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Factor H: a new target to treat

Richard Pouw

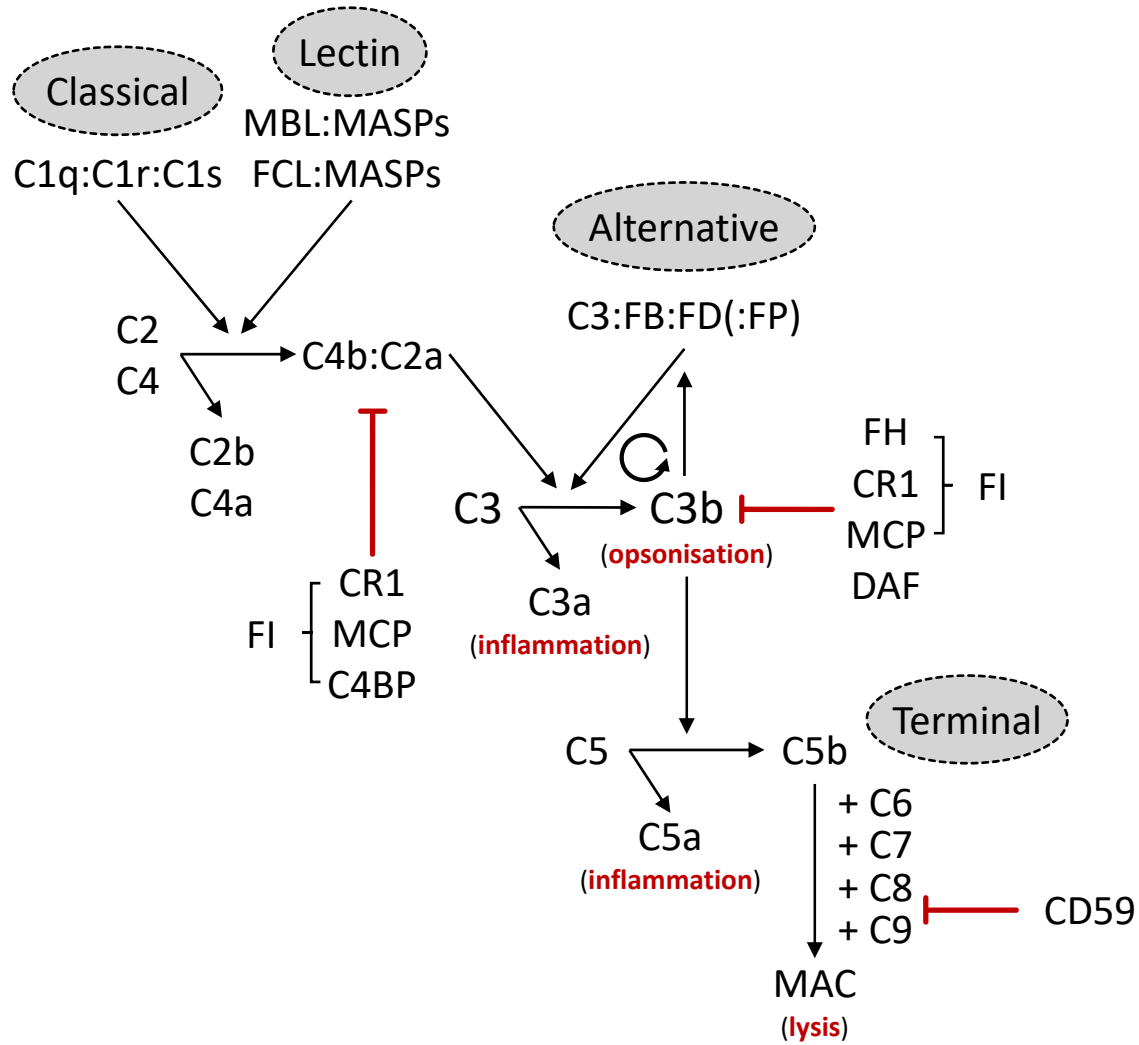
Immunopathology, Sanquin Research

Pediatric Hematology, Immunology & Infectious diseases, Emma Children's Hospital, AMC

