

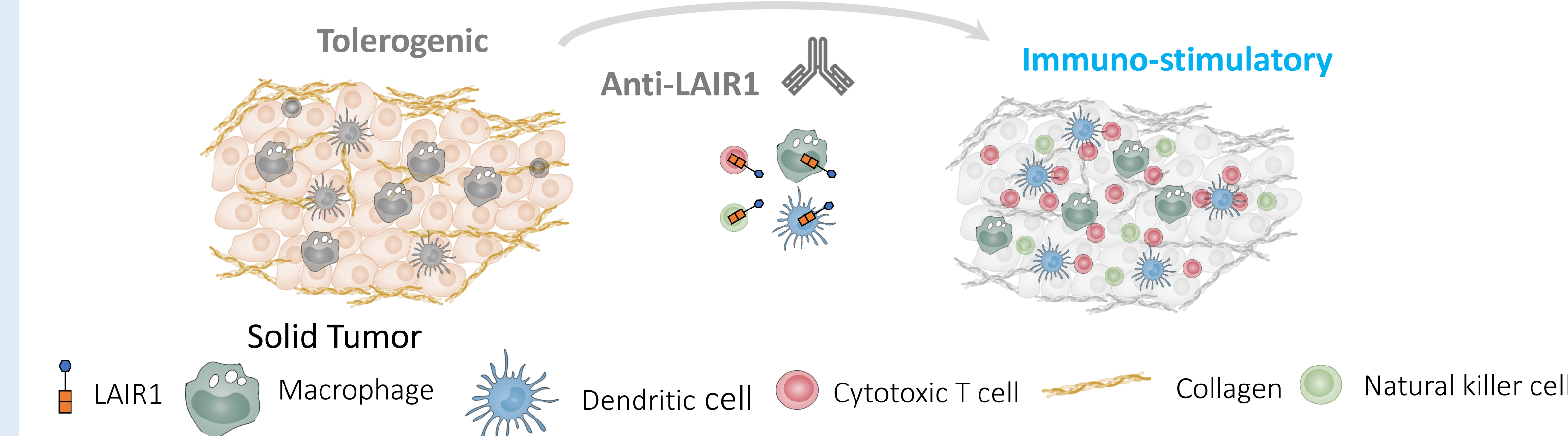
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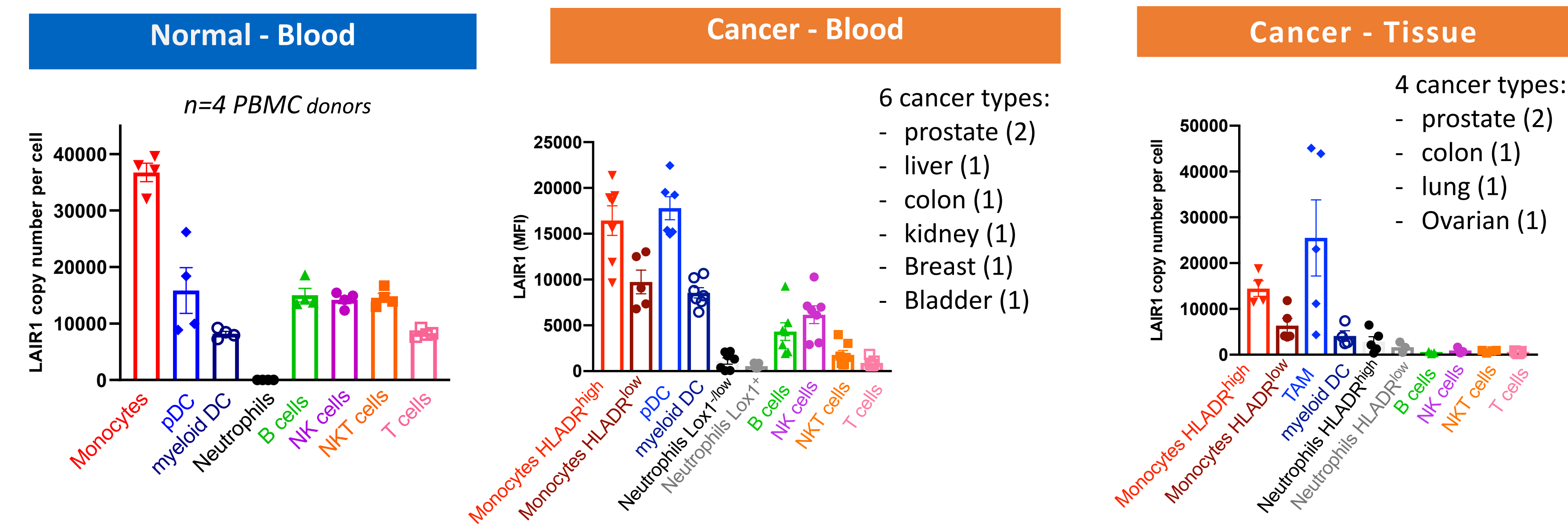
Background and rationale

