Comment on Hu et al, page 1911

Divining T-cell targets for cancer immunotherapy

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In the current issue of Blood, Hu et al present the results of interesting studies confirming the utility of a novel approach to identify and validate potential targets of T-cell responses that could serve as potential therapeutic targets for cancer immunotherapy, including for hematologic malignancies.¹

For millennia, humans have sought to divine the future, using approaches that range from dowsing for hidden water or predicting the course of events by diverse methods including tarot cards to astrology to palmistry. Lengthy tomes the length of modern medical textbooks have been written about many of these pseudoscientific approaches. Even in J. K. Rowling’s Potterverse, where conjuring, potion making, and magical herbology are considered standard and accepted disciplines, divination is considered an inexact science and is once described as “one of the most imprecise branches of magic.”²

Unfortunately, in our less magical world, the divination of putative targets of T-cell responses has similarly lagged behind its companion fields of vaccine development for pathogens, and the development of increasingly impressive immunotherapies using either checkpoint inhibitors or antigen-specific genetically modified T cells, including chimeric antigen receptor (CAR-T) therapies. The enthusiasm for the latter approach, in particular, is now palpable, with hematologists seeing truly unprecedented responses for patients receiving CD19-directed CAR-T therapies for both acute lymphoid leukemia in children and young adults and aggressive non-Hodgkin lymphoma (NHL) of older adults.³⁴ In the coming year, it is likely that we will see additional approvals for CD19-targeted T-cell therapies, and very possibly an approved approach to target B-cell maturation antigen (BCMA) in myeloma patients,⁵ given promising early trial results.

Although these advances in hematology are truly electric, many of us are also concerned that the current buzz around CD19 and BCMA may fade if additional targets for these and other immunological therapies do not quickly follow. Our ability to further expand these approaches to a broad range of other targets for cancers is something we should not take for granted. Although a discussion of an ideal antigen is beyond the scope of this commentary, we can look at CD19 to know that it is an antigen widely expressed on healthy and malignant B cells. There is acceptable on-target toxicity (leading to transient B-cell aplasia and hypogammaglobulinemia) and significant, yet typically nonfatal, off-target effects that may include cytokine release syndromes and neurotoxicity.⁶ Although antigen escape may occur and is associated with relapse of both acute lymphoblastic leukemia and NHL, CD19 is typically expressed consistently enough to yield reliable responses in most treated subjects. Similarly, BCMA seems to have similar characteristics, making it a promising target in plasma cell malignancies.

However, for immunotherapy to broadly succeed beyond a few selected blood cancers, the pace and quality of target antigen discovery must increase dramatically, or the limited availability of suitable targets will prove the greatest bottleneck to success, especially for solid tumors.

For this reason, the studies presented here by Hu and colleagues provide real hope that applying novel systems to identify and validate antigen discovery will yield a greater pipeline of targets for cancer-specific T cells and vaccines. The clever system devised by the investigators (see figure) includes 3 major steps: (1) using a functional measure of stimulated T-cell activity (eg, IFN-γ production), antigen-activated T cells were isolated and cloned using a novel and rapid single cell sequencing approach to identify the TCRαβ repertoire of reactive cells; (2) the newly identified TCRs were then expressed into a Jurkat line lacking a native TCR (following targeted CRISPR-Cas9 knockdown); and (3) the TCR expressing transduced cell line is then screened for reactivity against candidate antigens by reporter expression, validating their specificity.

In their elegant work, the authors first demonstrate that peripheral blood monocellular cells from healthy donors could be stimulated with a broad commercial peptide mixture containing candidate antigens from multiple pathogenic viruses (“CEF”) and that this approach successfully identified and yielded demonstrably active virus-specific TCR sequences, including those recognizing cytomegalovirus (CMV), influenza, and Epstein-Barr virus. They then demonstrated that peripheral blood monocellular cells from melanoma patients previously immunized with a personalized neoantigen vaccination could yield TCR sequences that were clearly recognizing relevant melanoma neoantigens. Finally, the authors turned to chronic lymphocytic leukemia (CLL) patients and showed that dominant TCRs could be identified that recognized candidate neoantigens from
a putative CLL driver and confirmed its functional activity and HLA-restricted specificity.

