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Adoptive T cell transfer: imagining the next generation of cancer immunotherapies

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Cancer immunotherapy is rapidly moving from a promising approach to a real therapeutic option for patients with cancer. Driven by the clinical success of immune-checkpoint inhibitors and cellular therapies based on the adoptive transfer of naturally occurring and gene-engineered T lymphocytes, cancer immunotherapy has recently been heralded as a scientific breakthrough by the *Science* magazine. While these immunotherapeutic strategies can induce complete and durable tumor regressions in a significant fraction of patients, current response rates remain inadequate underscoring the need to further improve these types of treatments [1, 2]. In this issue of *Seminars in Immunology* we have gathered experts in the field of adoptive T cell therapy and asked them to envision the next generation of cancer immunotherapies. How should T cell-based immunotherapies evolve in order to enhance the antitumor efficacy of transferred cells? What would be the best approaches to circumvent the inhibitory constraints imposed by the tumor microenvironment? Which strategies should be implemented to reduce on-target and off-target toxicities associated with these procedures?

The authors identified three main areas of intervention that could be tackled to develop safer and more effective T cell-based immunotherapies. The first area of intervention is centered around ‘tumor targeting’. A major factor limiting the successful use of adoptive immunotherapy is that a large number of targetable antigens expressed by tumors are also found at low levels in normal tissues. Given the extraordinary ability of a T cell to recognize very few peptide-MHC complexes and the toxicities observed in clinical trials targeting self/tumor antigens, it is unlikely that a therapeutic window exists for safely targeting shared antigens *via* T cell receptor (TCR) engagement [3]. To circumvent these on-target toxicities, combinatorial antigen detection systems have been developed to confer tissue-selectivity to tumor-redirected T cells engineered with a TCR or a chimeric antigen receptor (CAR). Geldres *et al*. [4] discuss some of these strategies including the use of iCAR (CAR

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engineered to deliver a inhibitory signal) and AND-gate CAR T cells (T cells co-transduced with two separate CARs: one that provides suboptimal activation and a second recognizing a different antigen, which provides a co-stimulatory signal). Targeting antigens more selectively expressed by tumors, including cancer-germline antigens, oncoviral antigens, and neoantigens, however, represent theoretically a safer option. Debets *et al.* [Debts et al. Seminars in Immunology 2016] weigh up the pros and cons of targeting each of these classes of antigens and discuss the characteristics of an ideal target antigen. The authors emphasize that not only the selectivity of expression in tumors but also the ability to trigger robust T cell responses and possibly the involvement of the antigen in oncogenic processes should be key criteria for antigen selection. Once thought to be an insurmountable task, the possibility to prospectively identify tumor neoantigens targeted by tumor infiltrating and circulating T lymphocytes has become a reality thanks to the next generation sequencing revolution and advances in bioinformatic analyses [5, 6]. Lu and Robbins [7], starting from a historical perspective, provide an overview of this rapidly evolving field. The authors also describe evidence supporting a prominent role of neoantigens in the induction of tumor regression in patients receiving cancer immunotherapies and discuss the benefits and challenges of developing T cell therapies targeting neoantigens.

On the other side of the tumor antigen recognition equation are the targeting receptors. Debets *et al.* [Debts et al. Seminars in Immunology 2016] describe the diverse strategies that can be implemented to enhance the expression and functionality of the TCR. Should a TCR be obtained from tolerant or non-tolerant repertoires? How much should TCR affinities be enhanced by mutagenesis of complementary-determining region loops? The authors warn about the paradoxical functional decline that can be observed when using TCRs with supra-physiological affinities. Moreover, they buttress the need for stringent assessments of the TCR reactivity – especially for TCR genetically enhanced and/or isolated from a non-tolerant repertoire – to limit potential off-target toxicities. Geldres *et al.* [4] discuss how the individual components of the extracellular and intracellular regions of CAR molecules affect T cell function and survival. Apart from the evident importance of the targeting scFv portion and the well-established contribution of the co-stimulatory domains, the authors outline recent evidence underscoring the significant impact that the hinge fragment can have on CAR T cell properties.