Blood and Beyond

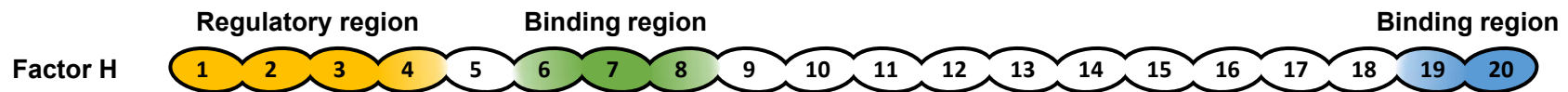
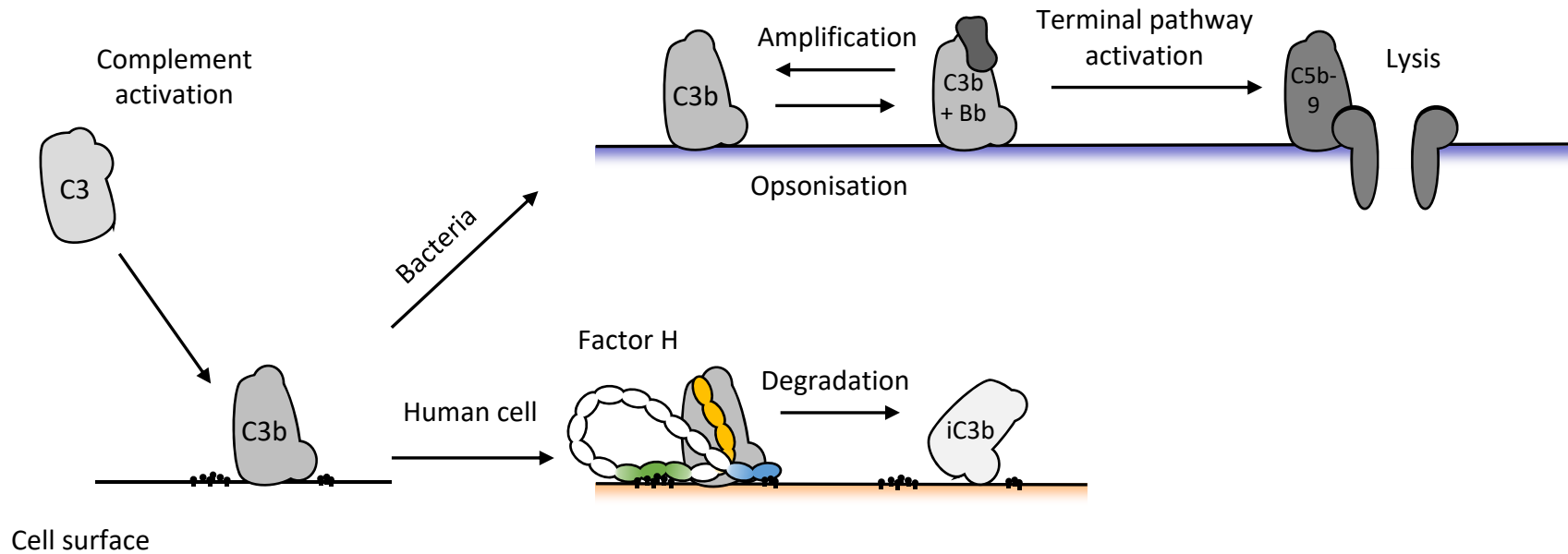


