Therapeutic potential of AO-176, a next-generation humanized CD47 antibody, for hematologic malignancies

W. Casey Wilson, Myriam N. Bouchlaka, Benjamin J. Capoccia, Ronald R. Hiebsch, Michael J. Donio, Robyn J. Puro, Alun J. Carter, Prabir Chakraborty, Pamela T. Manning, Robert W. Karr, Vicki Sung and Daniel S. Pereira
Arch Oncology, 4320 Forest Park Avenue, St. Louis, MO 63108 and 2000 Sierra Point Parkway, Brisbane, CA 94005

Abstract

Inhibitors of adaptive immune checkpoints have shown promise as cancer treatments. CD47 is an immune checkpoint receptor broadly expressed on normal tissues and overexpressed on several tumors. Binding of CD47 to signal regulatory protein-α (SIRPα) by macrophages and dendritic cells triggers a “don’t eat me” signal that inhibits phagocytosis enabling escape of immune surveillance. Blocking CD47/SIRPα interaction promotes phagocytosis reducing tumor burden in numerous xenograft and syngeneic animal models.

We have developed a next generation humanized CD47 antibody, AO-176, that not only blocks the CD47/SIRPα interaction and induces phagocytosis of hematologic and solid tumor cells, but also exhibits several unique functional properties. The first property is the ability of AO-176 to induce direct tumor cell killing. Recently, Raji, K562 and MOLT-4 as well as solid human tumor cell lines by a cell autonomous mechanism (not ADCC). Secondly, AO-176 exhibits preferential binding to tumor cells, normally including red blood cells (RBC), endothelial cells, skeletal muscle cells and epithelial cells. AO-176 also does not affect the function of any of these primary cells when assessed as an agonist. The second property is its enhanced binding to various hematologic (J raj & MOLT-4) or solid tumor (AO-176) cells is particularly profound and different from other reported anti-CD47 antibodies. AO-176 also does not induce hemagglutination of RBCs. These properties are expected not only to decrease the antigen sink, but also to minimize off-target clinical adverse effects observed following treatment with other reported BSC binding anti-CD47 antibodies. Consistent with this attribute, AO-176 was virus and highly efficacious in vivo experiments.

Together, the unique properties and anti-tumor activity of our next generation anti-CD47 antibody, AO-178, distinguishes it from other CD47/CD163/CD164 targets acting as a potent agent in preclinical development.

AO-176: A Next-Generation Humanized anti-CD47 mAb

- Blocks CD47/SIRPα interaction to induce phagocytosis of tumor cells
- Selectively and potently binds to human CD47 on tumor cell lines
- Reduced binding to normal cells, negligible binding to human RBC, no hemagglutination
- Greater binding affinity at acidic pH
- Direct killing of tumor cells (non-ADCC) via a Programmed Cell Death Type III mechanism and immunocytotoxic cell death
- Anti-tumor activity in human xenograft models
- Promotes immune cell recruitment and release of cytokines and chemotactic factors

AO-176 Induces Phagocytosis of Hematologic and Solid Tumor Cells

AO-176 Preferentially Binds Tumor vs. Normal Cells With Negligible Impact on Red Blood Cells and Normal Cells

AO-176 Binding of CD47 and Direct Killing Activity Increases at Acidic pH

AO-176 Inhibits Hematological Tumor Growth In Vivo And Promotes Macrophage/Dendritic Cell Recruitment and Cytokine Induction

Conclusions

AO-176 is a next-generation CD47 antibody that is differentiated from current clinical agents targeting the CD47 axis as follows:

- AO-176 efficiently induces phagocytosis of a variety of hematologic and solid tumor cell lines and direct killing activity
- AO-176 demonstrates preferential binding to tumor versus normal cells, especially RBCs
- AO-176 shows enhanced binding and function at acidic pH levels seen in the tumor microenvironment, a potential mechanism for enhanced tumor targeting
- AO-176 has shown significant tumor growth inhibition in vivo, likely driven by recruitment of macrophages and DCs

Recruitment of these innate immune cells leads to the release of cytokines and chemokines within the tumor microenvironment that may aid in tumor efficacy.

AO-176’s unique killing profile coupled with phagocytosis induction and preferential binding to tumor versus normal cells suggest that AO-176 will have an improved therapeutic index compared to current clinical candidates.