PRECLINICAL CHARACTERIZATION OF LAE111, A POTENT ANTI-LILRB1/LILRB2 ANTAGONIST BISPECIFIC ANTIBODY

Minhua Zhang*, Rong Wu, Chaojun Cai, Xiang-Ju Justin Gu. Laekna Therapeutics, Shanghai, China

Background
Immunosuppressive tumor microenvironment is known to contribute to tumor immune evasion and resistance to checkpoint inhibitors. LILRB1 (ILT2) and LILRB2 (ILT4) are immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing immune inhibitory receptors, which are highly expressed on tumor infiltrated immune cells (myeloid/NK/T cells for LILRB1 and myeloid cells for LILRB2). Both receptors recognize a broad spectrum of human leukocyte antigen (HLA) (e.g., HLA-A, HLA-G, etc.) and some non-HLA ligands. Upon binding to the ligands, LILRB1 and LILRB2 trigger inhibitory signaling to suppress both innate and adaptive immune response in the tumor. Targeting LILRB1/LILRB2 with bispecific antagonist antibody could offer a feasible approach to counteract immunosuppression in the tumor and achieve durable response to anti-PD1/PD-L1 antibody therapy.

Methods
Anti-LILRB1 and anti-LILRB2 monoclonal antibodies (mAb) were obtained via mouse hybridoma approach. Anti-LILRB1/LILRB2 bispecific antibodies were engineered using humanized sequence of lead anti-LILRB1 mAb and anti-LILRB2 mAb. Lead bispecific antibodies were characterized in a panel of functional assays together with the competitor’s anti-LILRB1 mAb (15G8), anti-LILRB2 mAb (MK4830 and J19) and anti-LILRB1/LILRB2 dual mAb (NGM707), which are currently being tested in the clinical trials. In vivo target engagement and efficacy of selected anti-LILRB1/LILRB2 bispecific antibodies and dual mAb NGM707 were evaluated in CD34+ NOG-EXL mice SK-MEL-5 CDX model.

Results
Lead anti-LILRB1 mAb and anti-LILRB2 mAb were selected based on their binding affinity, blocking activity (mainly against HLA-G binding) and in vitro efficacy in functional assays. Bispecific antibody LAE111 generated based on the sequence of lead mAb has demonstrated superior in vitro efficacy in a panel of functional assays (NK activation, phagocytosis, LPS/OKT3-induced TNFα release in PBMC) comparing to the existing competitors, suggesting its best-in-class potential (table 1). LAE111 induced more DC cell activation comparing to the combination of anti-LILRB1 mAb and anti-LILRB2 mAb. It further activated T cell response when combining with anti-PDL1 antibody. In vivo, LAE111 induced more target engagement change comparing to NGM707, and reduced tumor volume in CD34+ NOG-EXL mice SK-MEL-5 CDX model.

Conclusions
We have identified anti-LILRB1/LILRB2 bispecific antibody LAE111 with potent antagonist activity on both targets and acceptable developability. Comparing to existing competitors, LAE111 has demonstrated superior activity on modulating myeloid, NK, T cell activity. Combination of LAE111 and PD1/PDL1 inhibitor markedly activated T cell response. These results support further development of LAE111 as a therapeutic for cancer.