Ra Pharma

Discovery of Orally Bioavailable Small Molecules for Inhibition of Complement C5

22nd Congress of the European Hematology Association

Madrid, Spain

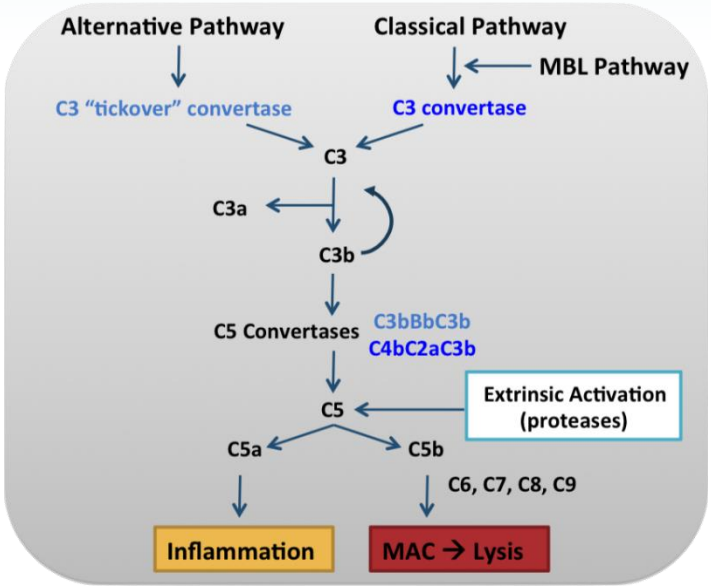
June 24, 2017

Forward Looking Statements

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the data on our preclinical program on orally bioavailable small molecules for inhibition of complement C5. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include the risks that Ra Pharma's product candidates, including RA101495, will not successfully be developed or commercialized; the risk that the results of preclinical studies may not be indicative of the results of clinical studies; as well as the other factors discussed in the "Risk Factors" section in Ra Pharma's most recently filed Annual Report on Form 10-K, as well as other risks detailed in Ra Pharma's subsequent filings with the Securities and Exchange Commission. There can be no assurance that the actual results or developments anticipated by Ra Pharma will be realized or, even if substantially realized, that they will have the expected consequences to, or effects on, Ra Pharma. All information in this presentation is as of the June 24, 2017, and Ra Pharma undertakes no duty to update this information unless required by law.

Complement Component 5: A Central Target for the Therapeutic Intervention of Complement Mediated Disorders

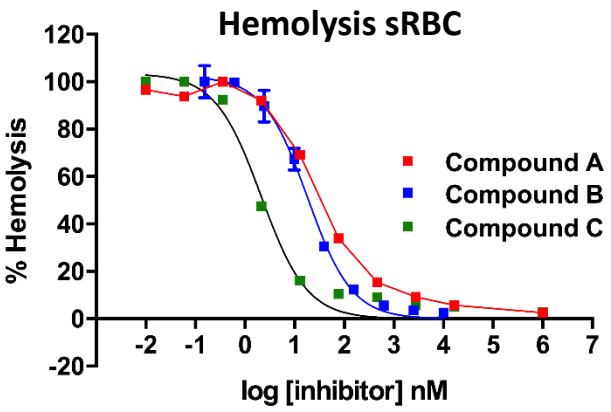
- 188 kDa, highly abundant protein
- C5 activation by cleavage results in the formation of the C5a anaphylotoxin and C5b, which initiates MAC (membrane attack complex) formation

