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.