It seems clear that this novel and systematic approach should yield relevant neoantigens that could result in vaccine and adoptive T-cell targets. However, there are caveats that should be noted. Our understanding of antigen recognition restricted by less commonly expressed HLA alleles lags behind our understanding of binding to common alleles, like HLA A2, which was first crystallized. Any expression system like the one devised here can be iteratively improved to better reflect native T-cell diversity and recognition, in order to yield increasingly better candidate TCRs most likely to have therapeutic value.

In summary, the novel and comprehensive approach outlined here has real potential to move the art of antigen discovery from its current place in the shadows of T-cell engineering to a more rapid and reliable approach to identify and validate targets for a broad range of human cancers. Given the current justified excitement about immunotherapy for blood cancers, there is a clear need for approaches like this one that can systematically identify novel targets for T-cell responses especially for solid tumors, including putative neoantigens. I am optimistic that studies like this one will help us fully unlock the promise of antigen-specific immunotherapy and move the previously inexact science of antigen discovery from the shadows into bright sunlight.

Conflict-of-interest disclosure: K.V.K. has served as an ad hoc scientific advisor to immunotherapy companies, including Kite/ Gilead, Novartis, Juno/Celgene, and Atara Biotherapeutics.

REFERENCES


Comment on Mueller et al, page 1936

CD44: expanding the toolKIT

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Expanding the universe of mast cell diseases beyond tyrosine kinase inhibitors, in this issue of Blood, Mueller et al find that the invasion receptor CD44 is both a biomarker of and potential therapeutic target for mast cell neoplasms.1

Patients with advanced systemic mastocytosis, a heterogeneous group including those with mast cell leukemia, associated hematologic neoplasms, or organ dysfunction related to mast cell infiltration, have the most aggressive disease and least favorable prognosis. Median survival for these unfortunate patients ranges from 6 to 36 months, on par with the most challenging myeloid malignancies. No approved therapies existed until April 2017, when the multikinase inhibitor midostaurin was approved based on an open-label study demonstrating a 60% overall response rate.2 Midostaurin, known best for targeting FLT3 in acute myeloid leukemia, also has recognized inhibitory activity against activated KIT. Alterations in KIT, most often the point mutation KITD816V, are canonical drivers of mast cell neoplasms, and more potent investigational inhibitors of KIT promise even deeper responses.3 These advances have highlighted the relevance of KIT in the initiation of mast cell disease. We’ve also learned that advanced disease is associated with multiple additional and familiar mutations in genes such as TET2, SRSF2, ASXL1, CBL, and RUNX1 that likely contribute to disease phenotype, progression, and treatment resistance.4

2018 is the year of the Mueller investigation. Eschewing geopolitics, Mueller et al focus instead on CD44, a stem cell marker/adhesion molecule known to be involved in homing to the niche and maintaining quiescence. Their study argues that CD44 is also relevant to the accumulation and survival of clonal mast cells in tissues. Using mast cell lines and primary patient samples, they find that CD44 is universally expressed on both normal and malignant mast cells, but with higher levels evident in clonal disease, and with expression levels increasing with disease severity. This gradient becomes more specific within progenitor populations, with CD44 expressed in advanced SM progenitors, but not in those from indolent disease and normal controls. Similarly, soluble CD44 is measurable in serum from patients with mast cell neoplasms, and levels are higher in patients with advanced systemic mastocytosis. In serial samples from a cohort of treated patients, soluble CD44 tracks with clinical response. In addition, higher levels of soluble CD44 negatively correlates with overall survival in advanced systemic mastocytosis.

Mechanistically, Mueller et al find that, unlike inhibitors of KIT, inhibitors of the Ras-MEK pathway and STAT5 inhibitors lead to downregulation of surface CD44 expression. And, to address CD44 more directly as a relevant therapeutic target, they find that RNA isolation-mediated knockdown of CD44 reduces tumor formation in a xenograft model. Taken together, CD44 appears to be both an invasion receptor in and biomarker of advanced systemic mastocytosis, and its regulation by RAS and STAT5 points at several potential therapeutic targets or combinatorial approaches.

Conflict-of-interest disclosure: E.H. has served as an advisor and received research support from Blueprint Medicines and Novartis Oncology.

REFERENCES


DOI 10.1182/blood-2018-08-865592 © 2018 by The American Society of Hematology