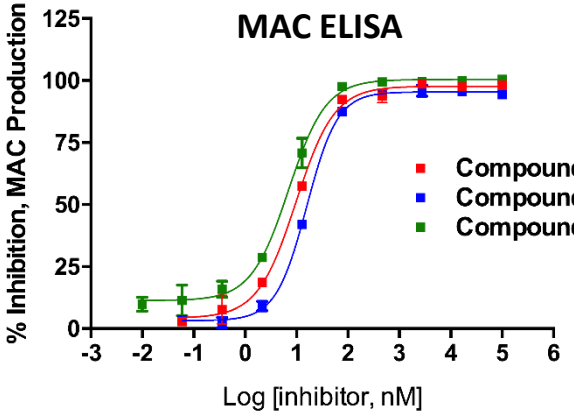


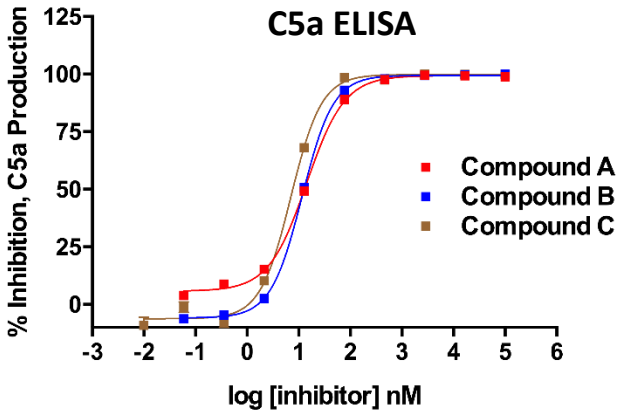
- Therapeutic Inhibition of C5 has resulted in observed clinical benefits in multiple disorders
  - Hemolytic anemia (PNH, aHUS)
  - Autoimmune disorders (rMG, C3G)

Discovery of Small Molecule (SM) Inhibitors of Complement C5

- In depth understanding of C5 structural biology gained with the macrocyclic peptide RA101495 (currently in Phase 2) justified search for SM C5 inhibitors
- Knowledge-based approach resulted in successful identification of SM inhibitors with a new and unprecedented mechanism of action (differentiated from mAb)
  - Displayed dose-dependent inhibition of hemolysis of antibody-sensitized sheep RBCs
  - Binds to C5 and prevents cleavage into C5a and C5b as determined by ELISA from the hemolysis assay supernatant



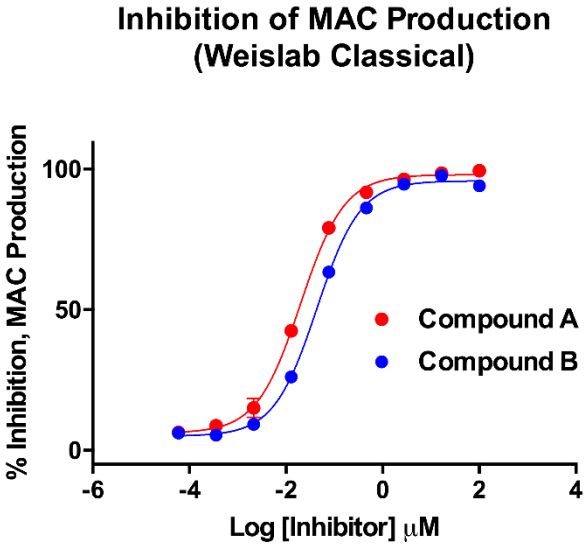


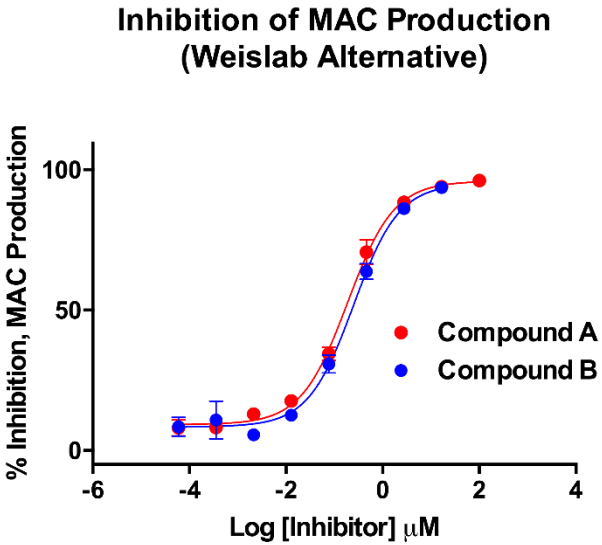


Compound	Hemolysis IC_{50} (nM)	MAC ELISA IC_{50} (nM)	C5a ELISA IC_{50} (nM)
Compound A	33	10	12
Compound B	17	16	14
Compound C	2	7	7

SM Inhibitors Block C5 Activation by Classical and Alternative Pathway C5 Convertase Complexes

- Inhibition of the classical (CP) and alternative (AP) pathway convertases demonstrated by using Weislab ELISA assays
- Consistent with the mechanism of inhibition, it is expected that the molecules will also inhibit Lectin Pathway (same convertase as Classical Pathway)

