Novel SIRP Antibodies with Differentiated Characteristics for Targeting Innate Immunity in Cancer

Gabriela Andrejeva, Benjamin J. Capoccia, Michael J. Donio, Ronald R. Hiebsch, Myriam N. Bouchlaka, Robyn J. Puro and Daniel S. Pereira
Arch Oncology, 4340 Duncan Avenue, St. Louis, MO 63110 and 2000 Sierra Point Parkway, Brisbane, CA 94005

P757

Abstract

Background. Unleashing the adaptive immune response from checkpoint blockade has shown therapeutic efficacy in oncology, although in a subset of patients. The ability of innate immune cells to acquire tumor-associated antigen and effectively present it to T cells is fundamental to a successful immune attack on cancer. Macrophage-mediated tumor cell phagocytosis can enact significant tumor clearance. In addition, macrophages represent the most abundant immune cell type in many solid tumors and are often linked to poor prognosis due to the ability of cancer cells to block phagocytosis and manipulate macrophages into facilitating malignant progression. The interaction of tumor CD47 with SIRPα on macrophages, dendritic cells and neutrophils presents such an immune blockade. We have previously presented data on AO-176, a clinical stage humanized anti-CD47 antibody that is highly differentiated among agents in this class of checkpoint inhibitors. We now evaluate a portfolio of novel anti-SIRP antibodies with differentiated properties as another approach to targeting the CD47/SIRPα axis.

Methods. We used solid-phase ELISA and cell binding assays to characterize target binding and blocking by our antibodies. Immunomodulatory effects were tested using *in vitro* phagocytosis, T cell stimulation by allogeneic dendritic cells and antigen-specific T cell assays.

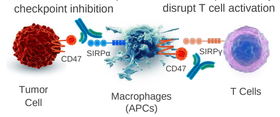
Results. Here we present novel discovery-stage antibodies that either bind human SIRPα variant 1 or both variant 1 and variant 2, the two most common variants in the human population. Our antibodies are unique and differentiated among reported anti-SIRP antibodies in that they induce phagocytosis of several solid and hematologic tumor cell lines as single agents. They also exhibit enhanced phagocytosis when combined with tumor-opsonizing antibodies, including our highly differentiated anti-CD47 antibody, AO-176. Finally, while our antibodies also bind with varying affinity to SIRPγ, they do not block SIRPγ in cell-based assays involving T cells. Consequently, they show no adverse effects on T cell proliferation or activation in allogeneic co-cultures of T cells with dendritic cells, and in a CMV antigen recall response assay.

Conclusions. Our novel anti-SIRP antibodies induce differentiated *in vitro* single agent and combination phagocytosis and show no adverse effects on T cell functionality. These data support their future development, both as single agent antibodies and in combination with other anti-cancer drugs.

SIRP: Important Innate Immune Checkpoint

SIRPα

- Complementary approach to blocking CD47
- Not expressed on RBCs



SIRPγ

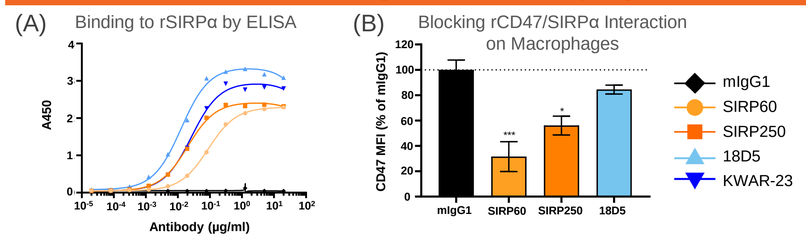
- Expressed on T-cells and activated NK cells, binds CD47 with low affinity
- The CD47-SIRPγ interaction is co-stimulating
- Targeting SIRPγ can modulate T cell activation and proliferation

Overview of Arch Oncology's Anti-SIRP Antibodies

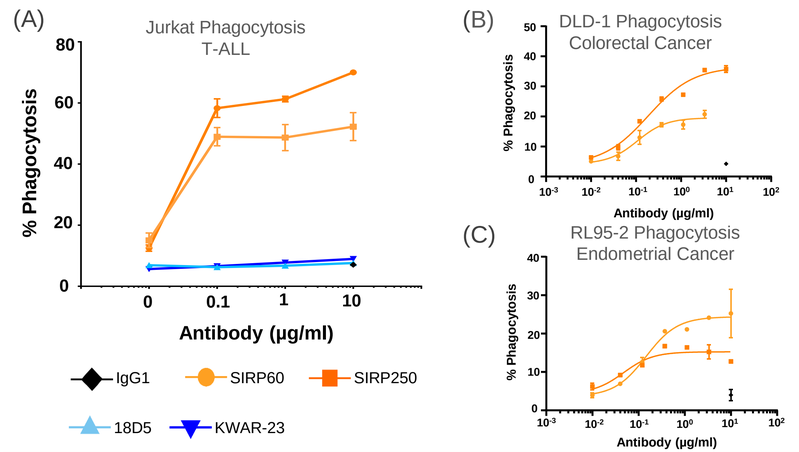
	arch oncology	arch oncology	OSE Immunotherapeutics	FORTY SEVEN
	SIRP60⁺	**SIRP250⁺**	**18D5⁺***	**KWAR-23⁺***
SIRPα Binding	High	High	High	High
SIRPα Variant Specificity#	V1	V1, V2	V1	V1, V2
Blocks cellular SIRPα/rCD47	Yes	Yes	Yes	Yes
Cellular SIRPγ Binding	Yes	No	No	Yes
Blocks cellular SIRPγ/rCD47	No	No	No	Yes
Single Agent Phagocytosis Activity	**Yes**	**Yes**	**No**	**No**
Combination Phagocytosis Activity	Yes	Yes	Yes	Yes
Inhibition of T cell proliferation	No	No	No	Yes

