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IOMX-0675, a LILRB1 / LILRB2 Cross-Specific Antibody That Repolarizes the Tumor Microenvironment to Drive Potent Anti-Tumor Activity

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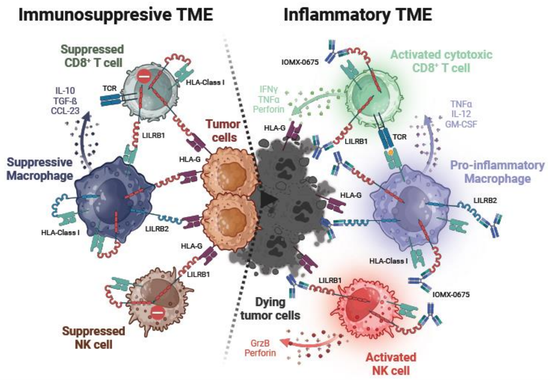
Introduction

The role of myeloid checkpoints in enabling tumors to evade immune responses has gained increased attention recently. LILRB1 (ILT2) and LILRB2 (ILT4) are immunosuppressive receptors in the leukocyte immunoglobulin-like receptor (LILR) family that bind classical and non-classical MHC-I molecules, such as HLA-G. Myeloid cells in the tumor microenvironment express both LILRB1 and LILRB2, while lymphoid cells only express LILRB1. Elevated LILRB1 and LILRB2 expression is often observed in non-responders to T cell checkpoint inhibitors, indicating a role in tumor resistance. Additionally, HLA-G, a main ligand for LILRB1 and LILRB2, is overexpressed in several solid tumors and linked to poor outcomes.

IOMX-0675 is a fully human, Fc-silenced monoclonal immunoglobulin G1 (IgG1) antibody, identified from iOmx' proprietary phage display library. It shows a highly differentiated binding profile, with selective, high-affinity binding to the inhibitory receptors LILRB1 and LILRB2, while sparing immune-activating LILRA1 and LILRA3. In autologous immune cell co-cultures, IOMX-0675 reprograms immunosuppressive macrophages in a dose-dependent manner, restoring lymphoid immune cell function. IOMX-0675 synergizes with anti-PD-1 treatment by stimulating cytotoxic T cells in an allogenic DC- and macrophage-MLR, enhances macrophage mediated tumor cell phagocytosis and pro-inflammatory cytokine secretion from stimulated PBMCs in whole blood. Additionally, in a CD34$^+$ stem cell-engrafted humanized mouse xenograft melanoma model, IOMX-0675 demonstrates potent anti-tumor activity and pharmacodynamic modulation of tumor-associated macrophages, mirroring the *in vitro* findings.

In summary, IOMX-0675 is a highly selective antibody that targets both LILRB1 and LILRB2 with minimal affinity for immune-activating LILRA family members. It effectively reprograms immunosuppressive myeloid cells and restores T cell activity in the tumor microenvironment, showing strong results both *in vitro* and *in vivo*. IOMX-0675's unique binding profile positions it as a best-in-class, dual-targeting myeloid checkpoint inhibitor with strong potential for broad anti-tumor activity - both as monotherapy and in combination with T cell checkpoint inhibitors across multiple solid tumors.



Conclusion

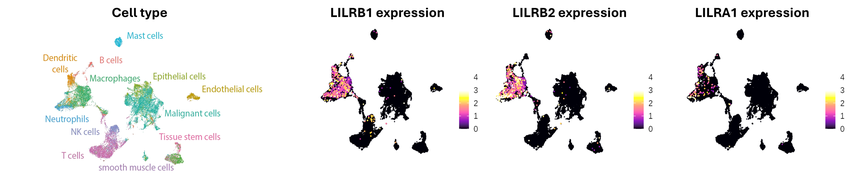
- IOMX-0675 is a fully human, Fc-silenced cross-specific antibody binding with high affinity to the immunosuppressive receptors LILRB1 and LILRB2, while sparing their closely related immuno-activating LILR family members LILRA1 and LILRA3.
- The highly differentiated binding profile of IOMX-0675 translates into remarkably superior potency in various *in vitro* functional immune cell assays and whole blood assay as compared to mono- or dual-targeting antibodies currently in clinical development.
- IOMX-0675 synergistically enhances αPD-1 therapy
- IOMX-0675 demonstrates its best-in-class potential by repolarizing the immunosuppressive tumor microenvironment *in vivo* and thereby inhibiting tumor growth in a fully humanized, myeloid engrafted melanoma tumor model.
- CTA was approved in Q2 2025