The complement system





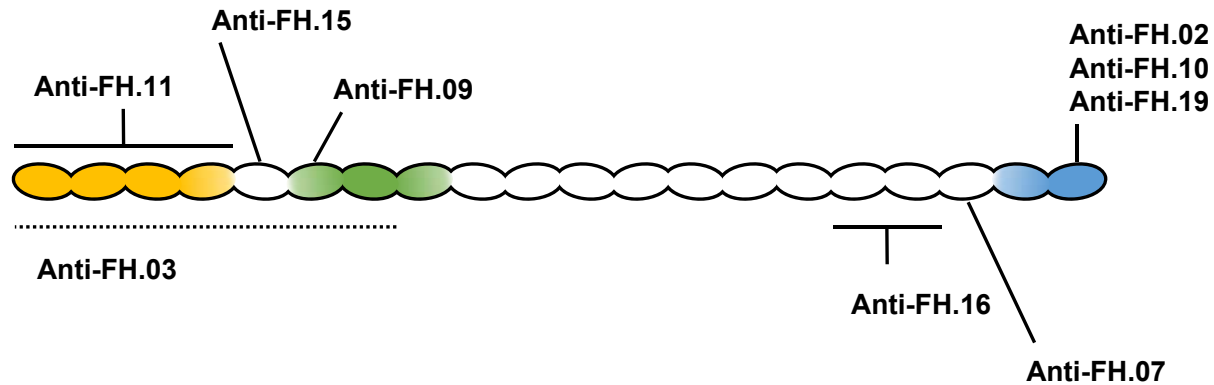
Factor H protects host cells



155 kDa
Abundant plasma protein: ~300 µg/ml



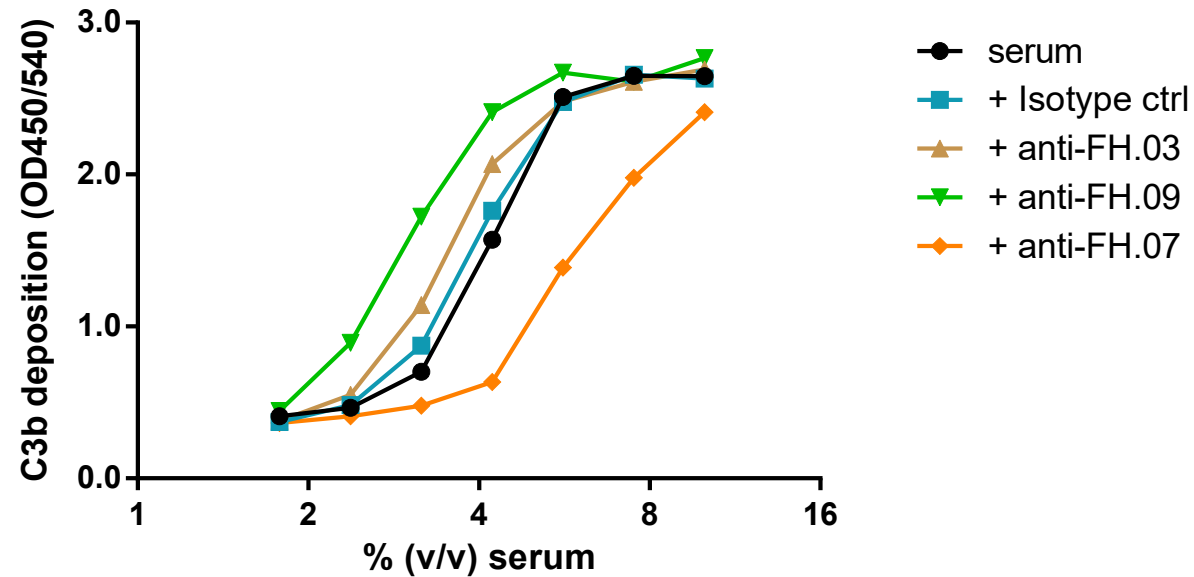
We have developed anti-FH antibodies against various domains



- In total 20 antibodies in 9 groups
- Epitope location mapped with fragments of FH
- Functional consequences of these antibodies?



Anti-FH.07 decreases complement deposition *in vitro*

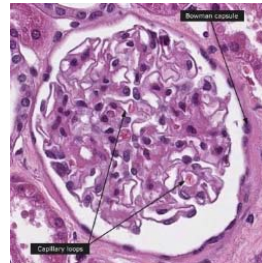
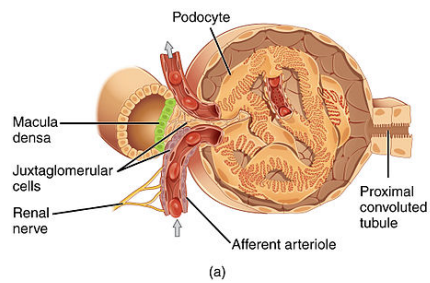


Zymosan coat
500 nm moAbs

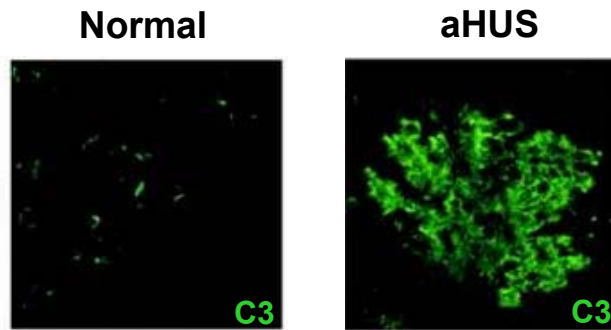
- Zymosan activates complement
- C3b deposition as read-out for complement activation
- Anti-FH.07 decreases C3b deposition



Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disease

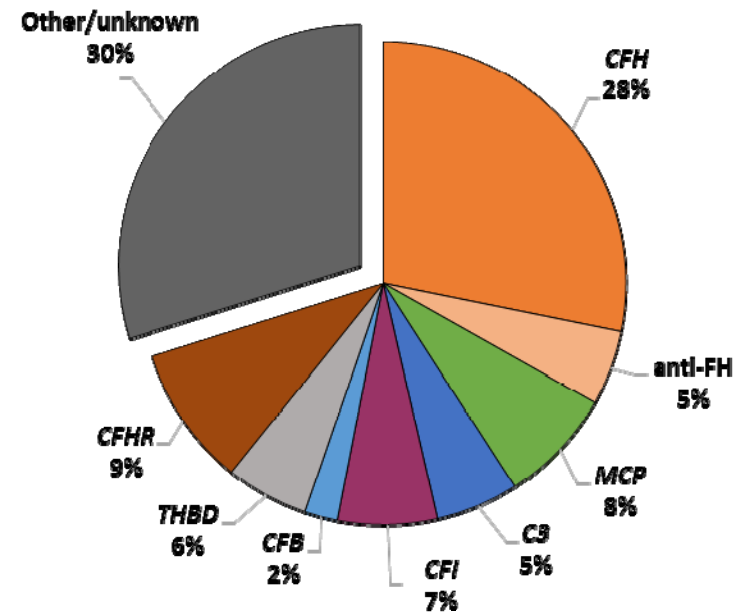


<http://www.proteinatlas.org>



From Goicoechea de Jorge *et al.* J Am Soc Nephrol. (2011)

