A Novel LAIR-1 Antibody Selectively Targets Acute Myeloid Leukemia (AML) Stem Cells

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Background: Significant unmet need exists for AML patients that are not responsive to standard-of-care (SOC) treatments. In addition, SOC patients usually relapse due to persistence of chemotherapy-resistant leukemia stem cells (LSCs). Therefore, identification of unique strategies to preferentially target LSCs, promote immune responses to AML and prevent relapse are highly sought after. AML LSCs and blast cells are characterized by the higher expression of leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1). LAIR-1 is a checkpoint receptor on T cells and myeloid cells that delimits immune cell activation when binding to endogenous collagen ligands. However, it has been demonstrated that LAIR-1 has differential activity in AML cells and may sustain AML survival signals since downregulation of LAIR-1 promotes AML cell death. We developed a LAIR-1 monoclonal antibody (mAb), termed NC525, that disrupts LAIR-1 mediated survival signaling and preferentially targets and kills LAIR-1 expressing AML LSCs and blast cells.

LAIR-1 Overexpression on AML blast and stem cells

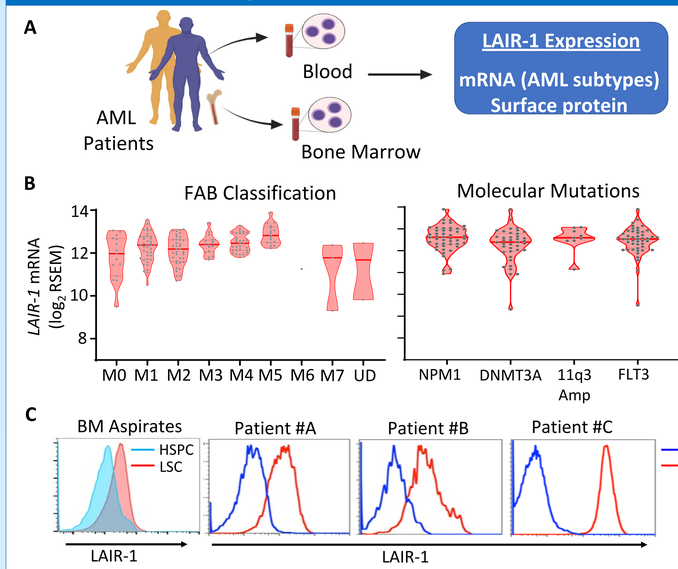
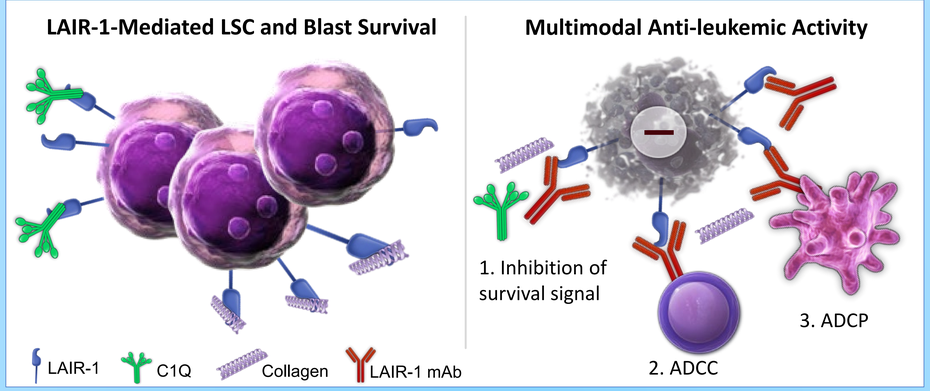


Figure 1. A. Schematic illustration of study design to determine LAIR-1 expression on AML blasts and leukemic stem cells. **B.** LAIR-1 mRNA expression in AML subtypes defined by FAB classification, and mutation status. UD denotes undetermined. **C.** LAIR-1 protein expression on the cell surface of leukemic stem cells (LSCs; $CD34^+CD38^-CD90^-CD45RA^{+/-}$ or $CD34^-CD117^+CD244^{+/-}$) vs hematopoietic stem and progenitor cells (HSPCs; $CD34^+CD38^-CD90^+CD99^-$) derived from bone marrow aspirates, and leukemic blasts from the peripheral blood of AML patients.

LAIR-1 mAb blocks LAIR-1 signaling and induces antibody dependent cytotoxicity and phagocytosis



LAIR-1 mAb blocks binding of natural ligand collagen and signaling

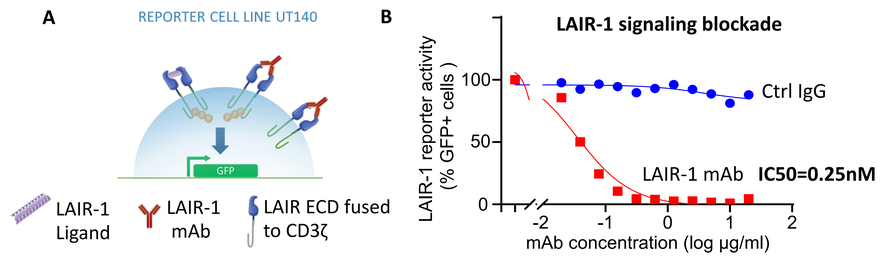


Figure 2. A. Schematic illustration of LAIR-1-TCRζ reporter assay using UT-140 NFκB-GFP cell line. **B.** LAIR-1 mAb blocks COLA1-mediated LAIR-1 signaling activity in a dose-dependent manner.

