical remission in patients with B-cell malignancies such as acute lymphoblastic leukemia or chronic lymphoid leukemia, although, this therapy has resulted in some toxicity in patients. Pegram *et al.* discuss the ongoing challenges of managing patients treated with CD19-targeted CAR-T cells, and for expanding CAR-T-cell therapy to effectively treat patients with other blood cancers including diffuse large B-cell lymphoma, follicular lymphoma, acute myeloid leukemia and multiple myeloma. In addition, alternative CAR target antigens and modifications are discussed with the aim to alter the tumor microenvironment for enhancing therapeutic responses delivered by CAR-T cells.

Cytokines are a key component for the success of adoptive cellular therapy and have an important role in *ex vivo* expansion, engraftment and persistence of adoptively transferred T cells. These cytokines are integral for mediating T-cell infiltration into the tumor and for maintaining T-cell effector function. Petrozziello *et al.* discuss the latest developments of the role of γc binding cytokines (IL-2, IL-7, IL-15, IL-21) for facilitating each of these key steps for mediating a successful antitumor response by adoptively transferred T cells.

The review by Kalaitsidou *et al.* raises the important issue of CAR-T-cell-induced clinical toxicity. They discuss the use of current preclinical models and their potential for predicting CAR-T-cell toxicity in patients. Each successive generation of CAR-T cells has not only increased their potency and potential therapeutic responses, but has also increased the chances of unwanted side effects including 'on-target, off-tumor' toxicity and cytokine release syndrome. Development and evaluation of CAR-T-cell therapy in xenotransplant models has precluded the broader understanding of the potential side effects of this therapy. This review discusses recent efforts to test CAR-T-cell therapy in self-antigen mouse models to better predict potential toxicity that may be encountered in the clinic.

Immune monitoring is a key element for ongoing development of CAR-T-cell therapy in the clinic. Accurate recording of data from clinical trials across different centers is a key for improving this approach and may help to drive strategies for utilizing CAR-T-cell therapy in combination with other immunotherapy drugs. Klaver Y *et al.* discuss the importance of careful characterization of the cell product and immune monitoring protocols to identify prognostic markers predictive of a clinical response and potential cytokine release syndrome. They discuss potential biomarkers that correlate closely with clinical responses by adoptively transferred T cells.

Also, featuring in this issue, a series of short commentaries by Jacob Schachter, Daniel Powell Jr and Nabil Ahmed that provide a current summary and prospects for tumor-infiltrating lymphocyte therapy in melanoma, and adoptive T-cell therapy for ovarian cancer and glioblastoma patients.

In summary, this special issue of *Immunotherapy* discusses exciting developments surrounding adoptive cellular therapy, and reviews new strategies to address current challenges of extending the effects observed against some B-cell malignancies and PTLD to a wider range of tumor types. It is anticipated that these developments will have a significant impact on the treatment of cancer patients with advanced metastatic disease in the future.

Financial & competing interests disclosure

This work was funded by Program and Project grants from the National Health and Medical Research Council (NHMRC) (#1013667 and #1030436, respectively). PK Darcy was supported by an NHMRC Senior Research Fellowship (#1041828). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Morgan RA, Dudley ME, Wunderlich JR *et al.* Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 314(5796), 126–129 (2006).

2 Robbins PF, Dudley ME, Wunderlich J *et al.* Cutting edge: persistence of transferred lymphocyte clonotypes correlates with cancer regression in patients receiving cell transfer therapy. *J. Immunol.* 173(12), 7125–7130 (2004).

3 Rosenberg SA, Yannelli JR, Yang JC *et al.* Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin 2. *J. Natl Cancer Inst.* 86(15), 1159–1166 (1994).

4 Brentjens RJ, Davila ML, Riviere I *et al.* CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci. Transl. Med.* 5(177), 177ra138 (2013).

5 Brentjens RJ, Riviere I, Park JH *et al.* Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood* 118(18), 4817–4828 (2011).

6 Grupp SA, Kalos M, Barrett D *et al.* Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N. Engl. J. Med.* 368(16), 1509–1518 (2013).

7 Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N. Engl. J. Med.* 365(8), 725–733 (2011).

8 Cohen JI, Bollard CM, Khanna R, Pittaluga S. Current understanding of the role of Epstein-Barr virus in lymphomagenesis and therapeutic approaches to ebv-associated lymphomas. *Leuk. Lymphoma* 49(Suppl. 1), 27–34 (2008).

9 Smith C, Khanna R. Generation of cytotoxic T lymphocytes for immunotherapy of EBV-associated malignancies. *Methods Mol. Biol.* 651, 49–59 (2010).