**Docket #:** S14-258

# Using Bispecific Antibodies to Target Cancer Cells for Phagocytic Removal

Stanford scientists have discovered that bispecific antibodies can selectively bind cancer cells and block the CD47-SIRPα "don't eat me signal" to efficiently clear tumors with negligible toxicity. Developing bispecific antibodies to target cancer cells for phagocytosis can be an innovative method to help eliminate tumors and treat various cancers, such as lymphoma and leukemia.

The interaction between CD47 and SIRPα transmits a "don't eat me signal" that inhibits phagocytosis as a mechanism for the immune system to identify self from non-self. Cancer cells commonly overexpress CD47 to take advantage of this signal and avoid elimination by phagocytosis. Efforts to block CD47 using recombinant variants of SIRPα have been explored as a therapeutic approach to promote the elimination of tumor cells. However, CD47 expression on normal cells serves as an 'antigen sink,' which reduces the efficacy of CD47 blockade and potentially leads to toxicity due to their phagocytosis. Previous studies have shown that therapeutic antibodies that bind tumor antigens to induce phagocytosis are synergistic with CD47 blockage, suggesting that a bifunctional protein that performs these two functions can be a viable option for specifically and efficiently inducing phagocytosis of cancer cells.

Bispecific antibodies designed by the Stanford researchers have low affinity for CD47, rendering them unable to bind normal cells expressing CD47 alone, and high affinity for the tumor antigen CD20, demonstrating selective binding to CD20/CD47 dual antigen-expressing tumor cells. Importantly, the treatment using these bispecific antibodies in mice transplanted or transfused with cancer cells resulted in a significant extension of their survival and depleted target cells in non-human primates with no observed toxicity. Consequently, bispecific antibodies have the potential to improve cancer treatments by targeting tumor cells for phagocytic elimination in patients.

**Figure:**

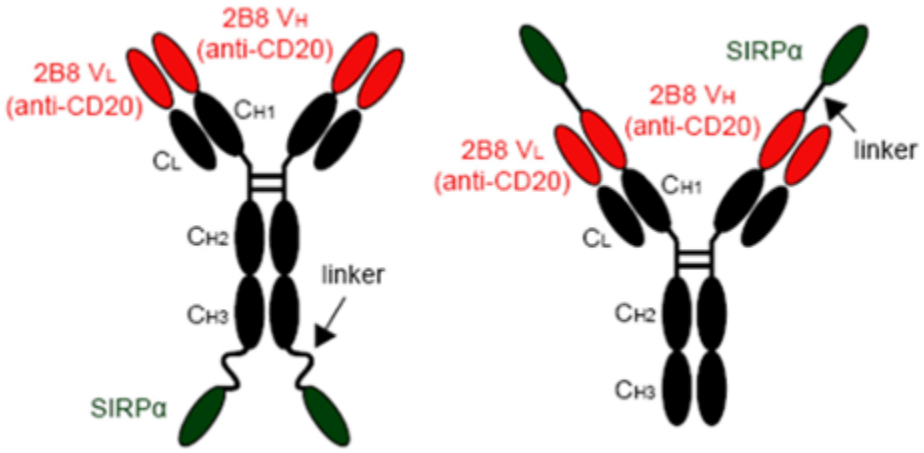



*Figure Description*: A schematic showcasing the design of the CD20/CD47 bispecific antibodies.

**Stage of Development:**
Preclinical – in-vivo

# Applications

- Development of bispecific antibodies to treat cancer
- Elimination of cancer cells in lymphoma and leukemia
- Increasing the efficacy of CD47 blockage by targeting cancer cells for phagocytosis

# Advantages

- Synergizes CD47 blockade with binding to tumor antigens and induction of phagocytosis
- Versatile method that can accommodate the targeting of a plethora of tumor antigens
- Function is confined to a single, bispecific antibody which simplifies formulations

## Publications

- Piccione, E. C., Juarez, S., Tseng, S., Liu, J., Stafford, M., Narayanan, C., ... & Majeti, R. (2016). SIRPα-antibody fusion proteins selectively bind and eliminate dual antigen-expressing tumor cells. Clinical Cancer Research, 22(20), 5109-5119.

## Patents

- Published Application: WO2016022971
- Published Application: 20180030142
- Published Application: 20180355053
- Issued: 10,087,257 (USA)
- Issued: 10,487,150 (USA)

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