Results

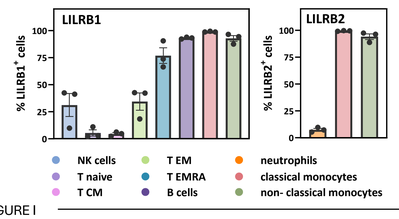
IOMX-0675 selectively modulates the immunomodulatory LILRB1/2 receptors

- Single-cell RNAseq analysis reveals co-expression of LILRB1, LILRB2 and LILRA1 on individual immune cells in tumor biopsies
- Flow cytometry analysis of PBMCs confirms high LILRB1 and LILRB2 protein expression levels on myeloid and lymphoid immune cell subsets
- IOMX-0675 demonstrates high affinity to the immunosuppressive LILRB1 & LILRB2 receptors, showing superior binding profile over a clinical αLILRB1/2 competitor by avoiding binding to LILRA1/3 molecules

A) Co-expression of LILR family members in the tumor microenvironment of cancer patients



B) LILRB1 / LILRB2 positive immune cell populations



C) Differential binding profile of IOMX-0675

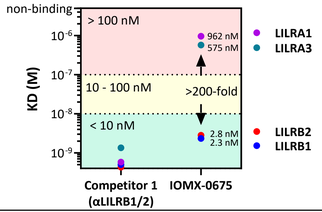


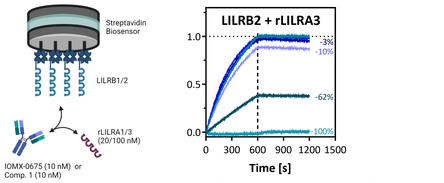
FIGURE I

A) Single-cell RNA sequencing (scRNAseq) datasets from Barkley et. al. 2022 Nat Genet, Lin et al 2020 Genome Med and Kim et al 2020 Nat Com. were analyzed using the Seurat R package. UMAP plots show cell annotations for LILRB1, LILRB2 and LILRA1 expression for breast cancer (n=4), colorectal cancer (1), lung adenocarcinoma (4), ovarian cancer (3) and pancreatic cancer (9). LILRA3 was not annotated in the analyzed data set. **B)** Whole blood from healthy donors (n=3) was analyzed by flow cytometry regarding LILRB1 & LILRB2 target expression on relevant immune cell populations (NK = natural killer, CM = central memory; EM = effector memory, EMRA = effector memory cells re-expressing CD45RA) **C)** Differential binding profile of IOMX-0675 against LILRB1/2 and LILRA1/3 compared to clinical competitor antibody (Competitor 1). Binding kinetics of both antibodies to LILRB1/2 and LILRA1/3 were measured by biolayer interferometry (BLI) on an Octet Red96e and fitted using a 1:1 binding model.

IOMX-0675 effectively repolarizes macrophages even in the presence of LILRA3

- Even in the presence of LILRA3 (& LILRA1, data not shown), IOMX-0675 shows high affinity to LILRB1/2 and repolarizes macrophages more effectively towards the M1-like phenotype than a clinical αLILRB1/2 competitor

A) Binding LILRB1/2 in the presence of LILRA3



B) Enhancement of M1-like macrophage phenotype in the presence of LILRA3

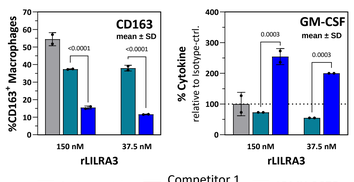


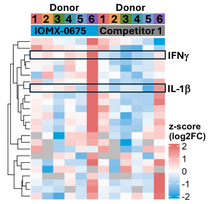
FIGURE II

A) Binding kinetics of IOMX-0675 or Competitor 1 (αLILRB1/2) at 10 nM to LILRB2 in the presence of 20 or 100 nM recombinant LILRA3 (rLILRA3). Interactions were measured by biolayer interferometry (BLI) on an Octet Red96e. **B)** Differentiation of monocytes from healthy PBMC donors and polarization to M1-like macrophages using M-CSF and LPS. Treatment with IOMX-0675 (1nM), competitor (1nM) or isotype control (5nM) in the presence of 37.5 or 150 nM rLILRA3. CD163 expression was analyzed by flow cytometry, supernatant GM-CSF by bead-based immunoassays. Results are shown as mean ± SD.