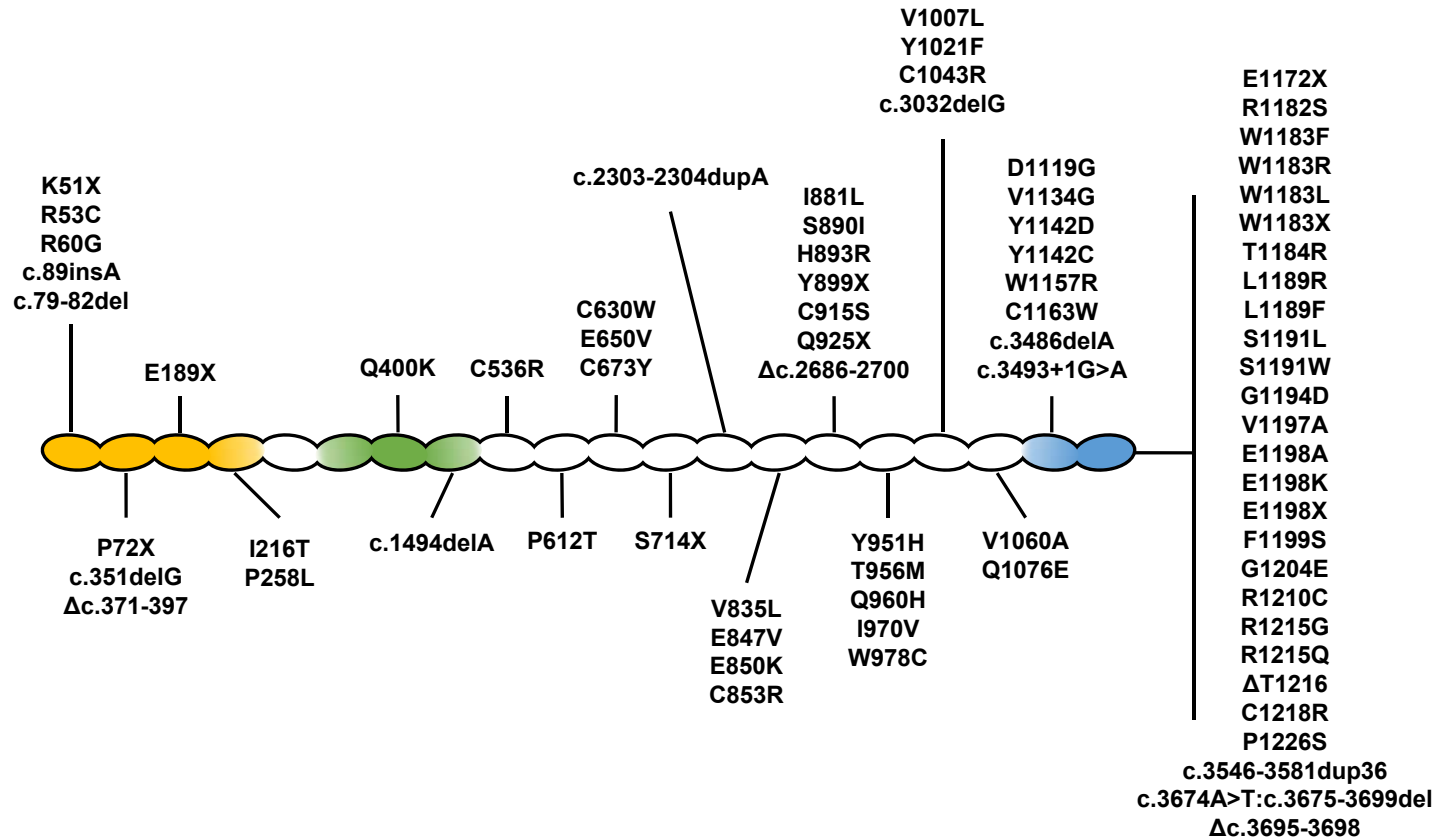
Mutations associated with aHUS



Adapted from Nester *et al.* Mol. Immunol 2015

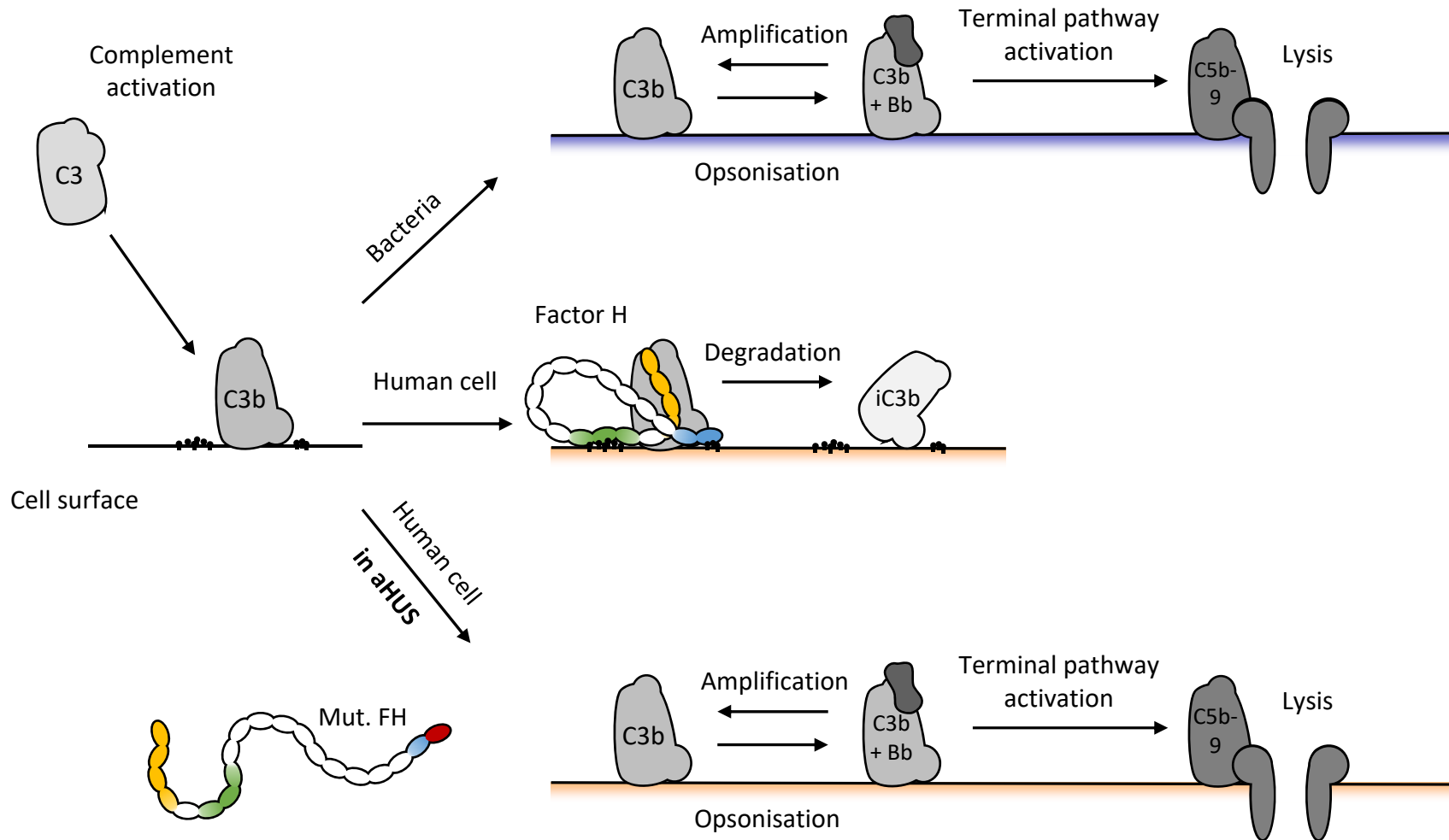


