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Alternative Pathway MASP-3 Inhibitor OMS906 Effectively and Potently Inhibits Complement-Mediated Hemolysis in Preclinical Models Mechanistically Similar to Paroxysmal Nocturnal Hemoglobinuria

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BACKGROUND

- MASP-3 is the proteolytic activator of pro-CFD, cleaving it to form mature CFD, a rate-limiting enzyme in the alternative pathway of the complement system[1] (**Figure 1**)
  - CFD controls cleavage of CFB to form alternative pathway C3 convertase, which drives an amplification loop that drives both C3b-mediated opsonization and terminal pathway activation[1,2]
- OMS906 is a humanized IgG4 mAb that binds to and inhibits MASP-3, thereby blocking maturation of CFD and downstream alternative pathway activity[3,4]
  - Data from mice and monkeys demonstrated that OMS906 is highly selective for MASP-3 and effectively inhibits alternative pathway activity[3]
- MASP-3 inhibition could provide therapeutic benefit in a variety of alternative pathway-mediated diseases, such as PNH[1,2]
  - In PNH, a rare and life-threatening disorder, RBCs lacking CD59 and CD55 regulatory surface proteins are targeted for rapid clearance via intravascular hemolysis and extravascular hemolysis due to alternative pathway dysregulation[5-7]
  - Clinical efficacy of OMS906 in a proof-of-concept study in patients with PNH has been reported[8,9]

OBJECTIVE

To provide mechanistic support for OMS906 in PNH using preclinical models of complement-mediated hemolysis that have mechanistic overlap with PNH

CONCLUSIONS

- *In vitro*, OMS906 inhibited PNH-like RBC lysis, providing evidence that MASP-3 inhibition blocks downstream terminal activity and thus intravascular hemolysis in PNH
  - OMS906 exposure also blocked alternative pathway-mediated C3b/iC3b/C3d deposition, providing support that MASP-3 inhibition prevents extravascular hemolysis associated with C5 inhibition in PNH
- *In vivo*, OMS906 improved survival of Crry$^{-/-}$ RBCs comparably to a CFB inhibitor, demonstrating that MASP-3 inhibition prevents the alternative pathway-mediated destruction of RBCs predictive of extravascular hemolysis
- As an upstream inhibitor, OMS906 is predicted to block intravascular hemolysis and, unlike C5 inhibitors, to prevent extravascular hemolysis in PNH[7]
- OMS906 is currently in clinical development for the treatment of PNH (NCT05889299; NCT05972967)[4,8–11]
  - Preliminary efficacy data from a treatment-naïve PNH patient population indicate that OMS906 prevents hemolysis, as supported by these preclinical data[8,9]
- OMS906, an antibody against MASP-3, demonstrates inhibition of the alternative pathway that underlies RBC destruction in PNH

Figure 1. MASP-3 is a Key Activator of the Alternative Pathway and a Novel Target for Treatment of PNH[1,2]

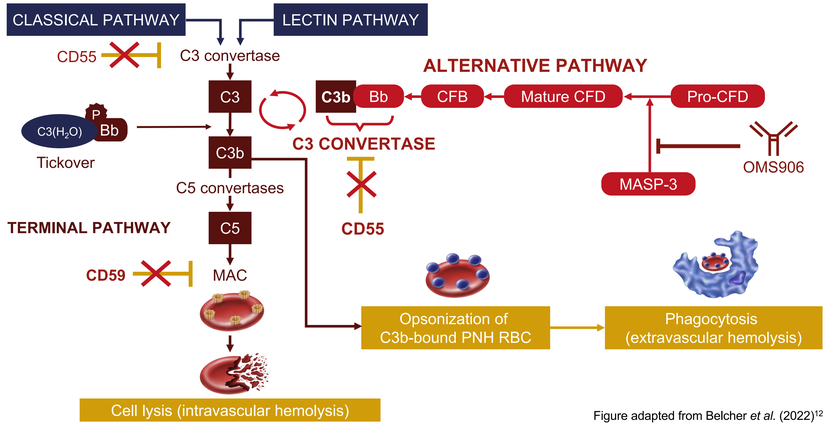


Figure adapted from Belcher *et al.* (2022)[12]

METHODS

In vitro

- The potency of OMS906 was assessed *in vitro* using RBCs deficient in CD55 and CD59 to mimic the physiological effects of PNH (ie, intravascular and extravascular hemolysis)
- Healthy human donor RBCs were treated with inhibitory CD55 and CD59 antibodies, then incubated under alternative pathway assay conditions with human serum (diluted to 50%) containing OMS906, anti-C5 IgG4 mAb, or an isotype mAb control
  - CFD-depleted serum was spiked with recombinant human pro-CFD to measure the effect of MASP-3 on conversion of pro-CFD to mature CFD
- The potency of OMS906, expressed as the IC_{50}, was assessed based on prevention of hemolysis of the PNH-like RBCs *in vitro*
  - Lysis was quantified by measuring hemoglobin released into sample supernatants using spectrophotometric absorbance
- The effect of OMS906 on inhibition of opsonization was assessed based on deposition of C3b cleavage products iC3b and C3d on the PNH-like RBCs
  - Opsonization was quantified by measuring fluorescently-labeled C3b-positive or C3d-positive cells relative to total number of live RBCs using flow cytometry

