suggest the potential to expand the use UM171 beyond HSCs.

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

REFERENCES

1. Chagraoui J, Girard S, Mallinger L, Mayotte N, Tellechea MF, Sauvageau G. KBTBD4-mediated reduction of MYC is critical for hematopoietic stem cell expansion upon UM171 treatment. *Blood*. 2024;143(10):882-894.
2. Carreras E, Dufour C, Mohty M, Kroger N, eds. *The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies*. Springer Nature; 2019.
3. Meaker GA, Wilkinson AC. Ex vivo hematopoietic stem cell expansion technologies: recent progress, applications, and open questions. *Exp Hematol*. 2023;130:104136.
4. Fares I, Chagraoui J, Gareau Y, et al. Cord blood expansion. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal. *Science*. 2014;345(6203):1509-1512.
5. Cohen S, Roy J, Lachance S, et al. Hematopoietic stem cell transplantation using single UM171-expanded cord blood: a single-arm, phase 1-2 safety and feasibility study. *Lancet Haematol*. 2020;7(2):e134-e145.
6. Subramaniam A, Zemaitis K, Talkhoncheh MS, et al. Lysine-specific demethylase 1A restricts ex vivo propagation of human HSCs and is a target of UM171. *Blood*. 2020;136(19):2151-2161.
7. Chagraoui J, Girard S, Spinella JF, et al. UM171 preserves epigenetic marks that are reduced in ex vivo culture of human HSCs via potentiation of the CLR3-KBTBD4 complex. *Cell Stem Cell*. 2021;28(1):48-62.e6.
8. Dhanasekaran R, Deutzmann A, Mahauad-Fernandez WD, Hansen AS, Gouw AM, Felsher DW. The MYC oncogene—the grand orchestrator of cancer growth and immune evasion. *Nat Rev Clin Oncol*. 2022;19(1):23-36.
9. Sakurai M, Ishitsuka K, Ito R, et al. Chemically defined cytokine-free expansion of human haematopoietic stem cells. *Nature*. 2023;615(7950):127-133.

https://doi.org/10.1182/blood.2024023827

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[1] 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 CD8αβ$^+$ 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.[2-8] Within the field of MM, antitumor activity of BCMA-targeting CAR-T cells has been shown.[2-4] 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$^+$ 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$^+$ 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$^+$ 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$^+$ 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$^+$ 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.

Conflict-of-interest disclosure: A.M.R. has received research funding from AstraZeneca, European Hematology Association, Transcan2-ERANET, and Italian Association for Cancer Research (Fondazione AIRC); and honoraria from Amgen, Celgene, Janssen, and Takeda. A.S. declares no competing financial interests. ■

REFERENCES

1. Bae J, Kitayama S, Herbert Z, et al. Differentiation of BCMA-specific induced pluripotent stem cells into rejuvenated CD8αβ$^+$ T cells targeting multiple myeloma. *Blood*. 2024;143(10):895-911.
2. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med*. 2023;389(4):335-347.

3. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019; 380(18):1726-1737.

4. Mateos MV, Weisel K, Martin T, et al. Adjusted comparison of outcomes between patients from CARTITUDE-1 versus multiple myeloma patients with prior exposure to proteasome inhibitors, immunomodulatory drugs and anti-CD38 antibody from the prospective, multinational LocoMMotion study of real-world clinical practice. *Haematologica*. 2023;108(8): 2192-2204.

5. Mailankody S, Devlin SM, Landa J, et al. GPRC5D-targeted CAR T cells for myeloma. *N Engl J Med*. 2022;387(13):1196-1206.

6. Del Bufalo F, De Angelis B, Caruana I, et al. GD2-CART01 for relapsed or refractory high-risk neuroblastoma. *N Engl J Med*. 2023; 388(14):1284-1295.

7. Yeku OO, Longo DL. CAR T cells for neuroblastoma. *N Engl J Med*. 2023;388(14): 1328-1331.

8. Brown MH, Dustin ML. Steering CAR T cells into solid tumors. *N Engl J Med*. 2019;380(3): 289-291.

https://doi.org/10.1182/blood.2023023037

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).[1] 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.[2,3] 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$^+$ T-cell CNS infiltration and interferon gamma (IFN-γ)-dependent chronic neuroinflammation, impaired neurological synapse function, and impaired behavior.[4]

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,[5] 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-γ 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-γ in the pathogenicity of CNS GVHD and the possible opportunities to disrupt this pathway with anticytokine strategies including the JAK-inhibitor ruxolitinib or IFN-γ 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.[6] 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,[7] and cognitive decline has shown evidence of CNS immune activation.[8] 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