Myeloid-derived suppressor cells (MDSC), tumor associated macrophages (TAMs), and collagen promote an immune-suppressive microenvironment in solid tumors. The Leukocyte Associated Immunoglobulin-like Receptor 1 (LAIR1) is an immune inhibitory transmembrane glycoprotein expressed on lymphocytes and myeloid cells. Known ligands for LAIR1 are collagen and proteins containing collagen-like domains, such as complement component 1q (C1q), and stromal protein Colec12. We hypothesize that LAIR1 is an immune checkpoint activated by its ligands during the continuous, anti-inflammatory, tissue remodeling process characteristic of solid tumors. Accordingly, LAIR1 expression is negatively correlated with patient survival in many solid tumors. Here, we used a novel LAIR1 antagonist antibody designed to mobilize anti-tumor immunity by disrupting the tolerogenic LAIR1 pathway in collagen-rich solid tumors.

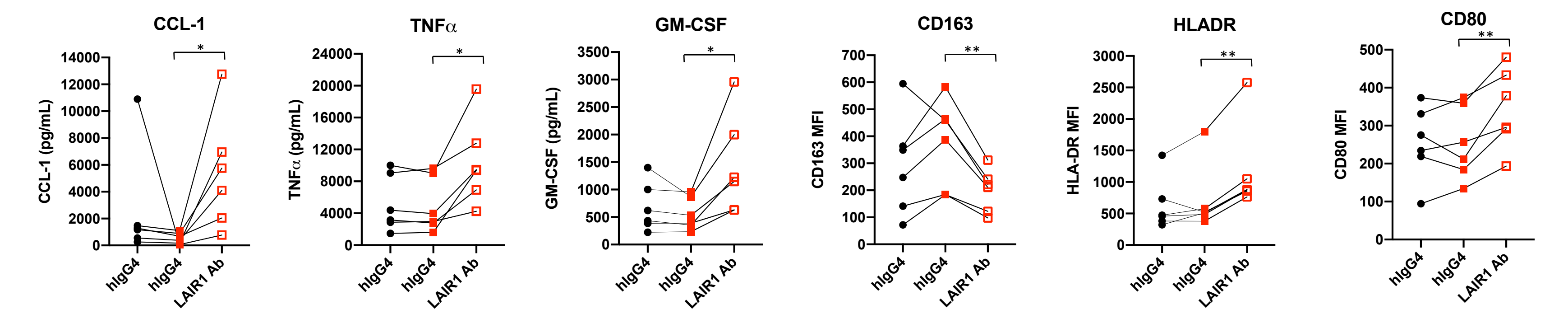
Mechanism of action



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

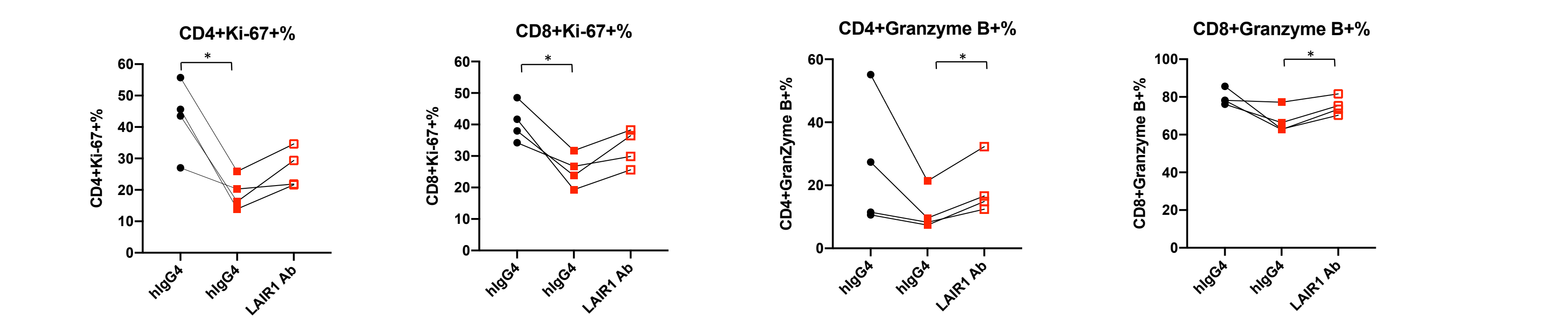


LAIR1 blocking Ab reverses collagen-mediated monocyte tolerogenic effect



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

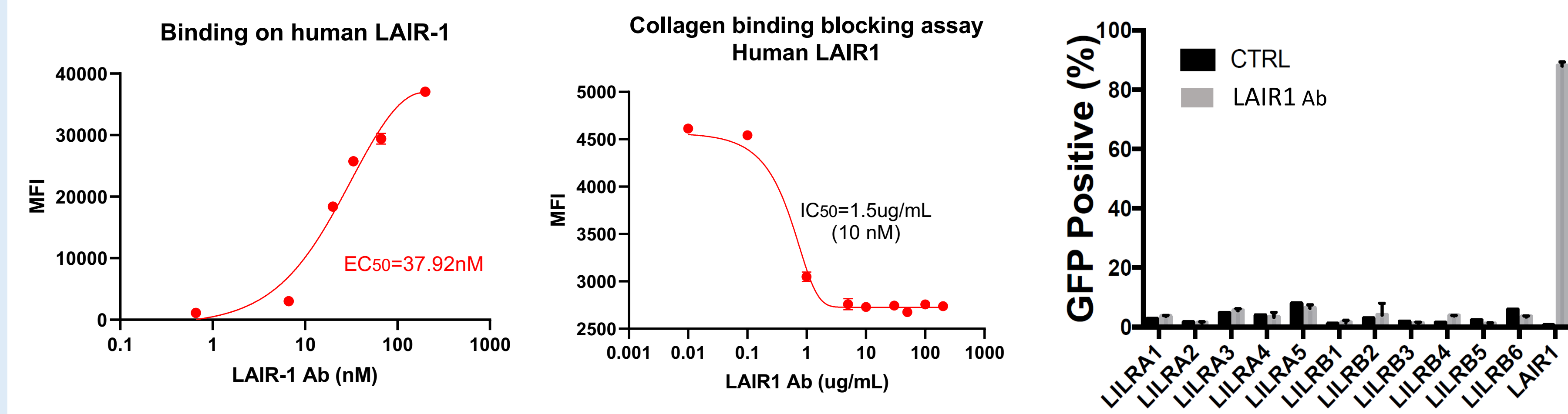


Purified T cells were stimulated for 48 hr and 72 hr with immobilized anti-CD3 at various concentrations in the presence of 10 ug/mL of antibodies and plate-coated collagen. T cell proliferation and degranulation were measured by intracellular FACS after 48 hr. Samples in black were BSA-coated and samples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