The surface binding region of FH is commonly affected in aHUS



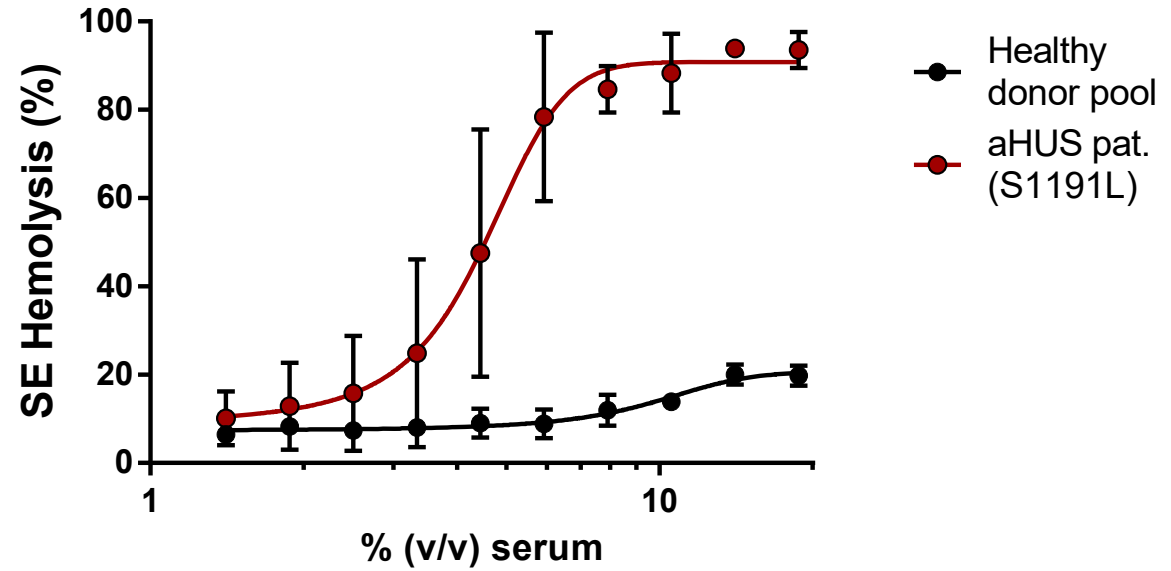
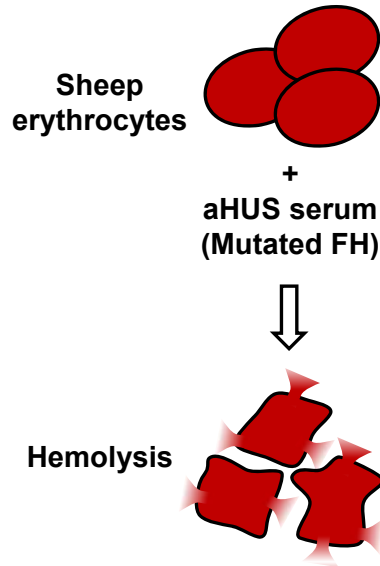


