# Adoptive T cell therapy of cancer

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This edition on Tumor Immunology is focused on the preclinical development and clinical testing of adoptive cell transfer (ACT)-based immunotherapies. The rationale for ACT is strong: it involves the administration of large numbers of highly selected cells with high avidity for tumor antigens. These T cells can be programmed and activated ex vivo to exhibit anti-tumor effector functions. This is important because tumor-specific T cells can be inactivated at early stages of cellular transformation [1]. Furthermore, T cell infusion may be preceded by 'conditioning' of the patient with lymphodepleting chemotherapy or total body irradiation, which enables the diminution of immunosuppressive cell types/ factors followed by the infusion of tumor-specific T cells [2].

Two different strategies for the source of the adoptively transferred T cells should be distinguished: naturally-occurring T cells and genetically engineered T cells. In humans with cancer, naturally-occurring autologous tumor-specific T cells can only reliably be grown from patients with melanoma. If the desired tumor-reactive T cell repertoire is normally not present, our task is to engineer such a repertoire [3]. Although limited to the one histology of melanoma, the adoptive transfer of tumor-infiltrating lymphocytes can be highly effective. The second strategy can be more broadly applied and is conceptually similar to the clinical use of recombinant antibodies such as Herceptin and Rituxan that target non-mutated target structures on human tumors. While highly attractive, clinical experiences with genetically engineered T cells are only starting to emerge.

Within this edition, we have aimed to bring together a number of linked reviews that collectively cover the three major issues that we see in the development of adoptive T cell therapy: 1). What antigens should be targeted? 2). What are the most effective cells to use? 3). How can ACT-based immunotherapies successfully be implemented in the clinic?

The notion that antigen choice is in our view a significant issue is perhaps surprising in view of the fact that –following a spate of activity in the 80's and 90's – antigen discovery efforts have in large part been abandoned in recent years. However, as discussed by Offringa [4], even though this prior research has revealed the identity of a large number of T cell antigens, in most cases it is unclear whether the targeting of these antigens with high affinity T cells would result in an acceptable toxicity profile. Notably, recent work on the induction of high avidity T cell responses against CEA and p53 in mouse models provides a very clear warning in this regard. In addition, evidence of significant on-target toxicity has also been obtained in a phase I trial

by Lamers et al. using receptor-engineered T cells [5]. Collectively these studies argue that there is a strong need for better datasets that can be used to predict the suitability of different antigens for adoptive T cell therapy. As a second related objective, it will become increasingly important to define which tumor-associated antigens can be considered tumor-rejection antigens, something that will be determined by factors such as the level and heterogeneity of expression and the likelihood of antigen loss.

A subsequent series of reviews focuses on the differentiation state and antigen reactivity of the cells that are utilized for adoptive T cell therapy. A first of these reviews by Berger and colleagues [6] draws upon data obtained from human trials and studies in non-human primates that examine the differentiation state of T cells used for adoptive cell therapy and the effect of the host environment that these cells encounter upon transfer. A highly informative study by the authors demonstrating that central memory cells rather than effector memory cells should be used as 'starting material' for *in vitro* expansion processes provides a strong incentive for the development of T cell isolation strategies that selectively yield those cells [7]. Likewise, the elucidation of the mechanisms through which the administration of lymphodepleting chemotherapy or total body irradiation enhances T cell persistence should form the starting point for the design of more refined strategies that may potentially achieve the same goal.

With few notable exceptions, adoptive T cell therapy of human cancer has focused on the generation of a tumor-reactive repertoire of CD8^{+} T cells. However, as outlined by Muranski and Restifo [8], there is significant reason to also investigate the potential of adoptive T cell therapy with CD4^{+} T cells, either as stand-alone therapy or in combination with tumor-specific CD8^{+} cells. The reason why work on adoptive T cell therapy with helper T cells has lagged behind is mostly practical. Due to the substantially higher diversity of MHC class II products, the incentive to map tumor-associated epitopes has been less, and few well-characterized tumor antigen-reactive receptors are currently available. However, with the first evidence of the potential of CD4^{+} cells emerging [9], a growing effort will likely be made in this field. As pointed out by Muranski and Restifo, in these efforts it will be of particular importance to define which polarization state of CD4^{+} cells should be aimed for.

Reviews by Sadelain and colleagues [10] and Bendle and colleagues [11] focus on the requirements for adoptive cell therapy with T cells that either carry chimeric antigen receptors (CARs) or T cell receptors (TCRs). The potential value of CAR-engineered T cells that allow MHC-independent recognition of tumor cells was recognized over 15 years ago [12]. However, the inability of first generation CARs to provide a signal for T cell proliferation formed a significant concern, and – possibly because of this – early clinical experiences with CAR-modified T cells have shown only very modest clinical effects. Notably, the development of second generation CARs that do allow expansion of T cells triggered through the chimeric receptor in preclinical experiments has led to the design of a series of new phase I clinical trials. These trials will provide an important test of the value of such second generation chimeric antigen receptors in the coming years and will help decide whether at this point in their development CARs do or do not form an attractive alternative over classical TCRs. The review by Bendle and colleagues [11] describes the results coming from a set of mouse studies that have aimed to define optimal conditions for adoptive transfer of TCR-modified T cells. Importantly, some of the models used to define such conditions have specifically focused on the generation of T cell reactivity against self antigens to which the endogenous T cell repertoire is non-responsive, thereby providing a critical test of the value of TCR gene modification to create a new repertoire. Key factors identified in these mouse studies have been the use of expression systems that yield high TCR expression, the use of lymphodepletion rather than vaccination to promote T cell persistence and the generation of T cell grafts that contain a high frequency of gene-modified cells. Future work in this field may assess the effect of gene modifications additional to the introduction of TCR genes on *in vivo* T cell function.

Furthermore, an assessment of the role of different helper T cell subsets would seem of interest. Finally, it would seem worthwhile to directly compare the relative value of T cells modified with either TCR or CAR genes in such murine models.

The final review in this issue by Rosenberg and Dudley [13] describes their extensive clinical experience with adoptive T cell therapy for patients with metastatic melanoma. The work by the NIH Surgery Branch in this field over the past years has provided a very strong impetus for the development of adoptive cell therapy with either tumor-derived T cells or TCR-engineered T cells. In addition, the finding by this group that lymphodepleting chemotherapy or total body irradiation has a strong beneficial effect on the clinical efficacy of ACT forms a striking illustration of how data obtained in clinical trials can form the starting point of preclinical research aimed at elucidating the underlying mechanisms [14].

What can we expect with regard to the future developments of adoptive T cell therapy? In the coming years, the use of more advanced culture protocols will surely enhance the *in vivo* function of adoptively transferred cells. In addition, a large new series of antigen receptors will be tested in clinical trials. In the longer term, it seems plausible that the engineering of T cell used in clinical trials will become increasingly advanced and we will make three predictions. First, the engineering of T cells that are insensitive to suppressive influences present within the tumor environment will likely be of value. Second, the use of T cells that do or do not become active based on the input of two or more receptors (i.e. that form logic gates) comprises a conceptually attractive strategy to further enhance the specificity of genetically engineered T cells. Finally, the output generated by signaling through such introduced receptors could potentially be manipulated to enhance the effectiveness against tumor cells that are less sensitive to the physiological mechanisms of T cell-mediated target cell death.

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