Characterization of Orally Bioavailable Small Molecule Inhibitors of Complement C5

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Ra Pharma®

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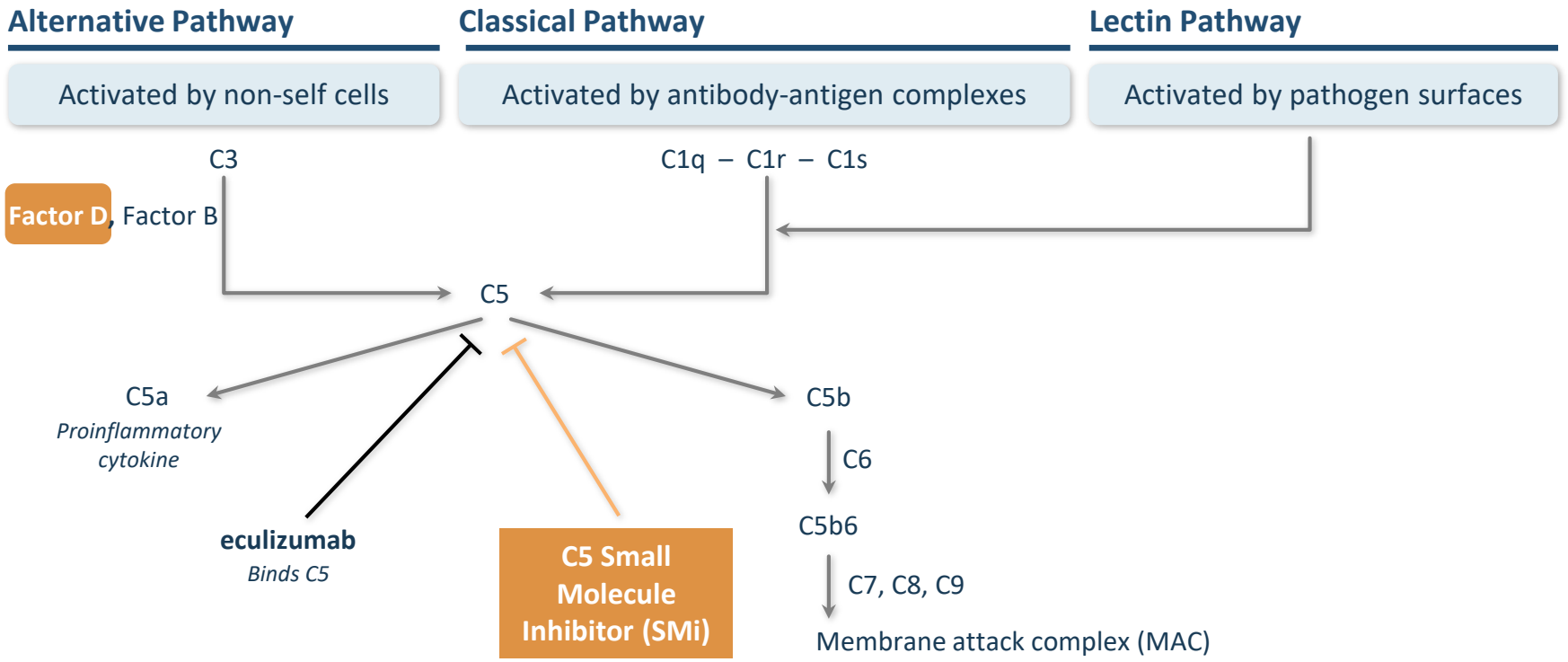
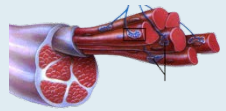
Complement C5: A Central Target for the Therapeutic Intervention of Complement Mediated Disorders



