Generation of anti-LAG-3 monoclonal antibodies for use in immunotherapy combinations

H. Toni Jun1, Patricia A. McNeely1, Greg Gold1, Brandon Hynes1, Laurence AltobellI11, Mark Chhoa1, Marilyn R. Kehry1, Yan Wang2, Haley Laken2 and David J. King1
1AnaptysBio, San Diego CA and 2TESARO Waltham, MA

Abstract
Inhibitory immune checkpoints maintain self-tolerance in the normal immune system but can be co-opted in cancer to allow tumor escape from immune surveillance. Validation of immune checkpoint inhibitors has been provided by antibodies (mAbs) that inhibit the CTLA-4 and PD-1 pathways, which have shown significant clinical activity alone and in combination. In mouse models, blockade of other T-cell inhibitory signaling checkpoints such as LAG-3 has also been shown to be effective. Combination anti-PD-1 and anti-LAG-3 therapy was explored in vivo in MC38 and Colon26 mouse syngeneic tumor models with mAbs to mouse PD-1 and LAG-3. In the MC38 model, the tumor-free animals were increased from 7/10 in the anti-PD-1 alone arm to 10/10 in the combination. In the Colon26 model, the numbers of tumor-free animals in the anti-LAG-3/anti-PD-1 combination group were 10/12 while anti-PD-1 alone had 3/12 tumor-free animals.

Overall, these data support combination cancer immunotherapy with anti-LAG-3 and anti-PD-1.

Complete Tumor Regressions with anti-LAG3 and anti-PD1 Combination in the MC38 Syngeneic Tumor Model

Increased Affinity of Anti-LAG-3 Candidate mAbs Generated by Somatic Hypermutation

Lead Anti-LAG-3 mAb Inhibits the Interaction of Soluble LAG-3 with MHC Class II

Lead Anti-LAG-3 mAb Potentiates IL-2 Secretion Alone and in Combination with an Anti-PD-1 Antagonist mAb in a Mixed Lymphocyte Reaction

Conclusions
• A high affinity anti-human LAG-3 antibody has been generated by humanization of a mouse monoclonal Ab coupled with in vitro somatic hypermutation
• LAG-3 inhibition with an anti-LAG-3 antibody displays potent activity alone and in combination with an anti-PD-1 antibody in an MLR assay
• Surrogate anti-PD-1 and anti-LAG-3 antibodies have activity in the MC38 and Colon26 tumor models alone and increased anti-tumor activity in combination
• These data suggest co-blockade of PD-1 and LAG-3 is worthy of further investigation