Characteristics of Proof-of-Concept LAIR1 Blocking Antibody

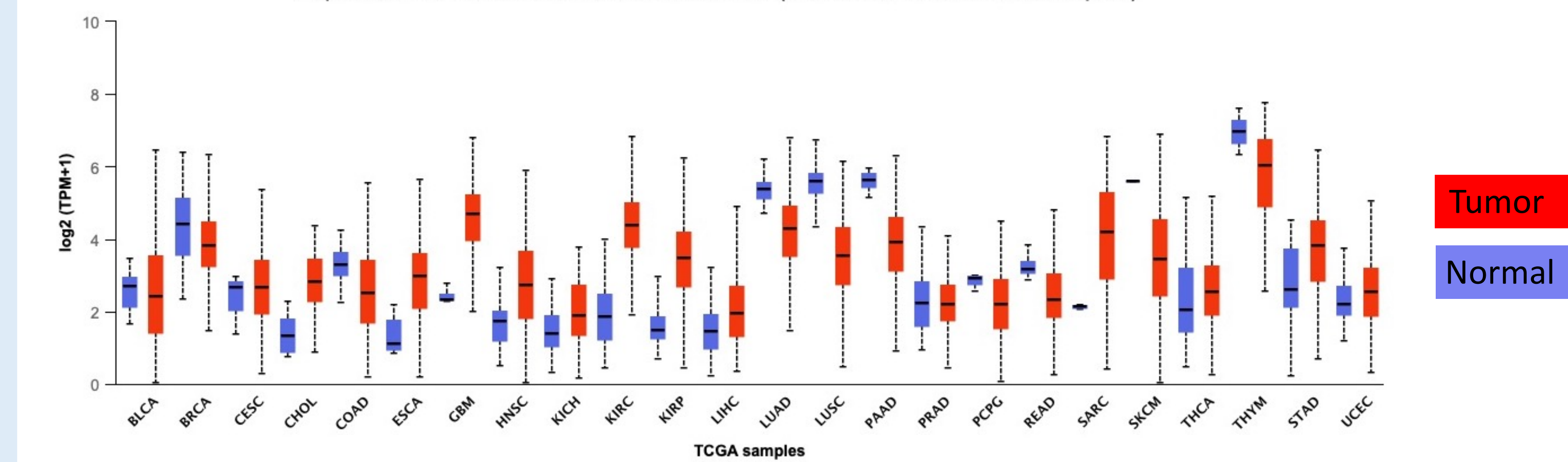
- Humanized IgG4_S228P with high affinity ($K_D=0.6$ nM, Octet) to human LAIR1
- No binding to GPVI (Glycoprotein VI), a receptor for collagen expressed on platelets

High affinity binding to human LAIR1 | Blocks Collagen binding to LAIR1 | No binding to other family members