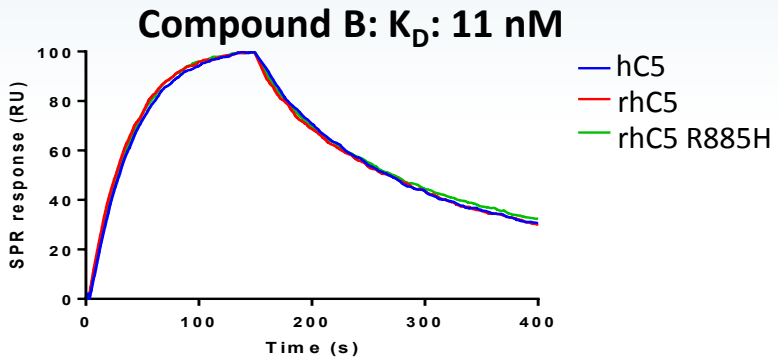




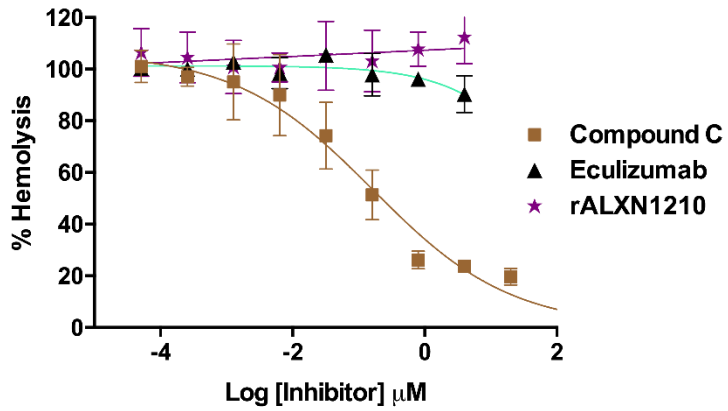
Compound	Wieslab CP IC_{50} (nM)	Wieslab AP IC_{50} (nM)
Compound A	20	187
Compound B	44	250

SM Inhibitors Offer Opportunities for Differentiation vs. mAb Approaches

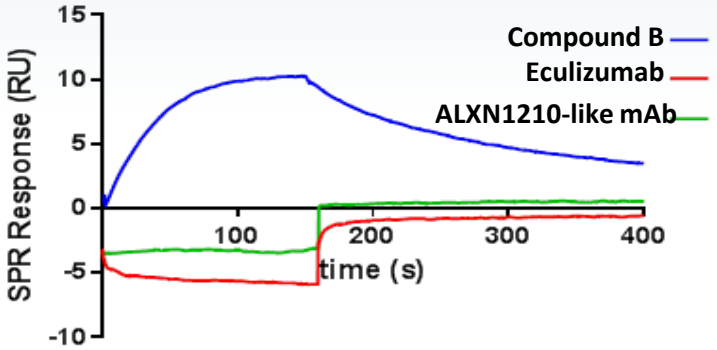
- Small molecule inhibitors bind C5 with polymorphism R885H with high affinity in a dose-dependant saturable manner



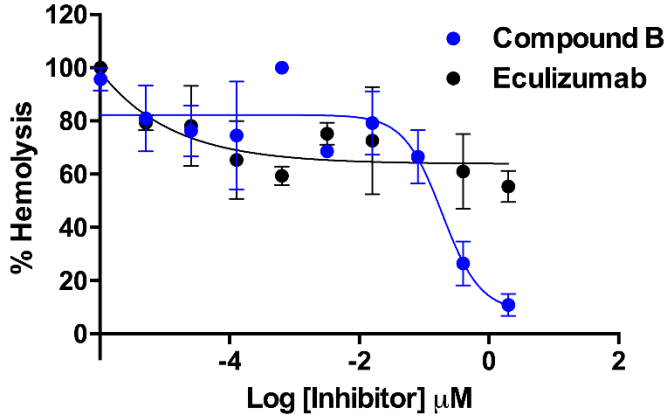
- Small molecules inhibit complement mediated hemolysis upon C5 R885H activation by the alternative pathway



- mAbs Eculizumab and ALXN1210 are not able to bind to C5 with polymorphism R885H