Multiple Indications

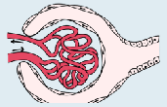
PNH: rupture of RBC

gMG: destruction of neuromuscular junction



aHUS: hemolytic anemia, thrombocytopenia, and renal failure

LN: inflammation of kidney glomerulus



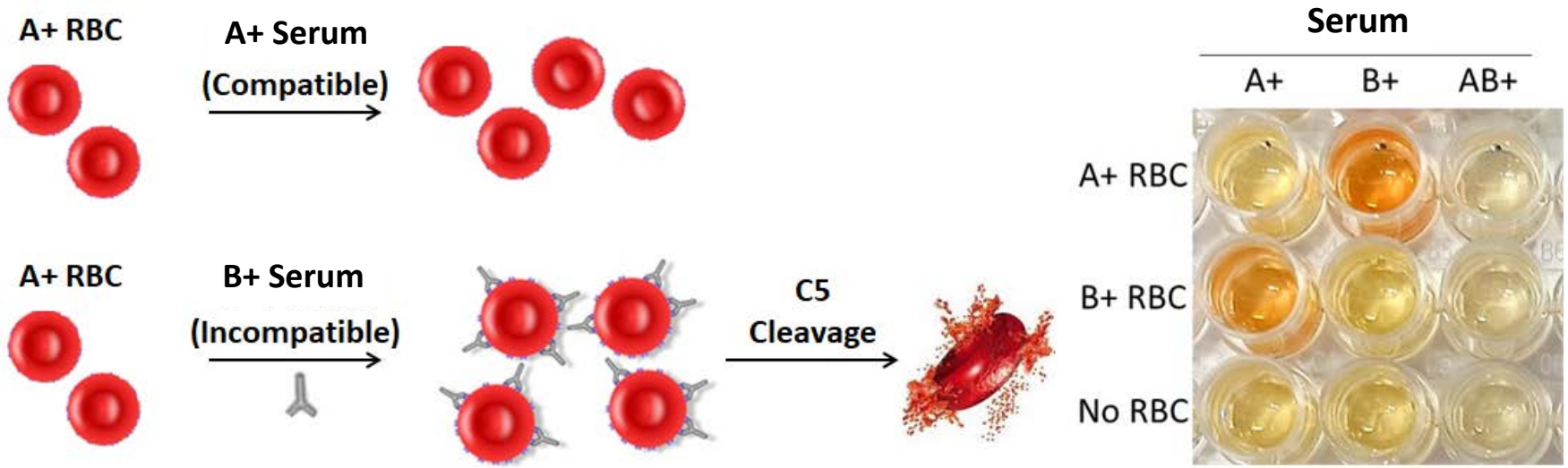
Properties of Small Molecule Inhibitors (SMi) of Complement C5

- SMi bind to cryptic site on C5 and prevent cleavage into C5a and C5b
- SMi block C5 activation by classical/lectin pathway and alternative pathway convertases; also prevents fluid phase C5 activation by Cobra Venom Factor
- SMi exhibit desirable drug-like properties

Property	Compound A	Compound B
Binding Affinity (K_D)	24 nM	2.5 nM
Solubility (pH 7.4)	~0.4 mM	~0.5 mM
EPSA	79	77
MW	~500	~500
HBD+HBA	5	5
CLogP	2.8	3.4
tPSA	80	72

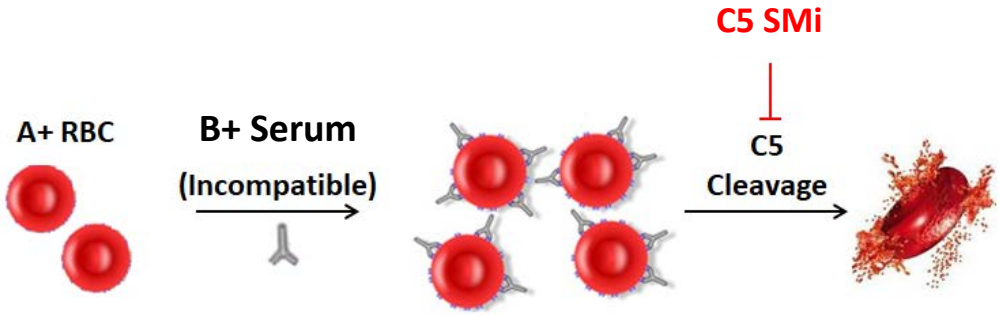
MAC-Driven Endpoint: ABO Mismatch Hemolysis Assay (90% Human Sera)

