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Targeted cellular immunotherapy for T cell malignancies

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In this issue, Maciocia *et al.* develop a novel T cell receptor beta (TCRB) constant C1 chain-directed cellular immunotherapy for the treatment of T cell malignancies.

Immunotherapy, a therapeutic modality that directs the immune system against tumor cells for the treatment of cancer, has been a front-line treatment for B-cell lymphoma for almost two decades. Antibodies against CD20, a pan B cell surface antigen, trigger effective antitumor responses in mature B cell tumors, and bispecific antibodies that bridge T cells and B cells can effectively direct cellular immune responses against malignant B cells¹. In addition, cellular immunotherapy with T cells expressing chimeric antigen receptors (CAR) –engineered single chain proteins capable of eliciting immune activation and designed to engage with a specific antigen of choice, such as the B cell specific surface protein CD19– has shown efficacy against an expanding number of B cell non-Hodgkin lymphomas¹. However, pan B-cell directed CAR T cells ablate both normal and tumor B cells resulting in B cell immunosuppression. Although this can be managed clinically, a more targeted strategy of significant promise is the use of CAR T cells with specificity against the immunoglobulin κ -light chain. Using this approach, both normal and malignant cells expressing κ -light immunoglobulins are ablated by κ -light chain-directed CAR T cells, yet normal λ light chain-expressing lymphocytes are spared, thus precluding the development of overt B cell immunodeficiency².

In contrast to the progress in combating B cell malignancies, the development of immunotherapies targeting T cells has been lagging behind, hampered by the technical constraints imposed by the potentially fatal immunosuppression resulting from the depletion of normal T lymphocytes targeted along with malignant T cell lymphoma cells. In this issue, Maciocia *et al.* exploit the monoallelic and clonal expression of the T cell receptor beta (TCRB) chain in the surface of malignant T cells to develop a targeted cellular immunotherapy for the treatment of T cell tumors.

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The T cell receptor (TCR) is a heterodimeric protein complex consisting of two chains named TCRA and TCRB, both encoded in complex loci organized in modules that undergo an orchestrated recombination process during T cell development³. The TCR plays a central role in the function of the adaptive immune system by mediating the recognition of peptides presented by the major histocompatibility complex (MHC) in the surface of antigen presenting cells, and this triggering an immune response⁴. The modular structure and recombination of the *TCRA* and *TCRB* genes enables the generation of a polyclonal and diverse population of T cells each armed with a different TCR and an immune system capable of recognizing a broad number of antigen specificities. In the case of the *TCRB* gene, multiple V segments, each encoding a different variable region, can be recombined into two consecutive modules consisting each of a D diversity segment, a number of J join segments and a C segment encoding for the C-terminal constant region of the protein. During early T cell development a first round of recombination can generate a functional TCRB chain containing V, D and J segments together with the first (C1) constant region. Yet, if the product of this first round of TCRB recombination is ineffective, a second round of rearrangements gives the T cell progenitor a new opportunity to generate a functional TCRB by joining upstream V segments with the next module of D and J elements associated with the second (C2) constant region. As a result, approximately one third of normal mature T cells express a TCR containing a TCRB C1 while two thirds express a TCRB containing a C2 constant region. In contrast, T cell leukemias and lymphomas show discrete rearrangements of the TCR loci reflecting their T cell clonal origin from a single cell. In many cases these clonal tumors also display surface expression of a TCR, which as in the case of normal T cells is restricted to contain either a TCRB C1 or a TCRB C2 chain.

Maciocia and coworkers exploited the TCRB C1 or TCRB C2-restricted pattern of TCR expression in T-cells to develop a CAR T cell immunotherapy strategy directed against TCRB C1 expressing T cells a means to deliver T cell specific antitumor effects while precluding the development of severe T cell immunodeficiency. To generate a TCRB C1-specific CAR, the authors analyzed TCR monoclonal antibodies that recognize only a fraction of mature T cells for their capacity to recognize selectively TCRB C1 or TCRB C2 proteins. One of these antibodies, named JOVI-1, showed marked TCRB C1 specificity and was shown to recognize a TCRB C1 specific epitope that is a result of a two amino acid difference between TCRB C1 and TCRB C2. By introducing the variable chains of this antibody, responsible for TCRB C1 antigen recognition, in an artificial single-chain TCR, they engineered a CAR that binds selectively to TCRB C1-containing TCRs. T cells expressing this CAR were able to effectively ablate normal and malignant T cells, but only if they express a TCRB C1-containing TCR (Fig. 1). Critically, while effective against monoclonal TCRB C1 tumor cells, the TCRB C1-restricted activity of these CAR T cells spared normal lymphocytes expressing TCRB C2 TCRs and avoided the development of overt T cell immunodepletion in a humanized mouse model of disseminated T-cell acute lymphoblastic leukemia.

The development of novel approaches for the treatment of relapsed and refractory T cell tumors is a priority in the field. The high frequency of membrane TCR expression in angioimmunoblastic T cell lymphoma (AITL) and peripheral T cell lymphoma not otherwise specified (PTCL NOS), two tumor types characteristically associated with poor prognosis,

makes these diseases particularly well suited for treatment with anti TCRB C1 CAR T cells. Moreover, TCR expression and signaling have been implicated as drivers of PTCL lymphoma cell growth and survival⁵, which could limit the capacity of clonal TCRB C1-expressing tumor cells to escape from CAR T cell mediated cell killing via downregulation of TCR expression. Yet, open questions remain regarding potential side effects derived from a reduced T cell repertoire composed only of TCRB C2 expressing T cells⁶. Also preservation of immune response could potentially limit the durability of the anti TCRB C1 CAR T cell antitumor response should patients develop anti-CAR neutralizing antibodies.

Despite these uncertainties the prospect of a T cell-directed cellular immunotherapy is an exciting advance with the potential to transform the treatment of some of the most refractory forms of PTCL. Finally, the development of high affinity CARs recognizing TCRB C2, would be a valuable next step for the authors' approach here, as this would enable the treatment of the remaining two thirds of T cell tumors expressing TCRB C2-containing TCRs.

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Figure 1.

Principles of anti-TCRB C1 CAR T cell therapy. **(a)** Expression of a CAR directed against a TCRB C1 specific epitope results in fratricide killing of normal T cells expressing TCRB C1 TCRs and the generation of a TCRB C2-restricted CAR T cell product. **(b)** Anti-TCRB C1 CAR T cells show cytotoxic activity against normal and tumor T cells expressing TCRB C1 TCRs yet they spare lymphocytes expressing TCRB C2 TCRs, thus precluding the development of severe CAR T cell-induced immunosuppression.