Cancer Immunotherapy Targeting CD47: Wild Type SIRPαFc is the Ideal CD47-Blocking Agent to Minimize Unwanted Erythrocyte Binding

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Introduction

- CD47 binds to SIRPα on the surface of macrophages and delivers a “do not eat” signal to suppress phagocytosis.
- Cancer stem cells and bulk tumor cells in acute myeloid leukemia (AML) and other malignancies overexpress CD47 and exploit this pathway to evade macrophage-mediated destruction.
- Blocking CD47 using its soluble ligand (SIRPαFc) or anti-CD47 antibodies has emerged as a promising strategy to neutralize the suppressive effects of CD47 and promote the eradication of tumor cells.
- One concern with CD47 blockade therapies is the expression of CD47 on red blood cells (RBCs), which has the potential to act as a large antigen sink and cause hematological toxicity. Animal experiments in mice have demonstrated successful tumor eradication using high affinity SIRPαFc variants and CD47-specific antibodies.
- In this study, we compared the RBC binding profile of wild type SIRPαFc to other CD47-specific agents.

Blocking the CD47 “Do Not Eat” Signal with SIRPαFc

- SIRPαFc binds to CD47 with nanomolar affinity.
- Blocks the interaction of CD47 with cell surface SIRPα.
- Enables macrophage-mediated killing of tumor cells.
- Exhibits potent in vivo anti-leukemic activity in AML xenograft models.
- Is in pre-clinical development as a therapy for AML.

Wild Type SIRPαFc Binds Very Poorly to Human RBCs Compared to Commercially-Available CD47 Antibodies

The Poor Binding of Wild Type SIRPαFc to RBCs is Specific to Humans

"Pre-clustering" CD47 on Human RBCs Leads to a Dramatic Increase in SIRPαFc Binding

Conclusions

- Wild type SIRPαFc binds very poorly to human RBCs compared to both commercial CD47 antibodies and proprietary CD47-specific agents (mAb and mutant high affinity SIRPαFc).
- Wild type SIRPαFc and CD47 molecules bind similarly to other CD47+ cells (including AML cells), indicating this phenomenon is unique to RBCs.
- The poor binding of SIRPαFc is specific to human RBCs; strong binding in monkey RBCs may overestimate the risk of hematological toxicity seen in non-human preclinical studies.
- The mechanism underlying low RBC binding is unclear, but may relate to the lack of necessity for CD47 on the erythrocyte membrane, and the inability of SIRPαFc to form high affinity clusters.
- Our wild type SIRPαFc fusion is the ideal CD47-blocking agent to reduce the potential RBC sink effect and reverse hematological toxicity.