IMMUNE-ONC therapeutics



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Background and rationale

The Leukocyte Associated Immunoglobulin-like Receptor 1 (LAIR1) is an immune inhibitory **Cancer - Blood** Normal - Blood transmembrane glycoprotein expressed on lymphocytes and myeloid cells. The known ligands for LAIR1 are proteins containing collagen-like domains including collagen, complement component 1q (C1q), and n=4 PBMC donors stromal protein Colec12. Myeloid-derived suppressor cells (MDSC), tumor associated macrophages 40000-(TAMs), as well as collagens, are important contributors of the immune-suppressive tumor 30000microenvironment, and LAIR1 expression is negatively correlated with patient survival in many solid tumors. These findings prompt us to investigate LAIR1 as a novel immuno-oncology target in collagen-rich 20000tumors. Utilizing LAIR1 antagonist antibodies, we aim to mobilize anti-tumor immunity by changing the collagen-induced tolerogenic state of the immune cells into proinflammatory. Mechanism of action Tolerogeni muno-stimulator Anti-LAIR1 **Characteristics of Proof-of-Concept LAIR1 Blocking Antibody** 😣 🤇 • Humanized IgG4_S228P with high affinity (K_D=0.6 nM, Octet) to human LAIR1 • No binding to GPVI (Glycoprotein VI), a receptor for collagen expressed on platelets Solid Tumor High affinity binding to human Blocks Collagen binding to Dendritic cell 🔘 Cytotoxic T cell 🛹 Natural killer cell LAIR1 Collagen Macrophage LAIR1 LAIR1 Collagen binding blocking assay Binding on human LAIR-1 Human LAIR1 LAIR1 expression up-regulated in some cancers 40000 Expression of LAIR1 across TCGA cancers (with tumor and normal samples) 30000 H 20000-10000-EC50=37.92nM 0.001 I AIR-1 Ab (nM) LAIR1 Ab (ug/mL)





High LAIR1 expression in certain T cell and macrophage signature enriched tumors



Antagonistic Antibodies Targeting LAIR1 Enhance T Lymphocyte Activation and Promote Inflammatory Phenotypes in Myeloid Cells

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LAIR1 is highly expressed on myeloid cells in peripheral blood and solid tumors

LAIR1 blocking Ab attenuates collagen-mediated immunosuppressive phenotype of myeloid cells



Cancer type 1 Cancer type 2

Cancer type 3 Cancer type 4 **Cancer type 5 Cancer type 6 Cancer type 7** Cancer type 8 **Cancer type 9 Cancer type 10 Cancer type 11 Cancer type 12**





LAIR1 blocking Ab reverses collagen-mediated monocyte tolerogenic effect



Purified monocytes were stimulated for 48 hr with 10 ng/mL of LPS in the presence of 10 ug/mL of antibodies and plate-coated collagen. Monocyte phenotype changes were measured by FACS and cytokines released were measured by Luminex. Samples in black were BSA-coated and samples in red were collagen-coated. Each line represents result from a different healthy donor. One-way ANOVA: *P<0.05, **P<0.01.

LAIR1 blocking Ab enhances T cell proliferation and degranulation in collagen-suppressed T cells



Purified T cells were stimulated for 48 hr and 72 hr with immobilized anti-CD3 at various concentrations in the presence of 10 ug/mL of antibodies and plate-coated collagen. T cell proliferation and degranulation were measured by intracellular FACS after 48 hr. Samples in black were BSA-coated and samples in red were collagen-coated. Each line represents result from a different healthy donor. One-way ANOVA: *P<0.05.

LAIR1 blockade reverses collagen-mediated T cell suppression in autologous macrophage/T cell co-culture



- from TCGA (The Cancer Genome Atlas).
- LAIR1 is highly expressed on myeloid cells in peripheral blood and solid tumors by flow cytometry.
- POC humanized IgG4 (S228P) anti-LAIR1 antibody displays high affinity, specificity and potent antagonistic activity. • LAIR1 blockade attenuates collagen-mediated immunosuppressive phenotype of myeloid cells.
- LAIR1 blockade reverses collagen-mediated monocyte tolerogenic effect.
- cell co-culture.

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Summary

• LAIR1 mRNA expression is associated with macrophage and certain T cell infiltration in many solid tumor types

• LAIR1 blockade enhances T cell activation and proliferation in collagen-suppressed T cells and in macrophage/T