Giving T-cell bispecifics a helping hand

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In this issue of Blood, Sam et al demonstrate the translational potential of CD19-targeted CD28-mediated costimulation to ameliorate the therapeutic potential of the anti–CD19–anti–CD3 T-cell bispecific engager glofitamab in preclinical models, buttressing the rationale for an ongoing phase 1 clinical study.1

T cells are inherently specific for a single antigen presented in the context of major histocompatibility complex (MHC). Once engaged, the T-cell receptor (TCR) will trigger downstream activation culminating in T-cell degranulation, transcriptional regulation, and differentiation. However, if triggered in isolation, TCR-peptide–MHC engagement will lead to an incomplete and short-lived response, preventing adequate expansion, proliferation, and survival of both the T cell and the associated response. This specific TCR engagement is also known as signal 1. Two additional signals are required for a fully productive T-cell activation: signal 2 or costimulation mediated by receptors to ligand engagement of costimulatory molecules expressed on T cells such as CD28 (see the visual abstract in the article by Sam et al) and signal 3, which is cytokine support via the common γ-chain receptor (interleukin-2, -7, or -15). Although in principle signal 3 can be provided by the activated T cell in an autocrine manner, signal 2 needs to come from another cell. This pathway of activation applies to both health and disease. Although there is no reason to believe that this may be different in the context of T-cell–directed therapy, there is controversy as to its requirement in the context of bispecific antibodies.

The discovery of the pivotal role of T cells in cancer immune surveillance2 has heralded both their therapeutic use and targeting for therapeutic purposes in oncology.3 Therapeutics differentiate between the direct use of T cells (realized through engineering for specificity using chimeric antigen receptors [CAR]) and activation of endogenous T cells using blocking antibodies to key inhibitory pathways, so-called immune checkpoint inhibitors, or selective recruitment toward tumor cells using T-cell–activating bispecific antibodies.4,5 In hematology, only CAR T cells and bispecific antibodies have reached routine clinical use.

Until 2022, the field of bispecific antibodies in hematology was restricted to only blinatumomab, an anti–CD3–anti–CD19 activating bispecific approved in 2014 for monotherapy of refractory or relapsed pre-B-acute lymphocytic leukemia based on prolongation of overall survival.1 The years 2022 and 2023 have seen approval of no less than 6 T-cell–activating bispecific antibodies redirecting T cells against GPR5D (talquetamab), BCMA (elranatamab and teclistamab), as well as CD20 (ecprotitamab, glofitamab, and mosunetuzumab) for use in B-cell–associated or derived malignancies (namely multiple myeloma, follicular lymphoma, and diffuse large B-cell lymphoma). These pivotal events have established bispecific antibodies as an essential part of the treatment arsenal.

Glofitamab was approved in 2023 based on results of an uncontrolled phase 1–2 study in patients with refractory or relapsed diffuse large B-cell lymphoma with at least 2 lines of therapy, which, importantly, included an anti–CD20-based regimen.1 With an overall response rate of 50% and a complete response rate of 35% and responses ongoing at data presentation (74% and 87%, respectively), such efficacy is meaningful for this patient population but also demonstrates that most patient will not benefit from glofitamab in the long run, which is similar to the results with other bispecifics.

Glofitamab, like all T-cell–activating bispecific antibodies mentioned previously, engages CD3ε, thereby crosslinks the molecule in the vicinity of T and tumor cells and culminates in T-cell activation through parts of TCR signaling. As this strategy only mimics signal 1, Sam et al hypothesized that this physiologically suboptimal T-cell activation could be improved with the addition of signal 2 via CD28 engagement. Here, caution was warranted as CD28 agonism has been demonstrated to have the potential for superagonization of T cells16 and catastrophic side effects. Thus, the authors designed and selected such constructs that would be (1) targeted to a desired target cell via CD19 or another B-cell antigen and (2) be devoid of superagonistic properties but strictly dependent on signal 1. They succeeded in generating molecules with the desired properties and probed their lead compounds in preclinical efficacy and toxicity models employing humanized mice, proving synergy with glofitamab in the absence of exacerbated toxicity. In demonstration of the desired safety profile, they further provide serum cytokine data of the first patients dosed with this sequential combination, corroborating absence of exaggerated cytokine release.

The data provided in the article by Sam et al are promising and groundbreaking at 3 levels: (1) it develops a specific combination partner for an approved bispecific antibody (glofitamab) for immediate translation (ongoing), and (2) it evaluates preclinically an established fundamental immunological principle, which is then recapitulated by synthetic immunity, thus laying the ground for (3) systematic implementation and evaluation of costimulation for T-cell–activating bispecific antibodies to maximize their therapeutic impact. If proven clinically, this concept may establish a new paradigm for bispecific antibody therapeutics.

Although these prospects are important and exciting to the field, caution is warranted in the absence of robust and complete clinical data. We will need to see if the presumed beneficial safety profile suggested by preclinical and early clinical data goes hand in hand.
with clinically relevant amelioration of responses and outcome. Along the same lines, the carefully selected protocol and application schedule is complex with dosing in golfitamab at different doses, before introducing anti-CD19–anti-CD28 and eventually their combination. It may come with either issues of clinical implementation, or it may not recapitulate what has been seen in mice models for pure reasons of pharmakokinetic or distribution. Lastly, it remains to be demonstrated if such a concept will be more broadly applicable to other bispecifics or is a peculiarity of this target and molecule combination. A key question, as such a combination resembles more and more what a CAR would be giving to a T cell in terms of activating and costimulatory signals, is how long-term outcomes will compare and to which level cost-to-benefit consideration will hold, when off-the-shelf approaches become more complex and time- and resource-consuming.

Exciting times are ahead, with a concept and molecules to watch carefully.

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2. GmBH, and Arcus Bioscience for work unrelated to the manuscript.

LYMPHOID NEOPLASIA

SMACing down relapsed T-ALL

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In this issue of Blood, Ávila Ávila et al 1 report that T-cell acute lymphoblastic leukemia (T-ALL) cells overcome anti-CD3 monoclonal antibody (mAb)-directed therapy by inducing tumor necrosis factor receptor (TNFR) signaling, leading to activation of the NF-κB pathway (see figure). Combining tepiluzumab, an inhibitor of CD3, with etanercept, a decoy receptor for tumor necrosis factor-α (TNF-α), inhibited human T-ALL patient-derived xenograft (PDX) growth in mouse models, suggesting the importance of this pathway. Remarkably, coadministration of birinapant, which mimics the downstream regulator secondary mitochondrial-derived activator of caspases (SMAC), redirected pro-survival TNFR signaling into a parallel, apoptotic program and led to growth suppression and even complete cure in one human T-ALL model. This combination therapy demonstrates how an unwanted cell-signaling outcome can be rechanneled to improve overall treatment efficacy. Anti-CD3 combination therapy can be a new bridge to allogeneic stem cell transplant.

Patients with T-ALL who fail to achieve a remission at the end of induction chemotherapy or who relapse have poor long-term survival. 2,3 Relapses can occur in 15% to 20% of children with T-ALL 3 and a significantly higher percentage of adults. Progress is being made in new therapeutic approaches with nelarabine, an antimetabolite prodrug, alone or in combination with chemotherapy, inducing upward of 62% complete remissions. 4 However, there remain patients who fail or do not respond to this therapy and require curative approaches.

In a set of articles published previously in Blood, Tran Quang and colleagues explored a novel approach to further