Cell Engager Summit

Speaker Interview

Exclusive Speaker Interview

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HARBOUR BIOMED

What is unique about Harbour BioMed's approach to developing cell engager therapeutics?

From a technology perspective, we are using heavy chain only antibody (HCAb) to build our HCAb-Based Immune Cell Engager bispecific antibody, e.g., HBICETM.

The HCAbs are generated from transgenic Harbour Mice® where mouse light chain VDJ genes have been knocked out, and the mouse heavy chain VDJ genes have been replaced with selected human VDJ genes. Therefore, the HCAbs are fully human sequence antibodies that have undergone in-vivo natural selection and maturation, and usually shows better druggability, with decreased immunogenicity risks or humanization/engineering needs, as compared to scFv or lama derived nanobodies. Without the constraints of light chain mispairing, HBICE shows significant flexibilities of geometry and format. The geometries of these "2+1", "2+2" or multivalent asymmetrical and symmetrical formats can be further optimized to adapt to different biology mechanism of actions, such as dual binding, crosslinking, clustering, and immune synapse formation. In comparison to other bispecific formats, the smaller size and better developability make HBICE an ideal technology to generate bispecific and multi-specific immune cell engagers.

From the biology perspective, we are building both 1st signal (CD3) and 2nd signal (4-1BB etc.) based T cell engagers and looking to expand to more immune cell types.

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Unlike in hematological malignancies, most solid tumors lack the expression of positive costimulatory molecules, e.g. 2nd signal, whereas 1st signal only-mediated T cell activation has been shown not to be strong enough for some exhausted T cells, or to a certain extent, even leads to T cell anergy or apoptosis after transient activation. Therefore, it is extremely critical to activate 2nd signal in solid tumors to provide a potent and sustainable effector T activation and proliferation, as well as memory T cell induction. Furthermore, the 2nd signal and tumor antigen dependent bispecific would be able to resolve safety issues involving many of those costimulatory monoclonal antibodies in clinic, such as CD28, 4-1BB, CD40. In fact, our TAAx4-1BB bispecific can only be activated in the presence of tumor associated antigen (TAA) due to TAA-mediated 4-1BB clustering. Thus, this also avoids liver toxicity resulted from nonspecific 4-1BB activation.

Could you share more about your product pipeline both at pre-clinical and clinical stages?

In the past four years, we have built a clinical and pre-clinical pipeline at Harbour. Our next-gen CTLA4 program is the first fully human heavy chain only antibody to enter clinical trial. As compared to previous CTLA4 therapies, our anti-CTLA4 HCAb has a tremendous improvement in Treg depletion and pharmacokinetic profile to enlarge therapeutic window. We are excited to report Phase 1 data in upcoming international conferences. In addition, we have developed COVID-19 neutralizing antibody through our collaboration with Utrecht University and Erasmus Medical Center last year. The antibody has been licensed to Abbvie and is currently undergoing clinical tests. We aim to benefit patients and contribute to fighting the battle against COVID-19 with the use of our technology and products.

On top of the clinical programs, we also have BCMAxCD3 and B7H4x4-1BB that are in preclinical stage. If you want to learn more about our other innovative products in preclinical stage, please visit our website at: www.harbourbiomed.com

What do you see as the biggest challenges facing those developing cell engager therapeutics?

Cell engager therapeutics have been showing promising efficacy in clinical trials in hematological cancers. However, they are less effective in solid tumors and also limited by the toxicity. From efficacy perspective, it is important to increase the penetration of cell engager molecules and cytotoxic T cells into tumor microenvironment, and overcome potential T cell exhaustion. On the safety front, the cytokine release syndrome (CRS) needs to be controlled, evidenced by the recent setback of BCMAxCD3 bispecific cell engager.

What does the community need to do to overcome those challenges?

The challenges need to be tackled from both biology and technology. For example, how can these engagers better recruit T cells into "cold" solid tumor? Can CRS be attenuated by optimizing anti-CD3 activity or changing its use of different activation arms, such as anti-4-1BB? With better design in geometry, epitope pairing and bispecific formats, this may help to improve the overall CRS related safety and immune cell engagement in cold tumor. Likewise, the responses can be further enhanced when combined with 1st signal cell engager and 2nd signal cell engagers or other agents. Lastly, the stringent cross-linking dependency and optimized anti-CD3 activity should be carefully monitored. I am confident that the cell engager direction will open a new era of cancer immunotherapy with more biology studies and bispecific optimizations.

What are the major clinical objectives that your group are aiming for over the next 18 months-2 years?

Our HBM9161 (FcRn antibody) and HBM9036 (anti-TNFα fragment) are currently in pivotal trial. We strive to transform into a biopharma with BLA in the next 18-24 months. With an increased number of innovative HBICE programs and novel target antibodies entering clinical trials, we are excited that the products generated from our powerful antibody technology platforms will eventually help patients.

What topics are you most looking forward to discussing with your peers at the Cell Engager Summit and why?

I am particularly interested in the topic of novel cell engagement directions for solid tumors, where the underperformance of cell engagers in solid tumor has been partially attributed to the weak penetration into solid tumor. However, I do not think that is the reason as there were successful examples of mAb and ADC in solid tumors. Instead, the right immune cell engagement including NK, macrophage, DC, besides just T cells, are probably more important for different cancer types depending on their respective tumor microenvironments. It will be interesting to see other approaches used to increase T cell infiltration and I understand that there are many academic and industry groups presently working on this field. I hope to have the opportunity to discuss this with the group through this exciting Cell Engager Summit.

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