

suggest the potential to expand the use of UM171 beyond HSCs.

**Conflict-of-interest disclosure:** The author serves as a consultant for ImmuneBridge Therapeutics. ■

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## IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on *Bae et al*, page 895

# Waking up exhausted BCMA-specific T cells in myeloma

**Antonio Sacco and Aldo M. Roccaro** | Azienda Socio Sanitaria Territoriale Spedali Civili di Brescia

**In this issue of *Blood*, Bae et al<sup>1</sup> have elegantly shown that an induced pluripotent stem cell strategy may epigenetically reprogram precursor exhausted B-cell maturation antigen (BCMA)-specific cytotoxic T lymphocytes into hematopoietic progenitor cells, which, in turn, differentiate into functional cognate antigen-specific CD8 $\alpha\beta$ <sup>+</sup> memory T cells that exert an antitumor effect in multiple myeloma (MM). Overall, these novel studies pave the path to novel strategies for targeting MM cells via an effective antitumor immunity-based approach.**

Adoptive cell therapy with the use of tumor cell–targeting chimeric antigen receptor T (CAR-T) cells has certainly shown significant clinical benefits in certain cancers, leading to prolonged remissions, and is probably curative in a subset of cases.<sup>2-8</sup> Within the field of MM, antitumor activity of BCMA-targeting CAR-T cells has been shown.<sup>2-4</sup>

However, the challenge of T-cell exhaustion and impaired immune function remain hurdles for the persistence of the antitumor activity of CAR-T cells. One of the main drivers of T-cell exhaustion is persistent antigen stimulation. This study, led by Bae et al, has implemented an induced pluripotent stem cell (iPSC) approach to revitalize and reprogram BCMA-specific T cells.

BCMA-specific CD8<sup>+</sup> memory cytotoxic T lymphocytes (CTLs) were epigenetically successfully reprogrammed, returning them to a pluripotent state that then developed into hematopoietic progenitor cells and differentiated into the T-cell lineage. These T cells were fully characterized, confirming the mature CD8ab<sup>+</sup> memory phenotype; coupled with a robust expression of costimulatory molecules, including CD38, CD28, and 41BB; and lack immune checkpoint or senescence markers, such as CTLA4, PD1, LAG3, TIM3, or CD57. These same markers were enriched within the parental precursor, exhausted BCMA-CTL.

Next, the authors investigated the functional status of the iPSC T cells, demonstrating their ability to proliferate and to exert an antitumor effect. In addition, the use of RNA sequencing showed specific transcriptional signatures mirroring the successful differentiation of iPSC clones into CD8<sup>+</sup> memory T cells. This sequencing approach is an important tool to facilitate the identification and selection of the most appropriate iPSC clones to be destined to CD8<sup>+</sup> T-cell lineage differentiation, especially when thinking about clinical application.

Overall, Bae et al have developed a well-defined, robust, and scientifically sound proof-of-principle platform to epigenetically reprogram BCMA-specific CD8<sup>+</sup> memory cytotoxic T lymphocytes as a promising strategy to promote an efficacious and long-term anti-MM immunity. More important, the findings of these studies may apply to a wider spectrum of cancers, thus covering solid tumors and hematologic malignancies.

We now anxiously await the translation of these exciting data to the clinical setting.

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## TRANSPLANTATION

Comment on *Adams et al*, page 912

# The brain may devise laws for the blood

David S. Ritchie | Peter MacCallum Cancer Centre and Royal Melbourne Hospital

**In this issue of *Blood*, Adams and colleagues have explored the impact of monoclonal antibody blockade of colony-stimulating factor 1 receptor (CSF1R) in models of central nervous system (CNS) chronic graft-versus-host disease (cGVHD).<sup>1</sup> Chronic GVHD is a pervasive syndrome of destructive donor-derived immune activation, uncontrolled acute and chronic inflammation, and progressive organ dysfunction following allogeneic stem cell transplantation. Overall, cGVHD is a major cause of mortality and morbidity following allogeneic stem cell transplantation and the major cause of impairment of activities of daily living and reduced quality-of-life measures.<sup>2,3</sup> Prior modeling from the same laboratory as the current article has determined that CNS cGVHD is driven by a unique population of CSF1-dependent, brain-infiltrating, bone marrow-derived major histocompatibility complex (MHC) class II-positive macrophages (BMDM), which promote a late CD4<sup>+</sup> T-cell CNS infiltration and interferon gamma (IFN- $\gamma$ )-dependent chronic neuroinflammation, impaired neurological synapse function, and impaired behavior.<sup>4</sup>**

Given the recent and promising development of a clinical strategy using CSF1R-directed monoclonal antibody axatilimab to deplete donor-derived inflammatory macrophages and thereby reverse sclerodermatous skin GVHD,<sup>5</sup> the authors hypothesized that therapeutic use of CSF1R-blockade and subsequent depletion of CNS BMDM could also prevent or improve the onset of CNS cGVHD. Surprisingly, in this model system, anti-CSF1R therapy was found to exacerbate behavioral and anatomic features of CNS acute GVHD when administered in the early posttransplant

period. Cellular changes within the CNS included depletion of microglia, a finding that was duplicated, along with acute GVHD behaviors, even in untransplanted control subjects treated with anti-CSF1R therapy. When anti-CSF1R therapy was used in the setting of established CNS cGVHD, therapeutic efficacy was limited as measured by nondepletion of BMDM and nonreversal of cGVHD-associated behaviors. All of these findings were reproduced by conditional depletion of CSF1R expression on BMDM, highlighting the regulatory role of the CSF1R pathway in the activation and

proinflammatory status of BMDM. Importantly, when IFN- $\gamma$  receptor-deficient grafts were used in these model systems, decreased expression of MHC class II on BMDM was observed and the animals did not develop neurological inflammation, reiterating the importance of IFN- $\gamma$  in the pathogenicity of CNS GVHD and the possible opportunities to disrupt this pathway with anticytokine strategies including the JAK-inhibitor ruxolitinib or IFN- $\gamma$  blockade with emapalumab. No doubt these agents will be the subject of future experiments using the model established by Adams and colleagues.

How, then, are we to interpret these model systems in clinical practice considerations of the prevention and management of cGVHD, particularly in the setting of the development of novel immune-modifying therapies such as anti-CSF1R monoclonal antibodies?

The apparent separation in the onset of beneficial treatment of systemic cGVHD while exacerbating CNS GVHD serves as a potentially cautionary tale in the development and monitoring of new anti-GVHD therapies. Neurotoxicity in allogeneic transplantation is a protean and multifactorial complication and may reflect the accumulated treatment burden of prior chemotherapy, nutritional deficiencies, polypharmacy, biochemical perturbations, chronic infections, and the psychological burden of chronic illness in addition to the potential vascular and immune-inflammatory effects of GVHD. Manifestation of neurological pathology is recorded in a third of transplant recipients acutely and in 60% of cases in long-term follow-up patients who often report symptoms of fatigue, decreased cognition, or impaired memory.<sup>6</sup> In most instances the causes of neurological symptoms are not definitively identified, and the possibility of CNS GVHD remains part of the differential diagnosis. Reported symptoms do not necessarily imply the presence of CNS cGVHD. In particular, fatigue alone does not appear to be associated with specific features of neuroinflammation,<sup>7</sup> and cognitive decline has shown evidence of CNS immune activation.<sup>8</sup> Collectively, although both the importance of identifying GVHD in the development of neurological sequelae of allogeneic transplant and the knowledge gaps of how best to incorporate and report CNS GVHD in prospective studies