AL009 is a Multi-Siglec Inhibitor Engineered to Bind Myeloid Cells That Enhances Innate and Adaptive Immunity to Cancer

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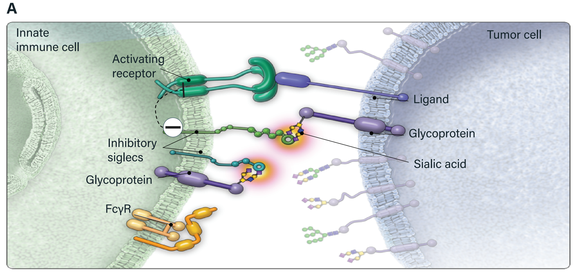
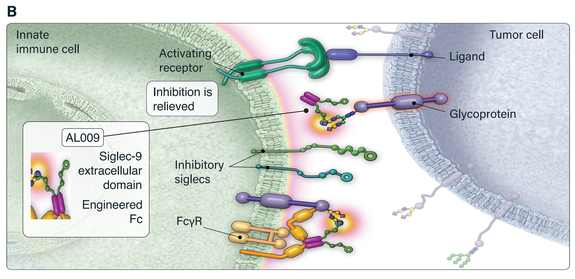
Background

- Inhibitory sialic acid-binding immunoglobulin-type lectins (Siglecs) are a family of cell surface receptors expressed predominantly on myeloid cells that function to promote immune tolerance (**Fig 1A**)[1,2]
- A multitude of inhibitory Siglecs on myeloid cells become engaged in sialic acid-rich tumor microenvironments, suggesting that disrupting the Siglec-sialic acid signaling axis could confer therapeutic benefit in cancer[3,4]
- AL009 is an engineered Siglec-9 extracellular domain Fc fusion molecule that acts as a sialic acid trap and repolarizes suppressive myeloid cells to activate an anti-cancer immune response (**Fig 1B**)

Figure 1. A. Diagram of Siglec-Sialic Acid Mediated Immune Suppression. B. Diagram of AL009 Preventing Siglec-Sialic Acid Mediated Immune Suppression



Deactivated anti-tumor cell response: Siglecs bind to sialic acid, inhibiting signaling that would normally activate an innate immune cell.



Activated anti-tumor cell response: AL009 binds sialic acid, relieving Siglec-induced inhibition and allowing activation signaling to proceed.

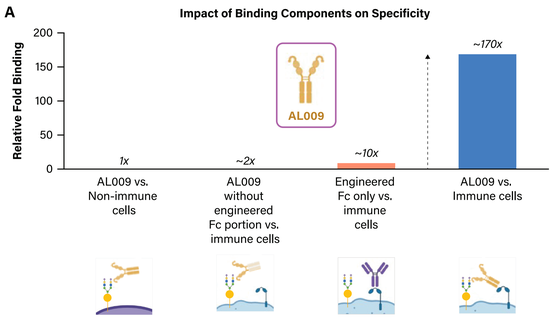
Methods

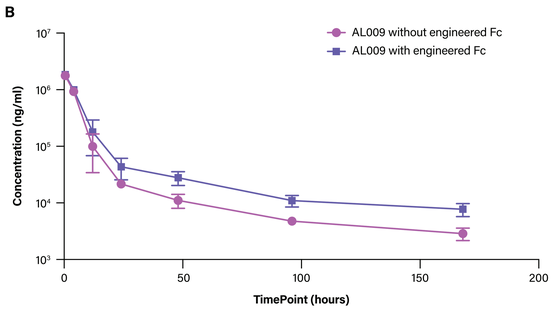
- AL009 cell binding was analyzed by flow cytometry using cultured human tumor cell lines and myeloid-derived suppressor cells (MDSCs) or macrophages differentiated from primary human monocytes.
- PK analysis and initial toxicology screening of AL009 was conducted in cynomolgus monkeys in a non-terminal study.
- Binding to immune cell subsets in whole human blood was analyzed by flow cytometry with fluorophore-labeled AL009.
- AL009m (AL009 with a mouse Fc) was fluorophore-labeled and intravenously injected into B6 mice to analyze biodistribution via ex vivo tissue imaging over time.

Results

- AL009 design enhances immune cell specificity to optimize targeting
  - AL009 displays cooperative binding with sialic acid and Fc gamma receptors on myeloid cells and shows an improved pharmacokinetic (PK) profile compared to a non-engineered Fc (**Fig 2**)

Figure 2. A. Impact of AL009 Binding Components on Specificity of Binding. B. PK Profile of AL009 With and Without Engineered Fc

