Accelerating personalization of immune therapies for blood cancers

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Cancer patients responding to immune checkpoint blockade usually bear tumors that are heavily infiltrated by T cells and express a high load of neoantigens, indicating that the immune system is involved in the therapeutic effect of these agents, and strongly supports the renewed interest in cancer vaccine strategies. Idiotypic determinants of a lymphoma surface Ig, formed by the interaction of the variable regions of heavy and light chains, can be used as a tumor-specific antigen, and effective vaccination using idiotype proteins was demonstrated recently in a positive controlled Phase III clinical trial (Schuster [Kwak] et al. ***J Clin Oncol*** **2011**). These variable region genes can also be cloned and used as a DNA vaccine, a delivery system holding tremendous potential for streamlining vaccine production. To increase vaccination potency, we are targeting the vaccine to antigen-presenting cells (APCs) by fusion of the antigen with a sequence encoding a chemokine (MIP-3α), which binds an endocytic surface receptor on APCs. Lymphoplasmacytic lymphoma (LPL) is a low grade, incurable disease featuring an abnormal proliferation of Immunoglobulin (Ig)-producing malignant cells. Asymptomatic patients are currently managed by a "watchful waiting" approach, as available therapies provide no survival advantage if started before symptoms develop. LPL is an excellent model to test our vaccine since patients have both an intact immune function and low tumor burden. We are evaluating the safety and feasibility of this next-generation DNA vaccine in a **first-in-human clinical trial currently enrolling** asymptomatic LPL patients (Thomas ST et al. [Kwak] ***BMC Cancer*** **2018** Feb 13;18(1):187.
doi: 10.1186/s12885-018-4094-2). This vaccine could shift the current paradigm of clinical management for patients with asymptomatic LPL and inform development of other personalized approaches.

Another personalized therapy, chimeric antigen receptor (CAR) T-cells, have the potential to revolutionize the treatment of cancers. Particularly in hematological malignancies, there are reports of promising clinical outcomes in advanced non-Hodgkin lymphomas (NHLs) with CD19-CAR T-cell therapy. However, disease relapse is problematic, and is thought to be caused by poor long-term persistence of the CAR T-cells, and loss of the CD19 target on tumors. Thus, there is an urgent need for improved novel CAR T-cell therapies directed at alternative targets.

The CAR T-cell platform relies on antibody-derived single chain fragments (scFv), which are genetically engineered into chimeric T-cell receptors, and that recognize target cell surface proteins on tumors. One potential target is B-cell activating factor receptor (BAFF-R), a tumor necrosis factor receptor superfamily protein (TNFRSF13C) specifically involved in B lymphocyte development and mature B-cell survival, that is primarily expressed on B cells and various subtypes of B-cell NHLs and ALL. We have recently developed a humanized therapeutic BAFF-R antibody with strong anti B-cell tumor activity (Qin H. et al. ***Clin Cancer Res*** **2018**).

Specifically, we adapted a scFv based on our humanized anti-BAFF-R antibody onto a second generation CAR platform containing CD3ζ and 4-1BB intracellular signaling domains. In response to BAFF-R-expressing malignant human B cells (NHLs, acute lymphoblastic leukemias, and chronic lymphocytic leukemias), our CAR T cells readily proliferated and secreted cytotoxic cytokines. We demonstrated both significant levels of BAFF-R CAR T-cell activation and malignant B-cell killing *in vitro*.

Established human NHL tumors in xenogeneic models were eliminated following BAFF-R CAR T-cell treatments *in vivo*. Remarkable tumor-free survival was repeatedly observed in human lymphoma xenograft models including JeKo-1 (mantle cell lymphoma) and Raji (Burkitt lymphoma) in NSG mice. We pursued optimization of CAR T-cell persistence by comparing three subsets of early stage T cells (central memory, T_{CM}; memory stem, T_{SCM}; and naïve, T_N) as potential starting material for CAR T cell generation. Our *in vivo* studies show CAR T cells from the T_N population retained highest potency eradicating established tumors at a minimal therapeutic dose compared to other subtypes. We also observed the long term anti-tumor effects conferred by CD8+ CAR T cells required the addition of CD4+ CAR T cells. Finally, we performed a head-to-head comparison of BAFF-R CAR T cells with CD19 CAR T cells in the Raji model. BAFF-R CAR T-cell treatment demonstrated long-term tumor free survival in all treated mice compared to the CD19 CAR T-cell treated cohort, which only showed delayed tumor growth ($P<0.01$).

Thus, BAFF-R CAR T cells demonstrate remarkable efficacy against B-cell malignancies. Targeting BAFF-R potentially addresses unmet clinical needs in B-cell NHLs and ALL, particularly in the setting of CD19 CAR-T-resistance or CD19-negative relapse.