In aHUS, FH fails to protect host cells

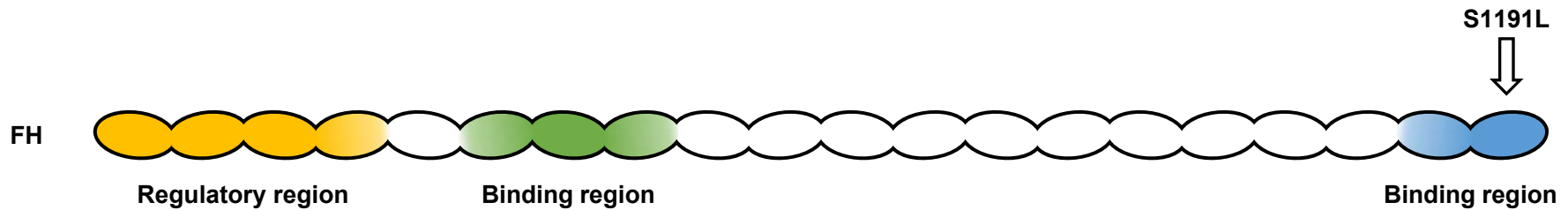




Sheep erythrocytes can be used to study FH function *in vitro*

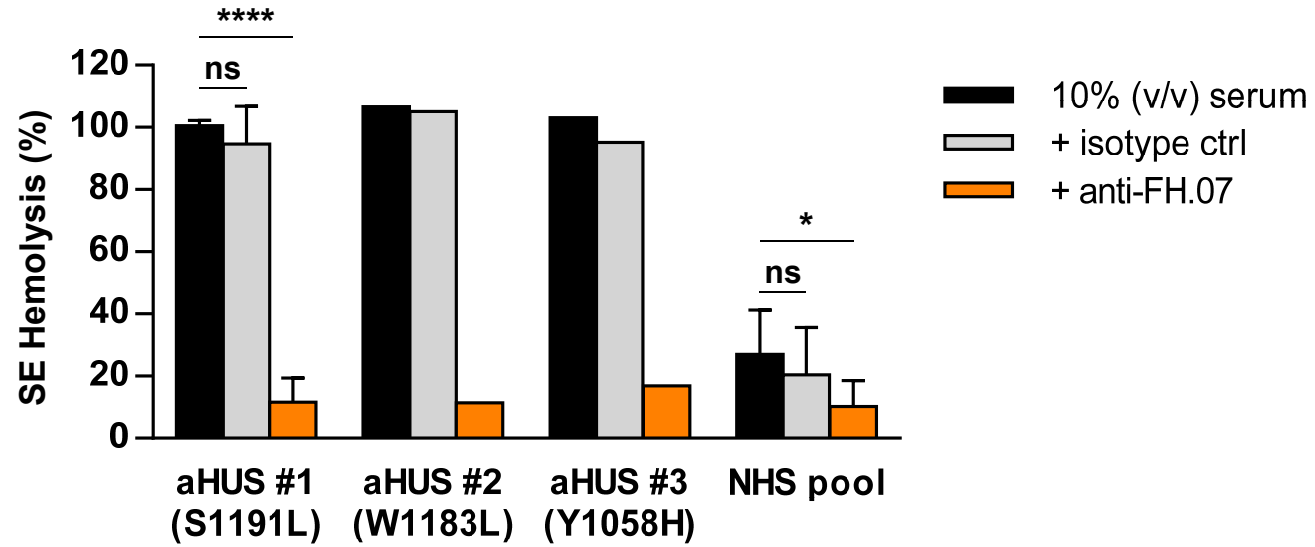