IOMX-0675 enhances pro-inflammatory cytokine secretion from stimulated PBMCs

- IOMX-0675 enhances pro-inflammatory cytokine secretion by both LPS-stimulated whole blood and αCD3-stimulated PBMCs, outperforming an αLILRB1/2 competitor

A) Cytokine secretion by LPS-stimulated blood



B) αCD3-stimulated PBMCs

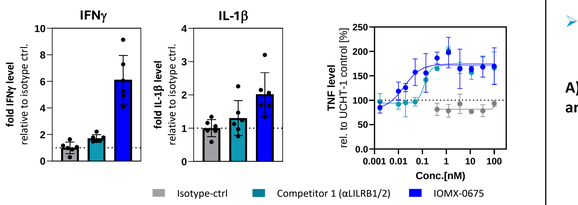


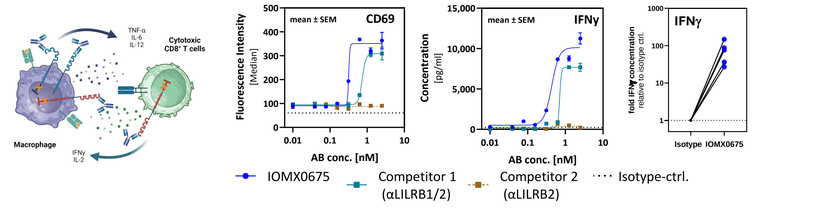
FIGURE III

A) Whole blood from healthy donors (n=6) was treated simultaneously with 10 nM LPS and 200 nM IOMX-0675, competitor 1 or isotype control for 48 hours. Cytokine release was quantified using nELISA. Data are normalized to 10 nM LPS isotype control and most differentially regulated genes are shown (left graph, heatmap). Exemplary cytokines are shown relative to isotype control as mean ± SD (right graphs). **B)** PBMCs from healthy donors (n=6) were treated simultaneously with the αCD3 antibody UCHT-1 (2.5µg/ml) and IOMX-0675, competitor or isotype control for 72 hours. TNF release was quantified using ELISA and is shown for one representative donor.

IOMX-0675 repolarizes macrophages, reactivates immunosuppressed cytotoxic T cells and enhances tumor cell phagocytosis

- Superior repolarization of M2-like macrophages by IOMX-0675 translates into stronger activation of immunosuppressed cytotoxic T cells compared to clinical competitors on the LILRB1/LILRB2 pathways
- Across multiple donors, IOMX-0675 consistently demonstrates robust activation of immunosuppressed T cells
- Macrophage repolarization by IOMX-0675 enhances tumor cell phagocytosis and correlates with receptor occupancy
- Dual targeting of LILRB1/2 by IOMX-0675 outperforms monospecific targeting of the receptors

A) Repolarization of M2-like macrophages and activation of autologous effector T cells in an *in vitro* co-culture assay



B) Enhancement of tumor cell phagocytosis through inhibition of the LILRB1/2 pathway

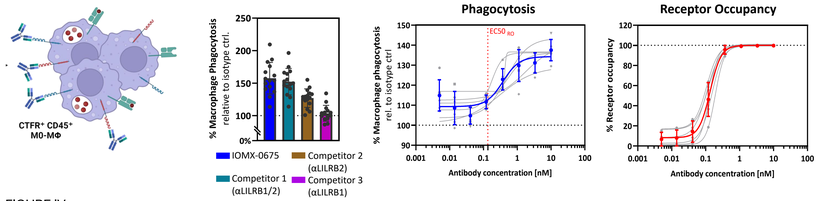


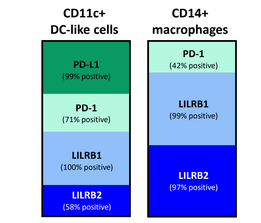
FIGURE IV

A) Monocytes were differentiated and polarized to M2-like macrophages and co-cultured with autologous T cells for 3 days. Treatment with IOMX-0675, competitor 1, competitor 2 or appropriate isotype control antibody was performed throughout the assay. Flow cytometry of T cells and supernatant analysis by bead-based immunoassays were done on day 11. IOMX-675 mediated IFNγ secretion relative to isotype control is shown across 5 donors (right graph). **B)** CTFR-labeled A375 tumor cells were co-incubated with *in vitro* differentiated M0 macrophages for 2h and treated with IOMX-0675, competitors 1-3, or isotype controls. Phagocytic activity was assessed by flow cytometry across 13 donors at 10nM IOMX-0675 as mean ± SD (left graph). Dose-dependent phagocytic activity (middle graph) as well as LILRB1/LILRB2 receptor occupancy (right graph) was analyzed for n= 6 donors by flow cytometry. Results are shown as mean ± SD of n=6 donors (blue / red line) and each donor individually (grey lines).