- Modeling incompatible transfusion reaction that causes intravascular hemolysis of donor erythrocytes
- Antibodies present in serum of donor cause strong and acute activation of classical cascade resulting in C3 deposition on RBC and MAC formation

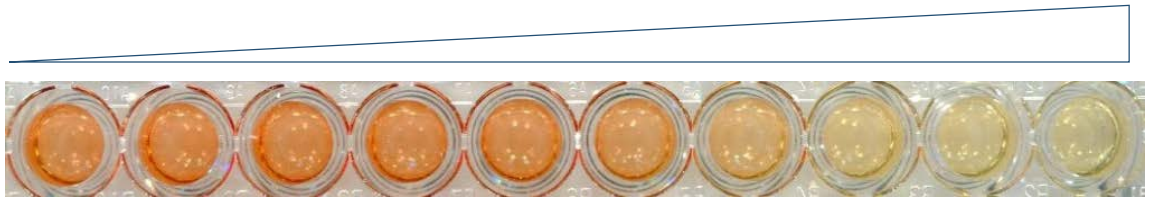


MAC-Driven Endpoint:
ABO Mismatch Hemolysis Assay (90% sera)

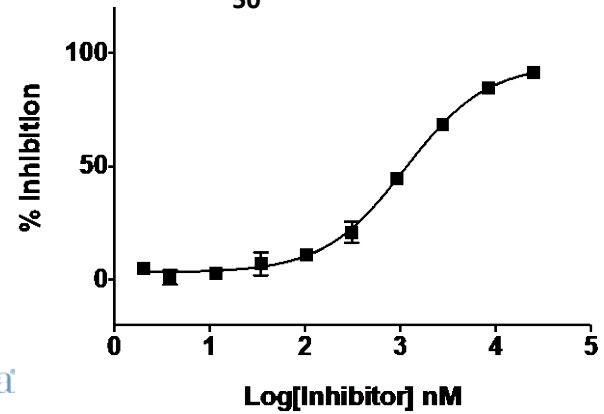
Potent SMi achieve full inhibition of MAC driven hemolysis