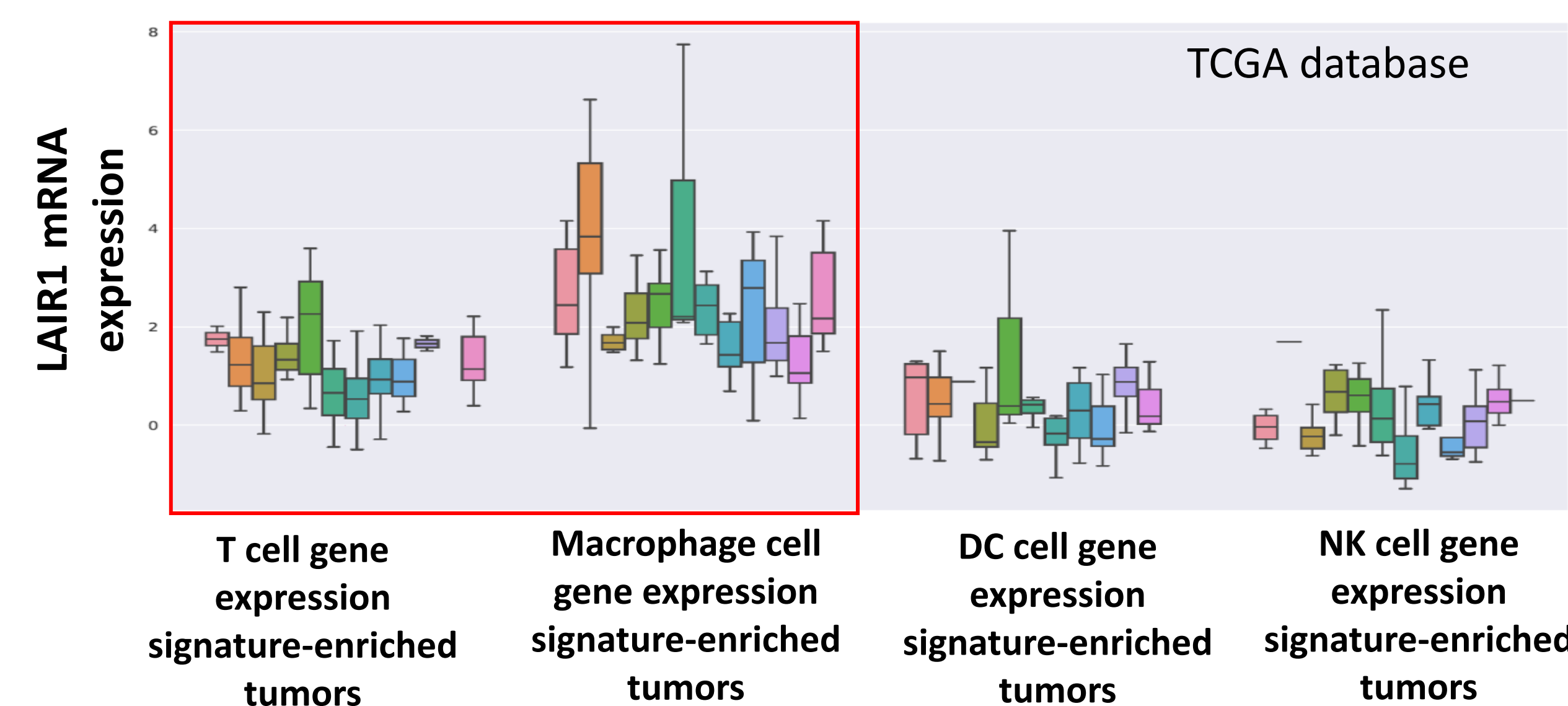


LAIR1 expression up-regulated in some cancers

Expression of LAIR1 across TCGA cancers (with tumor and normal samples)