In vivo

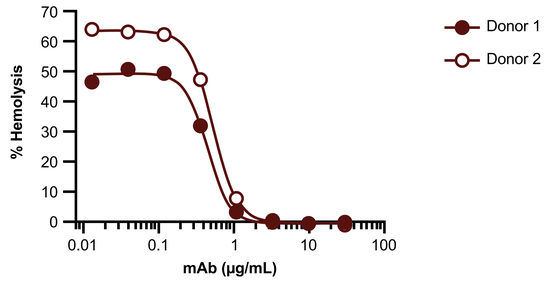
- The *in vivo* effect of OMS906 on survival of murine RBCs prone to rapid clearance was assessed using RBCs from Crry$^{-/-}$ mice, which lack a rodent-specific complement regulatory protein that blocks alternative pathway activation
- C57BL/6J male mice were intravenously injected with fluorescently labelled Crry$^{-/-}$ RBCs and received OMS906 or isotype mAb control via subcutaneous injection, or anti-CFB mAb or anti-C5 mAb via intraperitoneal injection
- Blood samples were taken daily until Day 14 and the remaining number of Crry$^{-/-}$ RBCs measured by flow cytometry

RESULTS

In vitro

- OMS906 inhibited terminal cell lysis in human PNH-like RBCs (**Figure 2**)
- Comparison of OMS906 concentration–response showed that the average functional potency (IC_{50}) was 0.5 µg/mL (~3nM)

Figure 2. Concentration-Effect Profile for Inhibition of Lysis of PNH-Like RBCs



- OMS906 exposure resulted in inhibition of opsonization in PNH-like RBCs (**Figure 3**)
- As expected, a C5 terminal complement inhibitor did not block alternative pathway-mediated opsonization compared with OMS906
- OMS906 prevented hemolysis without increasing opsonization (**Figure 4**)
- C5 inhibition decreased hemolysis with an increase in opsonization

Figure 3: C3d deposition on PNH-like RBCs treated with OMS906 and C5 mAb

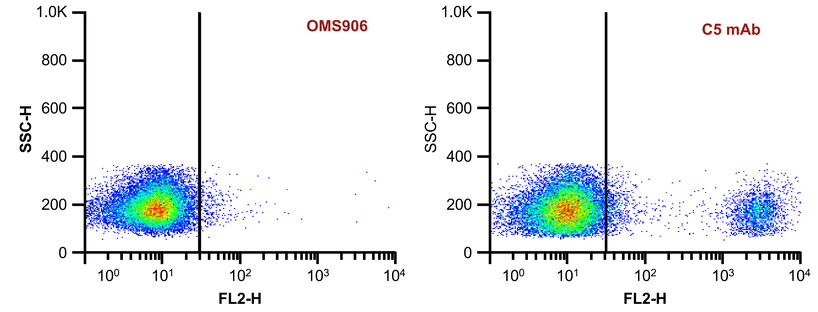
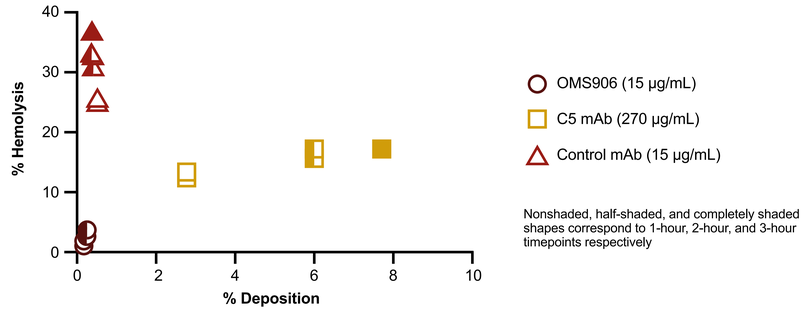


Figure 4: Time Course of Lysis and C3d Deposition at Maximally Effective Drug Concentrations

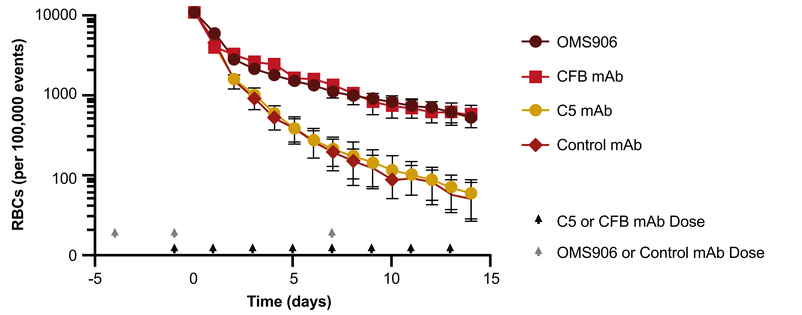


Nonshaded, half-shaded, and completely shaded shapes correspond to 1-hour, 2-hour, and 3-hour timepoints respectively

In vivo

- The rate of decline in number of Crry$^{-/-}$ RBCs was significantly slowed in mice treated with OMS906, in contrast to the rapid loss observed in isotype mAb control-treated and C5 terminal inhibitor-treated mice (**Figure 5**)
- OMS906 administration exhibited a rate of Crry$^{-/-}$ RBC survival comparable to the anti-CFB mAb group, but with less frequent dosing

Figure 5. Survival of Crry$^{-/-}$ RBCs in Mice Treated with OMS906, Anti-CFB mAb, Anti-C5 mAb, or Control mAb (Mean±SEM)



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ABBREVIATIONS

CFB, complement Factor B; CFD, complement Factor D; Crry, complement receptor 1-related gene y; IC_{50}, half-maximal inhibitory concentration; mAb, monoclonal antibody; MAC, membrane attack complex; MASP-3, mannan-binding lectin-associated serine protease-3; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SEM, standard error of the mean.

DISCLAIMER

- OMS906 is an investigational agent and has not been approved by any regulatory agency

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