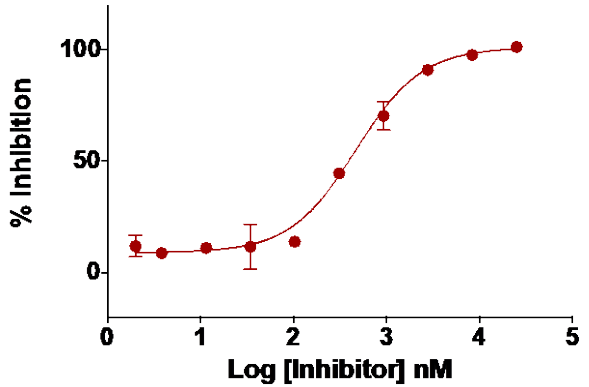
Compound B – Dose dependent response



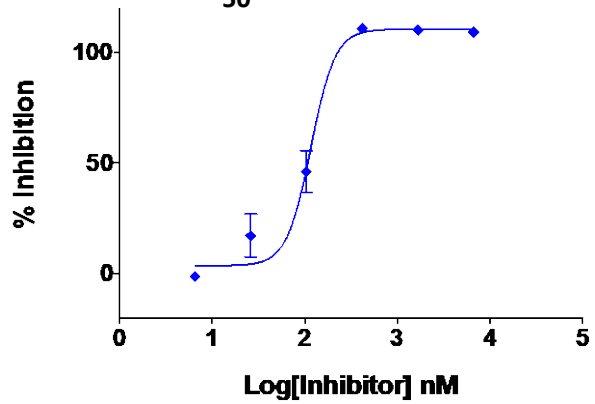
Compound A
IC_{50}: 1250 nM



Compound B
IC_{50}: 420 nM



Eculizumab (bivalent binder)
IC_{50}: 115 nM



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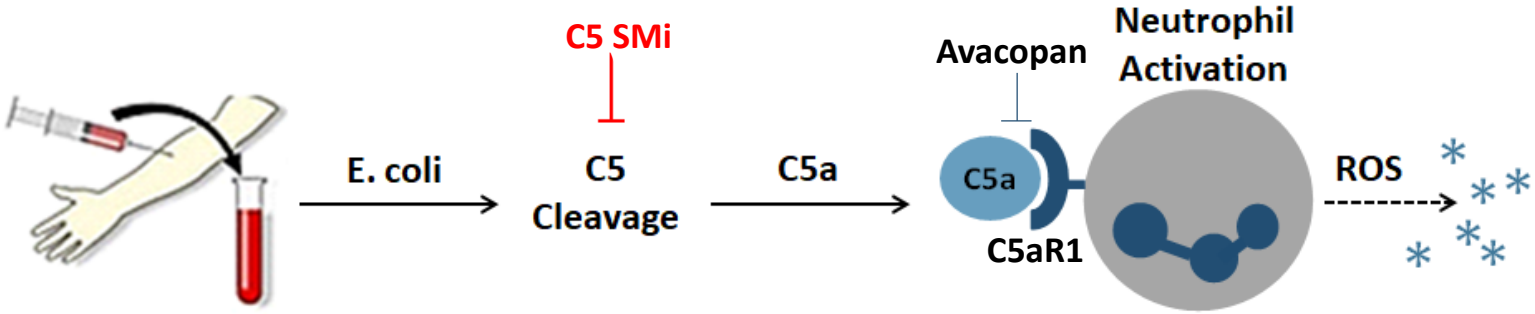
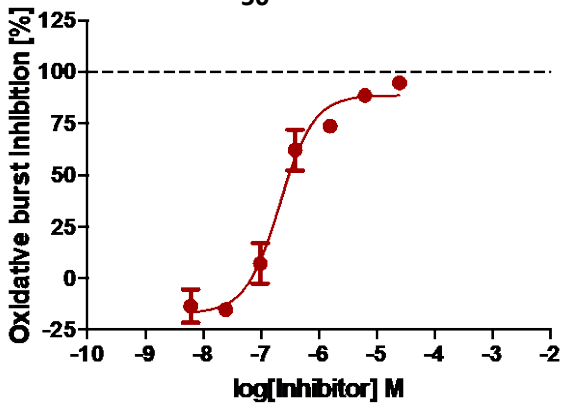
C5a-Driven Endpoint: Whole Blood Neutrophil Oxidative Burst

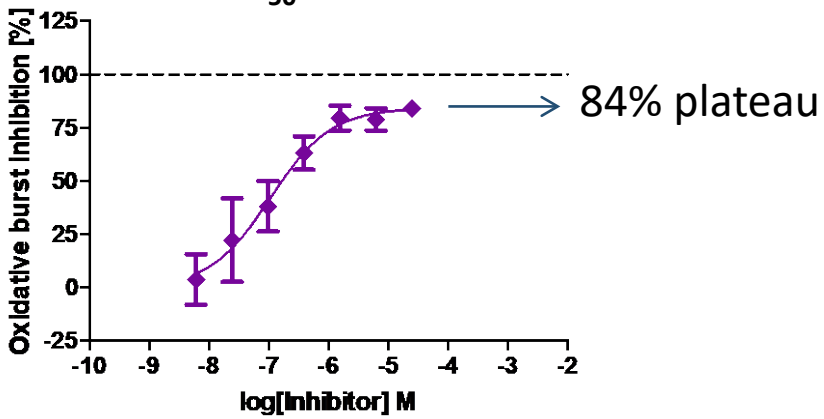
SMi compare favorably to C5aR1 antagonists in a bacterial complement-dependent neutrophil activation assay