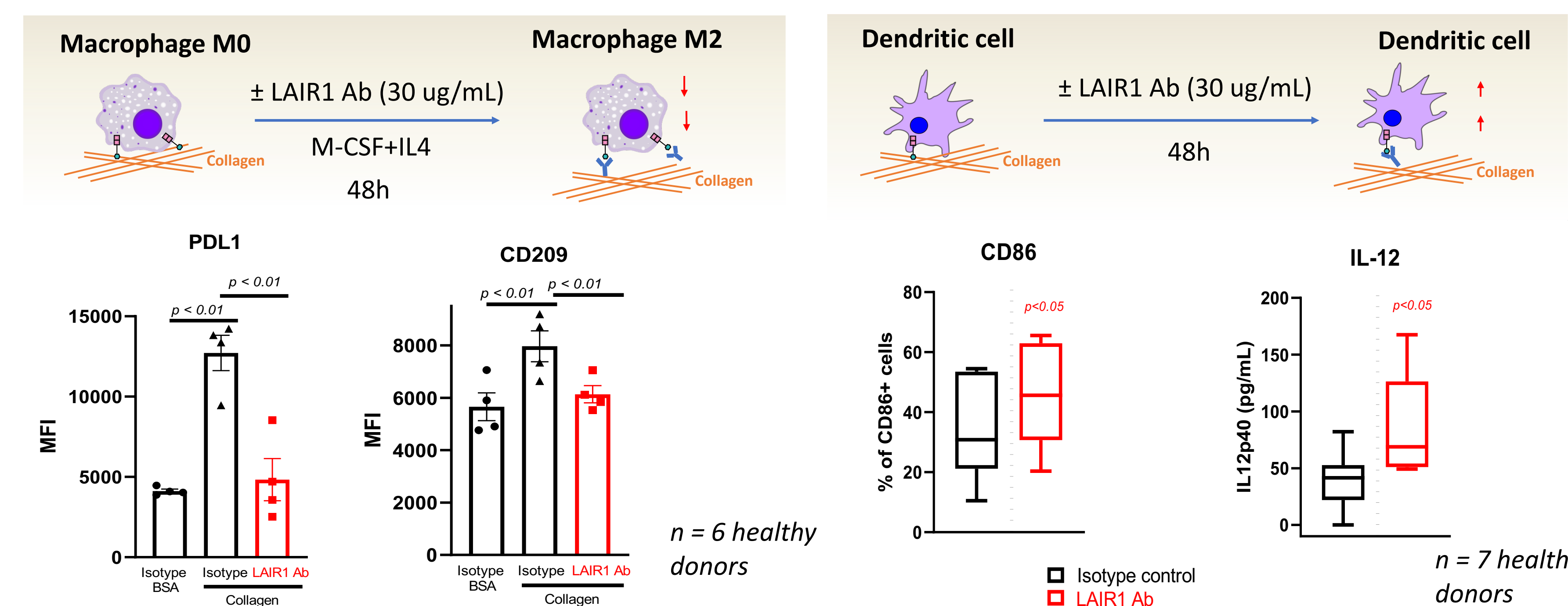


High LAIR1 expression in certain T cell and macrophage signature enriched tumors

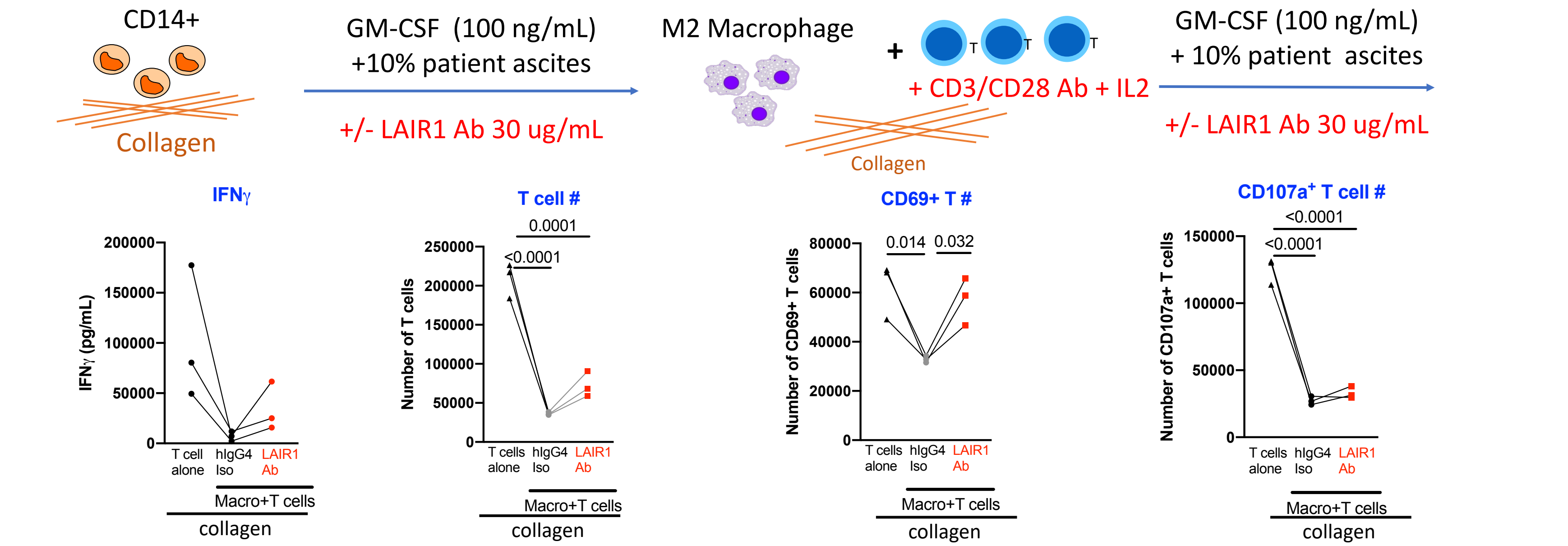


- Cancer type 1
- Cancer type 2
- Cancer type 3
- Cancer type 4
- Cancer type 5
- Cancer type 6
- Cancer type 7
- Cancer type 8
- Cancer type 9
- Cancer type 10
- Cancer type 11
- Cancer type 12

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



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



Summary

- LAIR1 mRNA expression is associated with macrophage and certain T cell infiltration in many solid tumor types 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.
- LAIR1 blockade enhances T cell activation and proliferation in collagen-suppressed T cells and in macrophage/T cell co-culture.