CD47 mAb SRF231 is a Potent Inducer of Macrophage-mediated Tumor Cell Phagocytosis and has Anti-tumor Activity in Preclinical Models

Alison M. Paterson1, PhD, Andrew C. Lake1, PhD, Caroline M. Armet, BS1, Rachel W. O’Connor1, BS, Jonathan A. Hill1, PhD, Emmanuel Normant1, PhD, Ammar Adam1, DVM, Detlev Biniszkiewicz1, PhD, Scott C. Chappel1, PhD, Vito J. Palombella, PhD3, Pamela M. Holland1, PhD
1Surface Oncology, 215 First Street, Cambridge, MA 02142, USA

BACKGROUND

CD47 is a broadly expressed cell surface protein that is over-expressed by multiple tumor types.1,2 CD47 acts as a macrophage chaperone (often referred to as a “do not eat me” signal). CD47 has multiple binding partners (Figure 1) and negatively regulates phagocytosis by interacting with the macrophage inhibitory receptor signal regulatory protein alpha (SIRPα).3,4 Agents that block the CD47-SIRPα interaction have therapeutic potential in that they restore phagocytic uptake of CD47+ tumor cells in vitro and attenuate tumor growth in vivo.

Here we characterize SRF231, one of a panel of fully human CD47 antibodies, and demonstrate that it exhibits the desired criteria for clinical development.

SRF231 BALANCES MINIMAL RBC EFFECTS WITH POTENT TUMOR CELL PHAGOCYTOYSIS

Effects on red blood cells

- CD47 is expressed on red blood cells (RBC) and regulates RBC clearance.
- Several anti-CD47 antibodies increase RBC phagocytosis and aggregation (hemagglutination).
- SRF231 displays no enhancement of RBC phagocytosis or aggregation in vitro (Figure 3).

Tumor cell phagocytosis

- Tumors evade innate immune system by over expressing CD47.
- SRF231 binding of CD47 targets tumor cells for phagocytosis and destruction.
- SRF231 enhances in vitro phagocytosis of primary tumor cells and tumor cell lines (Figure 4).

SRF231 TREATMENT LEADS TO MACROPHAGE ACCUMULATION IN TUMORS

- Macrophage accumulation observed in tumors from mice treated with SRF231.
- Immunohistochemistry (IHC) stains utilized to analyze the M1 (NOS) and M2 (CD163) balance of the myeloid cells.
- Tumors from SRF231-treated mice display increase in NOS/CD163 ratio.

SRF231 COOPERATES WITH ANTI-CD20 ANTIBODY

- Rituximab leads to depletion of CD20+ cells via both antibody-dependent cellular cytotoxicity (ADCC) and cellular phagocytosis (ADCP).
- Combination of SRF231 and anti-CD20 results in dramatic reduction in tumor burden and enhanced tumor clearance.
- Combination in vitro leads to higher levels of phagocytosis than either agent alone.

CONCLUSIONS

- SRF231 is a high affinity, fully human antibody against human CD47.
- SRF231 promotes robust tumor cell phagocytosis without inducing RBC phagocytosis or hemagglutination in vitro.
- SRF231 shows potent in vivo anti-tumor efficacy in preclinical models, either as monotherapy or in combination settings.
- SRF231 is currently in IND-enabling studies and is expected to enter clinical trials in 2017.

Table 1: Biacore analysis of the interaction between SRF231 and human CD47

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Analyte</th>
<th>Kd (M)</th>
<th>Assay Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human CD47-Fc</td>
<td>SRF231 Fab</td>
<td>8.256x10⁻⁹</td>
<td>Immobilized antigen + SRF231</td>
</tr>
<tr>
<td></td>
<td>SRF231 mAb</td>
<td>1.10x10⁻¹</td>
<td>+ SRF231</td>
</tr>
</tbody>
</table>

Figure 1: CD47 regulates the interaction between tumor cells and macrophages

CD47 is a type I integral membrane protein with one extracellular immunoglobulin variable-like domain and five membrane-spanning segments. CD47 takes part in several cis and trans interactions, including with integrins, thrombospondin-1, SIRPα (not shown) and SIRPβ1. Engagement of SIRPβ1 by CD47 leads to inhibition of macrophage-mediated phagocytosis. By targeting CD47 with SRF231, phagocytosis of tumor cells can be restored.

References