A second area of intervention concerns the functional qualities of the T cells to be transferred. It is now clear that the differentiation state of transferred T cells is a critical parameter affecting their ability to destroy tumors [8]. Busch *et al.* [Busch et al. Seminars in Immunology 2016] review emerging findings indicating that a subset of minimally differentiated memory T cells exhibit all characteristics of adult tissue stem cells. Despite overwhelming data indicating the benefit of using these less-differentiated, stem cell-like T cells [9], clinical trials have largely employed unselected naturally occurring tumor-reactive lymphocytes or tumor-redirected T cells derived from whole peripheral blood mononuclear cells. The authors provide an overview of the available approaches for clinical-grade T cell subset selection and argue that pre-selection of naïve or stem cell-like T cells is a powerful strategy for the generation of more potent and efficacious T cells. While the isolation of less-differentiated T cell subsets can be an effective strategy for generating superior TCR or CAR-engineered T cell products from patients' blood, it is impractical when using tumor-

infiltrating lymphocytes, which are often found in a state of senescence and functional exhaustion [10, 11]. Karagiannis *et al.* [12] after summarizing the current status of the field of cellular reprogramming, discuss how induced pluripotent stem cell (iPSC) technology could be used to rejuvenate tumor-infiltrating T cell populations.

Beyond altering the differentiation state of T cells, genetic engineering technology also offers the opportunity to modulate specific qualities of the T cell products. Small non-coding microRNAs (miRNA) have emerged as critical modulators of numerous cellular processes [13]. Because of their ability to simultaneously target multiple proteins within a given pathway or diverse molecules in converging pathways [13], genetic manipulation of miRNA is a particularly attractive strategy to employ to profoundly change T cell behavior. Ji *et al.* [14] outline our current understanding of miRNA biology in T cells and describe how specific miRNA could be exploited to fine-tune T cell receptor signaling and enhance T cell fitness and effector functions.

The third area of intervention regards the tumor microenvironment. Over the past decade, it has become increasingly appreciated that the malignant behavior of cancer is not solely dictated by tumor cells but also by the non-transformed vascular, stromal and immune cell constituents of the tumor masses [15]. These non-neoplastic cellular components of the tumor microenvironment are profoundly dysregulated and provide major barriers to tumor-reactive T cell infiltration, accumulation and antitumor functions. In two review articles, Arina *et al.* [16] and Beavis *et al.* [17] provide their perspective on potential approaches that could be implemented to reprogram the tumor microenvironment to enhance T cell-based immunotherapies. These strategies range from poorly specific maneuvers, such as radio- and chemotherapy to potentiate cancer cell immune-recognition and deplete immunosuppressive populations such as regulatory T cells and myeloid-derived suppressor cells, to precise molecular interventions to target immunosuppressive cytokine networks, immune checkpoints and metabolic enzymes with regulatory activities. Arina *et al.* [16] also discuss possible strategies that can enhance T cell trafficking and infiltration within the tumor masses, including the use of porous scaffolds, chemokines and agents capable of normalizing tumor vessels. The importance of T cell trafficking is also emphasized by Debets *et al.* [Debts et al. Seminars in Immunology 2016] who provide their own view on potential interventions aiming at enhancing the entry, migration and local accumulation of T cells in tumor tissues. Last but not least, Robert *et al.* [18] discuss the existing evidence and rationale supporting the use of immunotherapy, including adoptive cell transfer in combination, with targeted approaches and summarize ongoing clinical efforts evaluating the antitumor efficacy of immunotherapy in conjunction with tyrosine kinase inhibitors, HER family blockade, anti-angiogenic agents, histone deacetylase inhibitors, and cancer stem cell inhibitors.

In summary, after decades of work and promises, cancer immunotherapy has finally entered mainstream oncology on the wave of its clinical success in a subset of cancer patients. The reviews presented here provide an excellent overview of T cell-based immunotherapies and point to a bright future in which dramatic advances in safety, potency and accessibility are a reality. I hope you will enjoy reading these articles as much as I did!

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