⁺Murine IgG1 antibodies
*Competitor antibodies
V1 and V2 are the two most common variants of SIRPα in human population

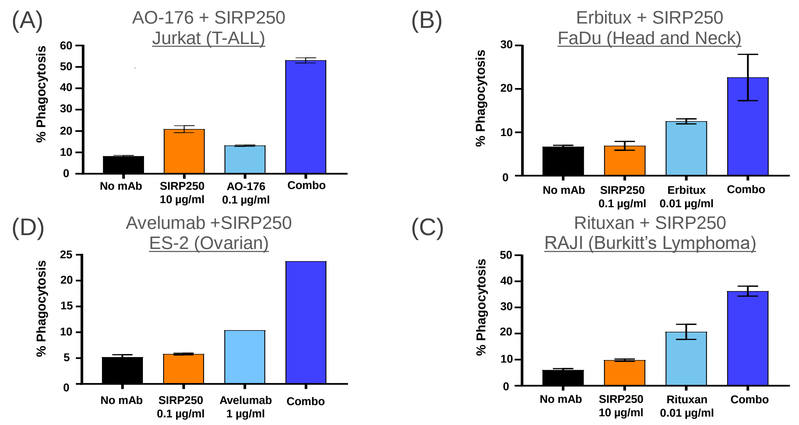
Anti-SIRP Antibodies Bind SIRPα and Block CD47 Binding to Human Macrophages



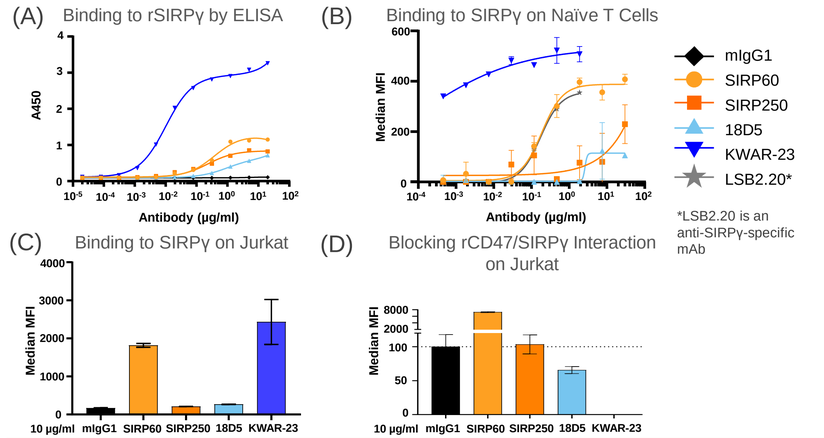
Single Agent Activity: Arch Oncology Anti-SIRP Antibodies Induce Phagocytosis of Multiple Tumor Cell Lines *In Vitro* Unlike Other anti-SIRP Antibodies in Development



Combination Activity: Arch Oncology Anti-SIRP Antibodies Induce Phagocytosis in Combination with Tumor Targeted Antibodies Including anti-CD47 Antibody, AO-176

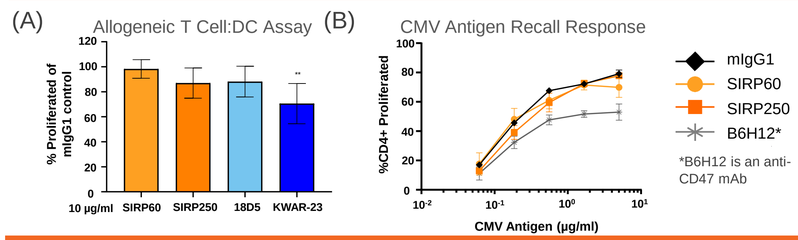


Arch Oncology Anti-SIRP Antibodies Do Not Block T Cell Binding to CD47 Regardless of SIRPγ Binding Potential Unlike Other anti-SIRP Antibodies in Development



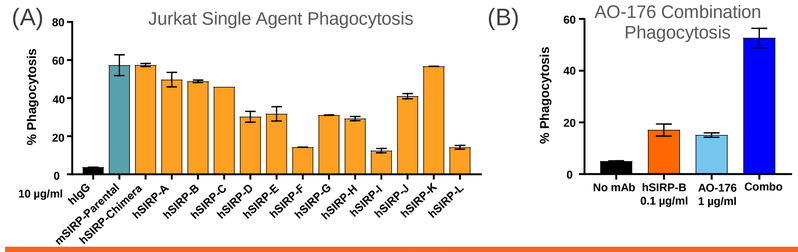
*LSB2.20 is an anti-SIRPγ-specific mAb

Anti-SIRP Antibodies Do Not Inhibit T Cell Proliferation in Allogeneic DC Stimulation or Antigen Recall Response Assays



*B6H12 is an anti-CD47 mAb

Humanized SIRP Antibodies Retain Single Agent and Combination Phagocytosis Induction Properties *In Vitro*



Conclusions

Arch Oncology has generated highly differentiated anti-SIRP antibodies for immuno-oncology:

- **The only anti-SIRP antibodies that exhibit single agent phagocytosis activity**
- **Demonstrate increased activity when combined with tumor-targeted antibodies including AO-176, a highly differentiated anti-CD47 antibody**
- **Show no detrimental effects on T cells**