LAIR-1 mAb induces ADCC mediated AML killing

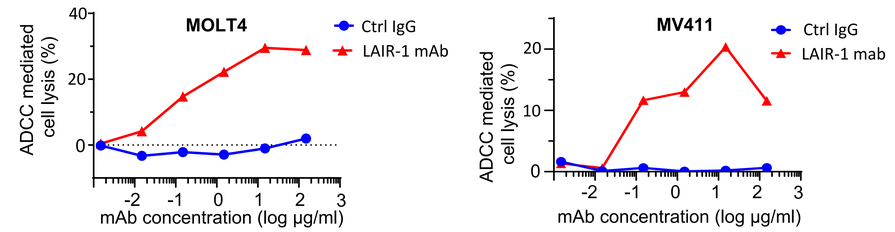


Figure 3. LAIR-1 mAb induces antibody dependent cytotoxicity on MOLT4 and MV411 cell lines in a dose-dependent manner in primary PBMC: leukemic cell coculture assay.

LAIR-1 mAb inhibits colony formation of AML LSCs

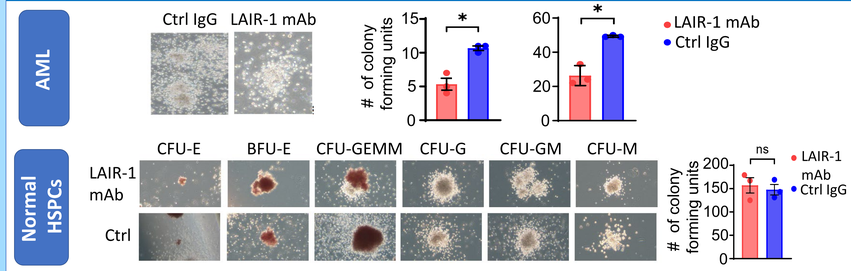


Figure 4. Effect of LAIR-1 mAb on the colony forming capacity of LSCs derived from two AML patients and HSPCs from a healthy donor using Methocult™ method.

LAIR-1 mAb eliminates AML cells via ADCP

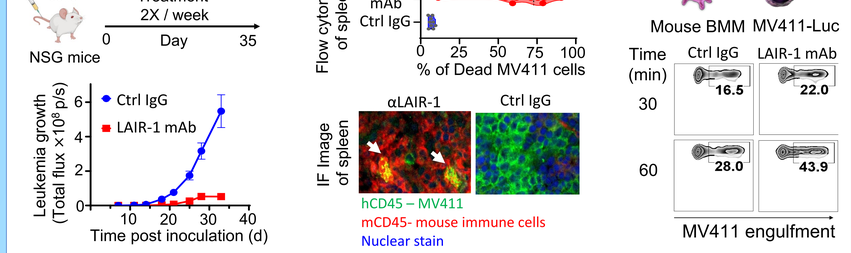


Figure 5. A. In-vivo CDX model of implanting MV411-Luc cells into NSG mice and treating with LAIR-1 mAb showed potent anti-leukemic activity even without transfer of human PBMCs. **B.** Flow cytometry and immunofluorescence analyses of spleens harvested on day 35 from CDX model. Arrows indicate MV411 cells undergoing phagocytosis. **C.** LAIR-1 mAb induces ADCP activity in an in-vitro phagocytosis assay utilizing Cell-Trace violet labelled mouse bone marrow macrophages (BMM) cocultured with MV411-Luc cells.

LAIR-1 mAb restricts AML progression in PDX models

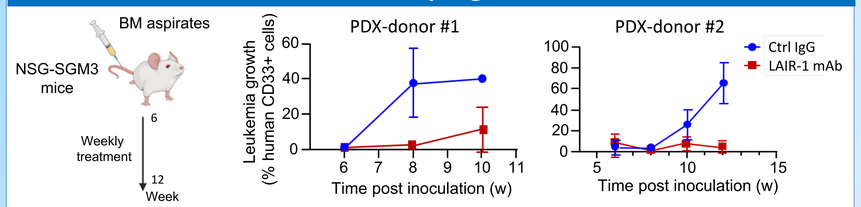


Figure 6. NSG-SGM3 mice were irradiated and implanted with BM aspirates from two AML patients. Mice were treated with mAbs on weekly basis from week 6 of BM implantation.

Conclusion: High expression of LAIR-1 on leukemic cells and its role in mediating survival signaling in LSCs makes it an attractive therapeutic target against AML. To this end, we developed a novel immunomedicine NC525, a LAIR-1 mAb, that potently eradicates LSCs and leukemic blasts while having a minimal effect on healthy HSPCs. We show that LAIR-1 mAb exerts its anti-tumor activity via disruption of survival signals in leukemic cells and Fc-mediated effector functions including ADCC and ADCP.