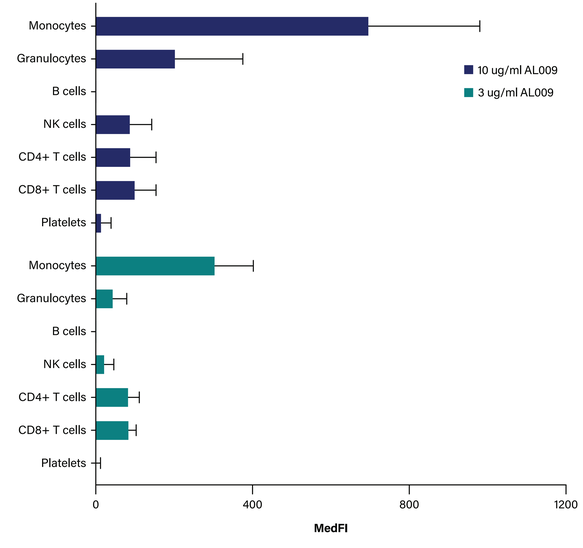




AL009 Binding to Myeloid Subsets

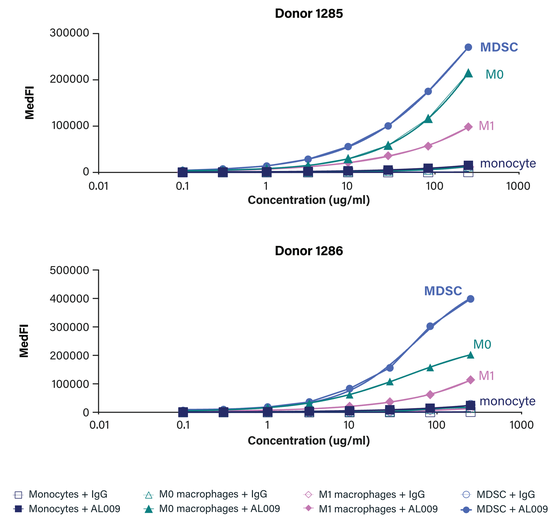
- In whole blood, AL009 preferentially binds to monocytes (**Fig 3**) and among myeloid subsets, AL009 preferentially binds MDSCs (**Fig 4**)

Figure 3. Preferential Binding of AL009 to Monocytes in Human Whole Blood



MedFI, median fluorescence intensity.

Figure 4. AL009 Preferentially Binds MDSCs

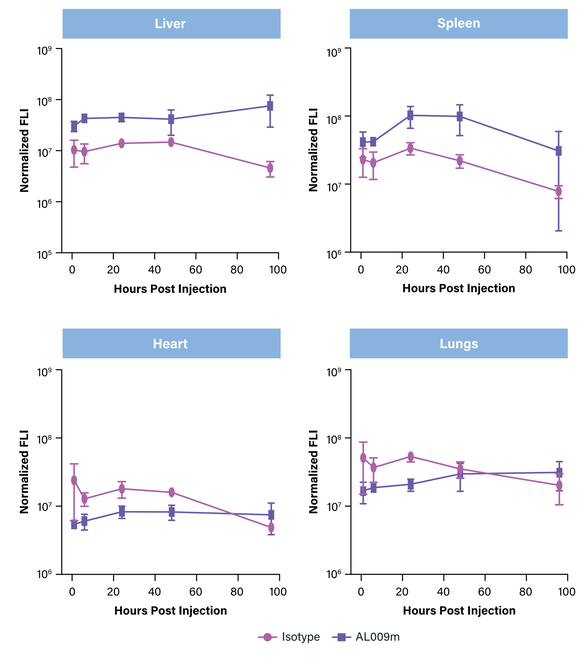


MedFi, median fluorescence intensity.
Peripheral Monocytes, M0 (M-CSF), M1 (M-CSF + IFN-g + LPS), MDSC (GM-CSF + IL-6)

Biodistribution of AL009

- Compared to an isotype control, AL009m was preferentially distributed to the liver and spleen (immune rich organs). In contrast, there was no enrichment in heart and lung (**Fig 5**)

Figure 5. AL009m Biodistribution Confirms Immune Targeting in Mice



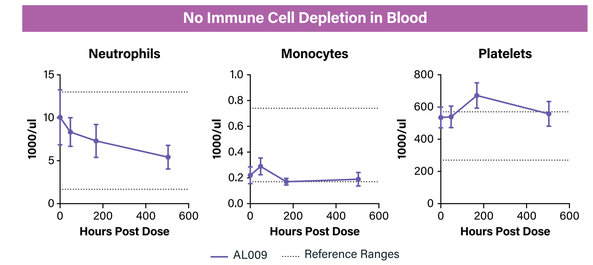
FLI, fluorescence line imager.

Toxicology Data for AL009

- Preliminary toxicology data in cynomolgus monkeys indicates that a single dose of 80 mg/kg AL009 appears well-tolerated and without clinically significant findings (**Fig 6**)
  - No immune cell depletion was detected in blood samples; neutrophils, monocytes, and platelets generally remained within reference ranges

Figure 6. Preliminary Toxicology Data From Cynomolgus Monkeys

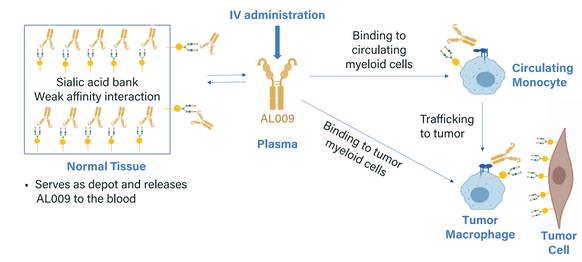
Study Drug Administration	Observations	Chemistry	Hematology
3F Cynomolgus Monkeys AL009 High Dose	None	No remarkable test findings	Mild anemia likely due to phlebotomy



AL009 Proposed Distribution Model

- As shown in the proposed distribution model, AL009 preferentially binds tumor macrophages and circulating monocytes that have the ability to traffic to the tumor (**Fig 7**)

Figure 7. Proposed AL009 Distribution Model



Conclusions

- The engineered Fc portion of AL009 leads to preferential binding to an immunosuppressive subset of myeloid cells
- The specific targeting of AL009 leads to repolarization of myeloid cells and activation of innate and adaptive immunity against tumors
- Pharmacologically relevant doses of AL009 appear well-tolerated in initial non-human primate studies, supporting further development for entry into clinical studies

References

1. Chen et al. *Elife*. 2014
2. Orr, S. J. et al. *Blood*. 2007
3. Rodriguez et al. *Cancers*. 2018
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