Sánchez-Corral *et al.* 2004

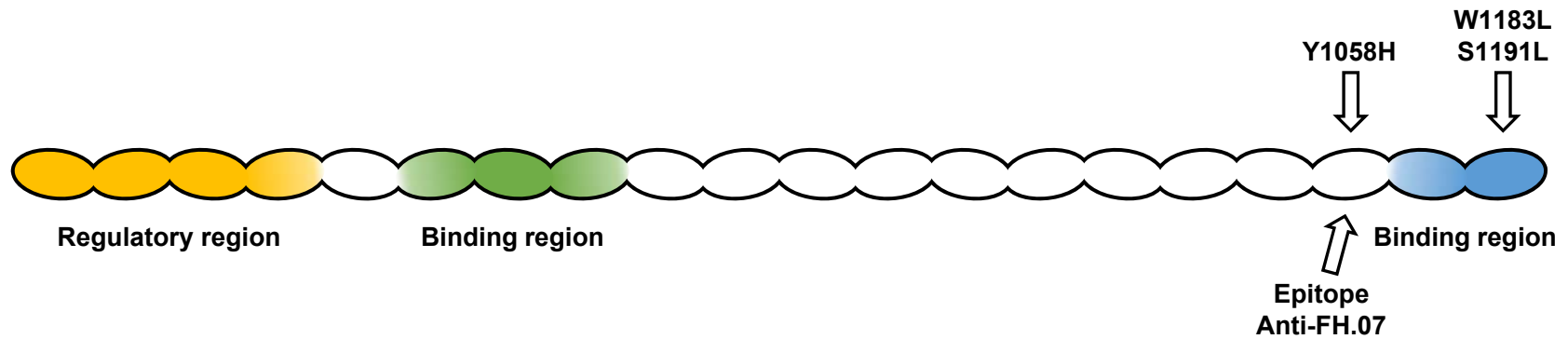




Anti-FH.07 can prevent hemolysis *in vitro* by potentiating FH

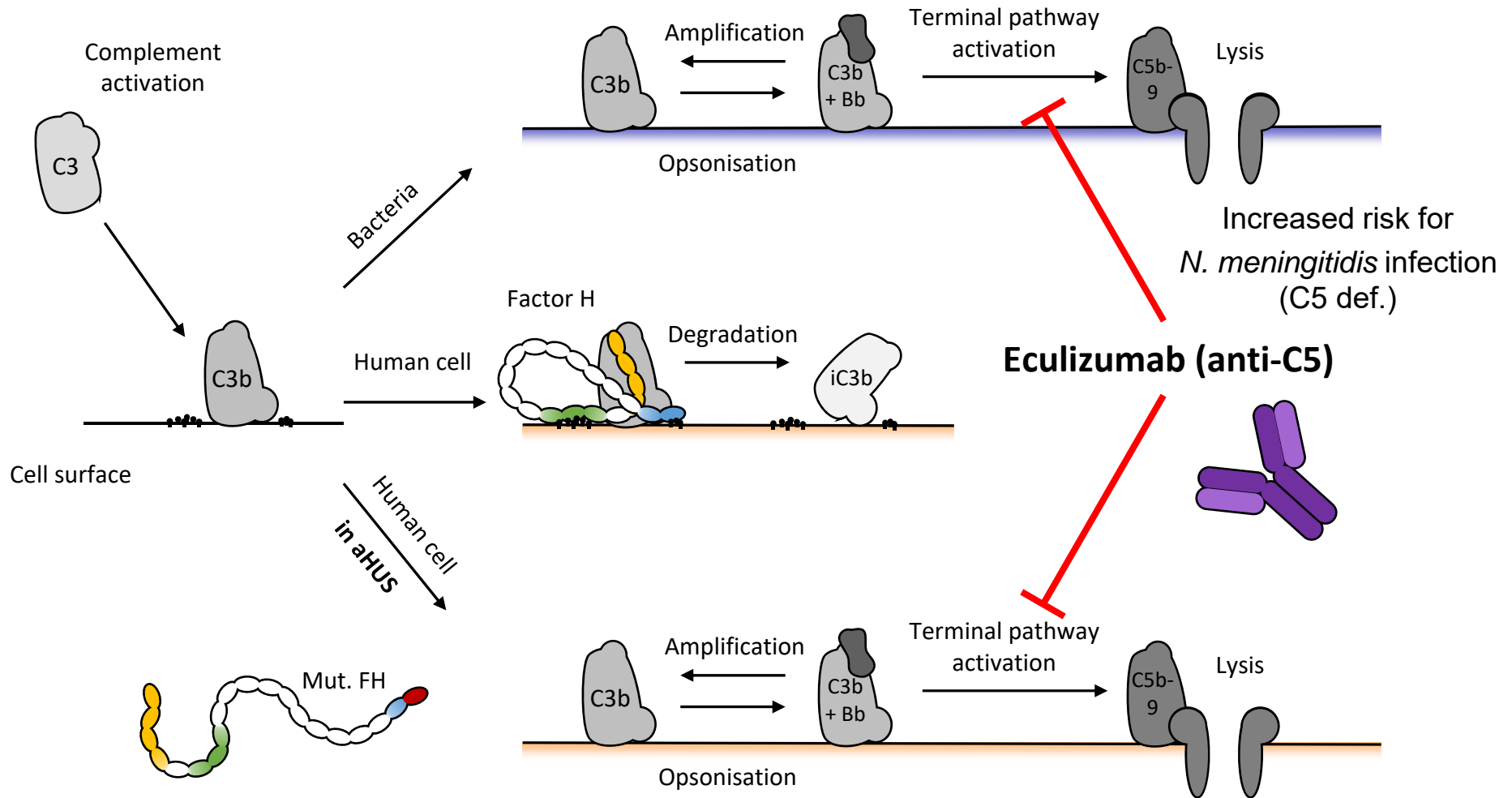


