“MBL-associated serine proteases”

Three MASP can form complexes with five possible pattern recognition molecules

Serine protease with pattern binding potential

Lectins, via carbohydrate recognition domains (CRD), bind molecular patterns on microbes or damaged/altered host tissue

Inhibitors expected to have broad applications in conditions involving inflammation and tissue damage
Targeting MASP Proteins

MASP Inhibitory MAb Programs

- **MASP-2 Inhibitor**: Narsoplimab
- **MASP-3 Inhibitor**: OMS906

The MASP inhibitor approach **preserves** classical pathway function

- LECTIN PATHWAY
  - Blocked Upstream
- ALTERNATIVE PATHWAY
  - Blocked Upstream
- CLASSICAL PATHWAY
  - Intact
Role of MASP-3 in AP Activity of Human Serum

MASP-3 Deficient Individual

- No protein
- + rMASP-3 (full-length)
- + rMASP-3A (catalytic mutant; full-length)

MAKP-1/3 Deficient Individual

- Rxn time = 0 min
- Rxn time = 15 min
- Rxn time = 45 min

Presence of MASP-3 is required to drive AP in human serum
Three Pathways of Complement

### Classical Pathway
- Immune complex
  - C1r/C1s
  - C4 + C2
  - CP/LP C3 convertase
    - C3
    - C3b
    - C5
    - C5b
    - Cell lysis

### Lectin Pathway
- Tissue injury
  - MASP-2
  - CFB
  - C6-9
  - MAC

### Alternative Pathway
- Immune complex
  - C1r/C1s
  - C4 + C2
  - AP C3 Convertase
    - C3b
    - Bb
    - AP C5 convertases
    - C5
    - C5b
    - C6-9
    - MAC

#### Anaphylatoxins
- C3a
- C5a

#### Opsonization and Phagocytosis
- Opsonization and Phagocytosis

#### Inflammation and Leukocyte Recruitment
- Inflammation and Leukocyte Recruitment
Three Pathways of Complement

Immune complex

C1r/C1s

C1r/C1s + C2 → CP/LP C3 convertase

Tissue injury

MASP-2

MASP-3

C4 + C2 → AP C3 Convertase

C3b

C3b

C3

C4

C2

C3

C5

C3b

Bb

Ba

C3b

C5

C5 convertases

Relative Concentration

- CFD: 1.6 -fold
- CFB: 50 -fold
- C3: 7 -fold
- C5: 98 -fold
- C5: 6 -fold

Normal Serum

MASP-1/3 Def

MASP-3 Def

Normal Serum

Pro-CFD

Mature CFD
Properties of OMS906

OMS906

Humanized monoclonal antibody highly potent and selective for MASP-3

Infrequent SubQ Administration

Convenient dosing regimen allows self-administration in an outpatient setting

OMS906 is designed to treat multiple alternative pathway-driven diseases with infrequent, SubQ delivery

Phase 1 clinical trial initiated 3Q 2020
CFD is matured by cleavage and release of activation peptide on the N-terminus of the protein.

CFD is present in plasma as pro-CFD following single dose of OMS906.
CFD status (pro vs. mature) can be used as direct measurement of MASP-3 inhibition.
OMS906 blocks systemic maturation of CFD and results in accumulation of Pro-CFD.

**Measurement of CFD Status**

**Single-Dose Monkey Study**

- **Mature CFD**
- **Pro CFD**

**Graph**

- CFD (μg/mL) vs. Time (days)
- Key:
  - Mature CFD
  - Pro CFD
Inhibition of the Alternative Pathway in Monkey

Number of Days of ≥ 90% Alternative Pathway Inhibition

<table>
<thead>
<tr>
<th>Bb Deposition on Zymosan</th>
<th>Fluid-Phase Ba</th>
<th>Hemolysis of Rabbit RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

Single dose is sufficient for sustained inhibition of the Alternative Pathway in monkey
Lowest levels of detectable mature CFD correlate with complete inactivation of the AP
Demonstration of Efficacy in Mouse Disease Models

- **In vivo** induction of AP with LPS
  - OMS906 decreases systemic BA levels caused by LPS injection into mice

- Collagen antibody-induced arthritis (CAIA) model
  - OMS906 decreases severity (and incidence) of arthritis

Systemic inhibition of CFD maturation is sufficient to block in vivo AP
OMS906 Potential in Paroxysmal Nocturnal Hemoglobinuria
Paroxysmal Nocturnal Hemoglobinuria (PNH) is a Rare, Chronic, Life-Threatening Complement-Mediated Blood Disorder

PNH is characterized by intravascular and extravascular hemolysis

Unmet Need Persists

~70%

of PNH patients continue to have low hemoglobin levels while on a C5 inhibitor\(^1,2\)

~1/3

of PNH patients require one or more transfusions a year while on a C5 inhibitor\(^3\)

Red Blood Cell Clearance in PNH

Intravascular Clearance

Extravascular Clearance

C5 MAb

OMS906

Phagocytic Cell
Demonstration of Efficacy in PNH Models

- **In vitro** destruction of human “PNH-like RBCs” (sensitized with αCD55/59 Abs)
  - Hemolysis
  - Opsonization (C3b/iC3b and C3d deposition)

- **In vivo** clearance of RBCs (Crry-/ mouse RBCs)
  - Primarily model of extravascular pathway of clearance
Red Blood Cell Clearance in PNH

- **Intravascular Clearance**
- **Extravascular Clearance**

Hemolysis → C3 Deposition → RBC Lysis

- C3 Deposition

Cellular Granularity

C3d Deposition

OMEROS
Model of Intravascular Lysis of PNH RBCs: Comparison with C3 and C5 Inhibitor

OMS906 demonstrates greater potency and greater degree of pathway inhibition than C5 mAb

<table>
<thead>
<tr>
<th>Relative Potency</th>
<th>OMS906</th>
<th>Compstatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5 MAb</td>
<td>~30-fold</td>
<td>~1000-fold</td>
</tr>
</tbody>
</table>

OMS906 vs. C5 and C3 Inhibitors

OMS906 (Donor 1) - Blue circles
OMS906 (Donor 2) - Green circles
C5 mAb (Donor 1) - Red squares
C5 mAb (Donor 2) - Orange squares
Compstatin (Donor 1) - Pink diamonds
Compstatin (Donor 2) - Green triangles

% Hemolysis vs. Inhibitor (nM)
Comparison to C3 and C5 Inhibition for PNH

OMS906 blocks a shared step in both pathways of PNH RBC clearance.

- C3b/iC3b Deposition
- Intravascular Clearance
- Extravascular Clearance

- 1 hr incubation
- 2 hr incubation
- 3 hr incubation

- OMS906 (15 μg/mL)
- C5 mAb (270 μg/mL)
- Compstatin (100 μg/mL)
- Iso Control (15 μg/mL)
Donor RBCs Survival

Cryr-/- RBC Survival

- OMS906 (5 mg/kg)
- Anti-FB (~40 mg/kg)
- Anti-C5 (~30 mg/kg)
- Isotype (5 mg/kg)
- Vehicle

- Anti-FB Dose (IP)
- OMS906 Dose (SC)

Time (days)

RBCs (per 100,000 events)
Potent inhibition of the alternative pathway

Classical pathway left intact

Treats both intravascular and extravascular hemolysis

Broad applications in conditions involving inflammation and tissue damage

Phase 1 (SAD/MAD) clinical program enrolling

Targeting monthly subcutaneous dosing