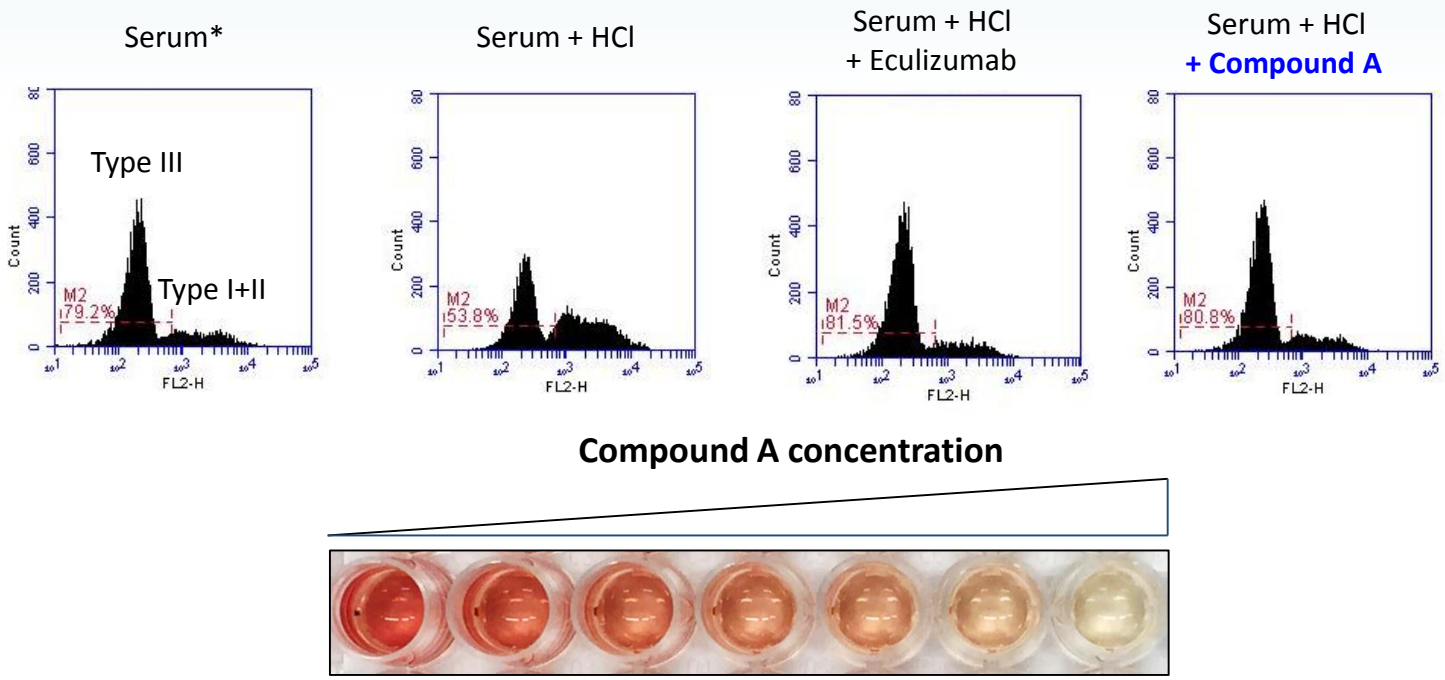


- Small molecules inhibit extrinsic (non-C5 convertase mediated) hC5 activation by plasmin (crosstalk with coagulation cascade)



Protection of Human PNH Type III Cells From Lysis by Small Molecule C5 Inhibitor

- SM inhibits complement mediated hemolysis of human PNH type III erythrocytes in a dose dependent manner



*18h incubation of PNH RBCs with 50% acidified serum. PNH RBCs provided by Dr. Jaroslaw Maciejewski

Lead Series has Drug-Like Properties and Crystallographic Data Allows Optimization via Structure-aided Design

- Desirable properties
  - ***e.g.* Compound B**: MW<500, HBD <5, HBA<10, cLogP<5, tPSA<100
- Highly selective: no known off-target effects
  - Good selectivity against hERG and CEREP(44) panel
- Pharmacokinetics studies in rat show favorable oral bioavailability
  - Up to 50% F after oral gavage dosing observed with analogs of lead series
- Multiple High Resolution co-crystal structures of C5 bound to SM have been obtained enabling structure aided design
  - Cryptic binding site on C5 revealed by SM (novel MOA)
  - Binding mode consistent with the activity observed across different assays
- Ra Pharmaceuticals plans to initiate IND enabling studies supporting SM program by Q4 2017

Acknowledgements

Ra Chemistry

- Michael Hale
- Vincent Galullo
- Derek LaPlaca
- Joseph Stringer
- Jaya Tikhe
- Peter Tran
- Craig Blain
- Qing Cao
- Kate Sherry
- Boling Geng

Ra Biology

- Emily de Koning
- Michelle Hoarty
- Kathleen Seyb
- Guo-Qing Tang
- Yalan Tang
- Douangsone Vadysirisack
- Jorge Reyes
- Zhong Ma
- Rohit Vyasamneni

Cleveland Clinic

- Jaroslaw Maciejewski