Compound B
IC_{50}: 313 nM



Avacopan
IC_{50}: 112 nM

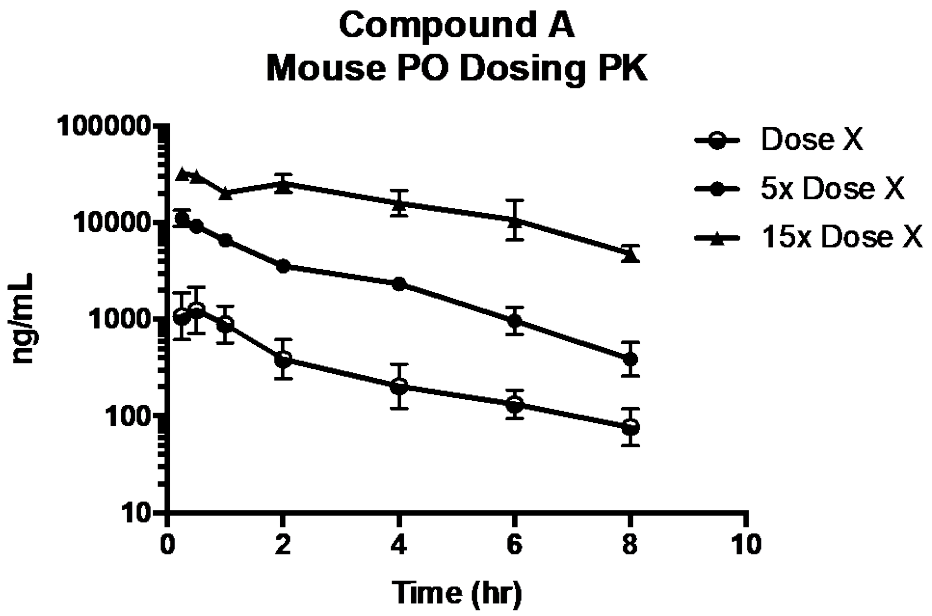


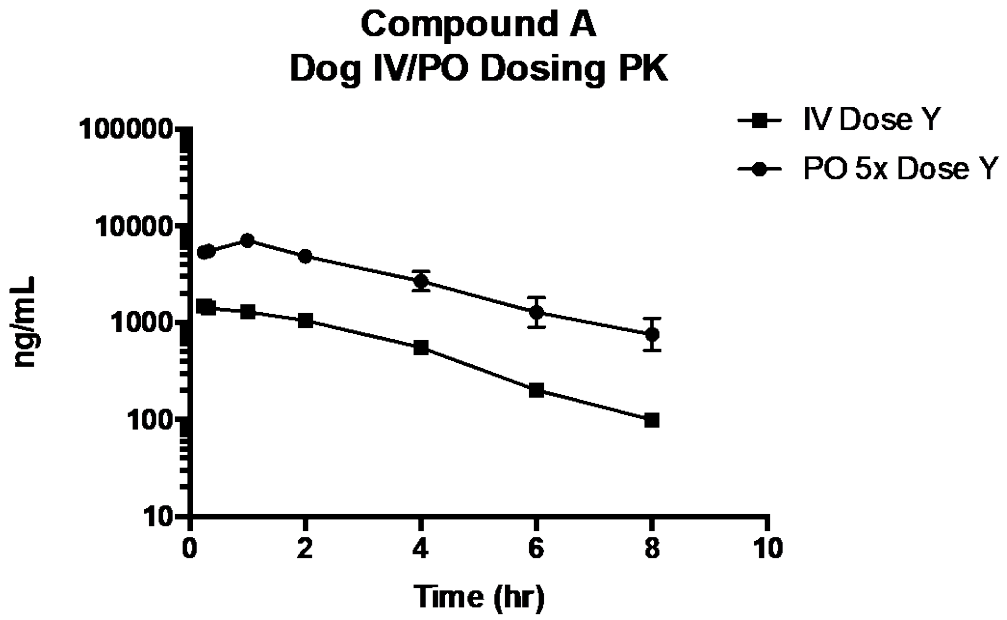
* 100% defined as response to Eculizumab at 2.85µM

Dose-Proportional Pharmacokinetics Observed in Lead Compound Series

In vivo DMPK (Mouse and Dog)

