



## **A major ligand for the inhibitory receptor LAG-3 has been identified and its blockade can potentiate anti-tumor T cell responses**

Lymphocyte-activation gene 3 (LAG-3) is a receptor that negatively regulates the proliferation, activation, and effector function of T cells. Currently, monoclonal antibodies that block the interaction of LAG-3 with its canonical ligand, MHC-II, are being evaluated for their antitumor activity in clinical trials. However, several antibodies that do not block the binding of LAG-3 to MHC-II have been shown to still promote T cell functions. For example, C9B7W, a popular anti-mouse LAG-3 antibody, enhances the proliferation, effector functions and anti-tumor activity of T cells *in vitro* and *in vivo* but does not block MHC-II binding. These studies raise the possibility that LAG-3 may bind to an unknown but functionally important ligand.

To identify potential new LAG-3 ligands Dr. Lieping Chen's group at Yale University's Department of Immunobiology employed their genome-scale receptor array (GSRA) technology. The GSRA system identified Fibrinogen-like protein 1 (FGL1) as a major binding protein for LAG-3. The authors confirmed this result by flow cytometry using an FGL1-Ig fusion protein and LAG-3<sup>+</sup> cells.

Following up with studies in mouse models, the investigators demonstrated that removing FGL1 via genetic engineering or with antibodies blocking the FGL1-LAG-3 interaction enhanced T cell responses. Additionally, the mice often slowly developed mild forms of autoimmune disease. Both findings suggest that LAG-3 binding to FGL1 can indeed dampen T cell activity. Moreover, in mouse models of cancer, blocking the FGL1/LAG-3 interaction boosted T cell activity and slowed tumor growth.

Next, Chen's team found that FGL1 is produced at strikingly high levels in various human cancers including lung cancer and melanoma. The researchers also found that higher levels of FGL1 in the blood of these cancer patients are linked to poor prognosis and resistance to anti-PD-1/PD-L1 therapy.

Overall, this research indicates that FGL1 is a major ligand for LAG-3 to suppress T cell responses and constitutes a new target for cancer immunotherapy.

In addition to the anti-mouse LAG-3 (clone C9B7W) used to block FGL1/LAG-3 interactions the authors used Bio X Cells anti-mouse CD8 and CD4 antibodies to deplete T cells *in vivo*.

See the complete article in Cell: [https://www.cell.com/cell/fulltext/S0092-8674\(18\)31502-2](https://www.cell.com/cell/fulltext/S0092-8674(18)31502-2)