IOMX-0675 enhances anti-PD-1 treatment in an allogenic mixed lymphocyte reaction

- *In vitro* differentiated dendritic-like cells express PD-1, PD-L1, and LILRB1, but low levels of LILRB2, whereas M0-macrophages show high expression of LILRB1, LILRB2, and PD-1, but lack PD-L1 expression
- High expression levels of LILRB1 and LILRB2 correlates with pronounced IOMX-0675 monotherapy effect in macrophage MLR
- Combined targeting of the LILRB1/2 and PD-1 axis leads to a synergistic induction of IL-2 by cytotoxic T cells in an allogenic DC- MLR assay

A) Differential expression profile of antigen-presenting cells



B) Synergistic effects of IOMX-0675 with anti-PD-1 in an allogenic DC-MLR

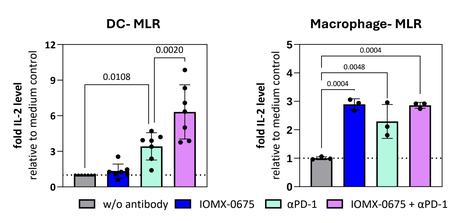


FIGURE V

A) Monocytes from healthy PBMC donors were differentiated into dendritic-like (DC) cells using GM-CSF, IL-4 and IL-10 or to M0-macrophages using M-CSF. CD11c$^+$-DC-like cells and CD14$^+$ M0-macrophages were analyzed for PD-L1, PD-1, LILRB1, and LILRB2 by flow cytometry. Data are displayed as mean of %-positive living cells. **B)** Allogenic T cells were added for a 5-day co-culture with IOMX-0675 and/or aPD-1 antibody treatment. IL-2 in supernatants (day 12) was analyzed via multiplex immunoassays or ELISA. Data represent n = 7 PBMC donor pairs (DC-MLR, left graph) as mean ± SD. One representative donor pair is shown for the macrophage MLR (right graph) with data points representing technical triplicates.

IOMX-0675 exhibits *in vivo* anti-tumor efficacy in a highly aggressive melanoma model

- In the highly aggressive A375 melanoma xenograft model, IOMX-0675 shows significant single-agent activity
- Inhibition of the LILRB1/2 pathway by IOMX-0675 or competitor 1 enhances T cell activation *in vivo*
- IOMX-0675 demonstrates its best-in-class potential by repolarizing the TME in contrast to a clinical competitor

***In vivo* anti-tumor study in a CD34$^+$ fully humanized, myeloid engrafted A375 melanoma model**

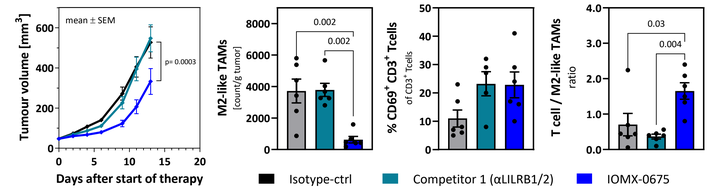


FIGURE VI

A375 melanoma tumor cells were implanted subcutaneously into NOG-EXL mice, fully humanized with CD34$^+$ stem cells from two donors. Randomized animals were treated twice weekly with 20 mg/kg IOMX-0675, competitor 1, or corresponding isotype control antibody. Tumor infiltrating immune cells were analyzed by flow cytometry. Activated CD69$^+$ CD3$^+$ T cells, CD68$^+$CD11c-HLA-DR$^-$ M2-like macrophages and the ratio of CD3$^+$ T cells versus M2-like macrophages are shown as mean ± SEM.

STATISTICAL ANALYSES

Unless otherwise indicated, graphs are representative of data from at least two independent donors. Sigmoidal dose–response curves were fitted to the data using 4-Parameter Logistic (4PL) nonlinear curve models for *in vitro* dose responses. Data points show mean ± SEM, unless otherwise noted. Significance was calculated using one-way ANOVA analysis including Tukey's multiple comparison analysis. Competitor antibodies were produced in-house based on patent derived sequences.