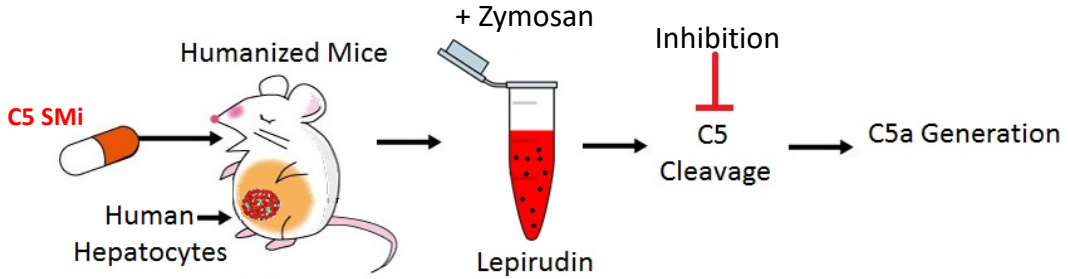
- Pharmacokinetics characterization in different species demonstrates dose-proportional exposure
- Excellent bioavailability after oral dosing across species



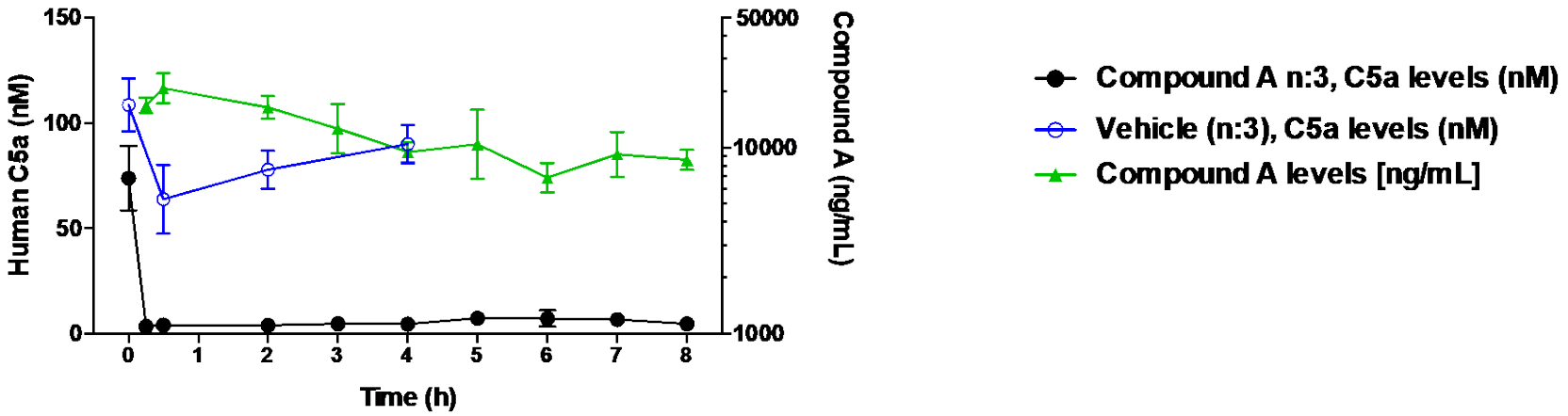


Humanized Liver Mouse Model: Inhibition of Complement C5 Following Oral Dosing

- SMi do not bind to mouse complement C5
- Immunodeficient mice transplanted with human hepatocytes provide circulating human complement



- Oral dosing of SMi results in full blockade of ex-vivo zymosan-mediated C5 activation (incubation in whole blood)



Summary: First-in-class Complement C5 SMi

- Exhibit favorable drug like properties and are orally bioavailable
- Demonstrated efficacy in rigorous, whole blood *ex vivo* models of complement activation
  - MAC mediated hemolysis: Potential use in PNH, aHUS, and MG
  - C5a mediated neutrophil oxidative burst: Potential use in ANCA vasculitis, neutrophilic dermatoses, inflammatory diseases
- Exhibit dose proportional exposure upon oral dosing and are highly bioavailable via this route in multiple preclinical species
- Oral dosing results in complete inhibition of complement C5 in humanized mouse model (evaluated using whole blood)
- GLP toxicology studies supporting initial evaluation in man to be completed by 1H19