n=1 for aHUS#2 and aHUS#3, n≥3 for aHUS#1 and healthy pool



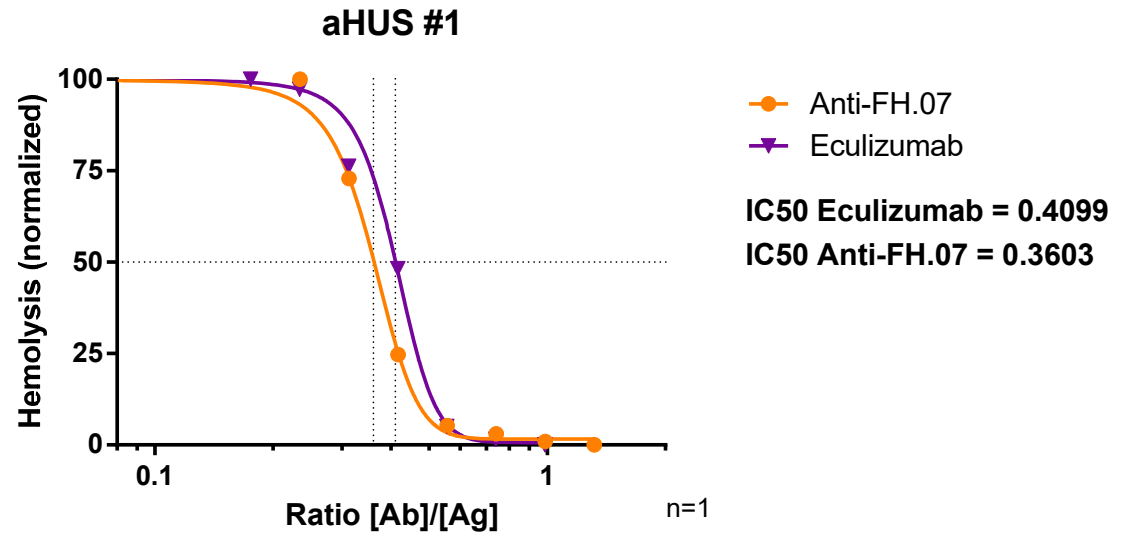
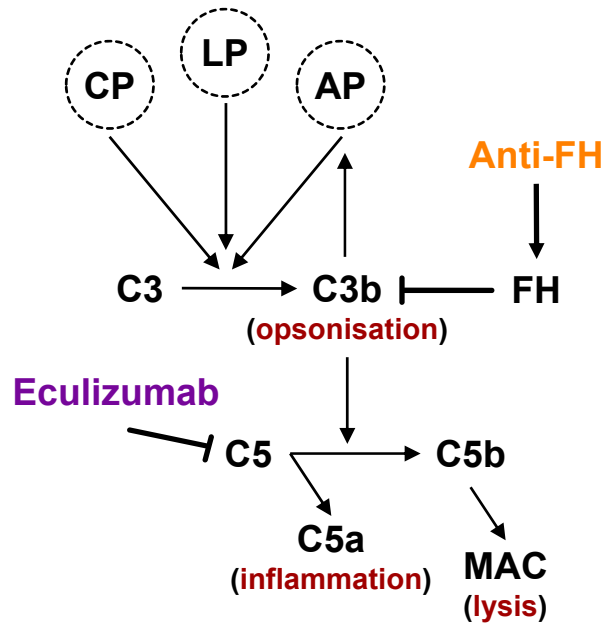


By blocking C5, Eculizumab prevents lysis





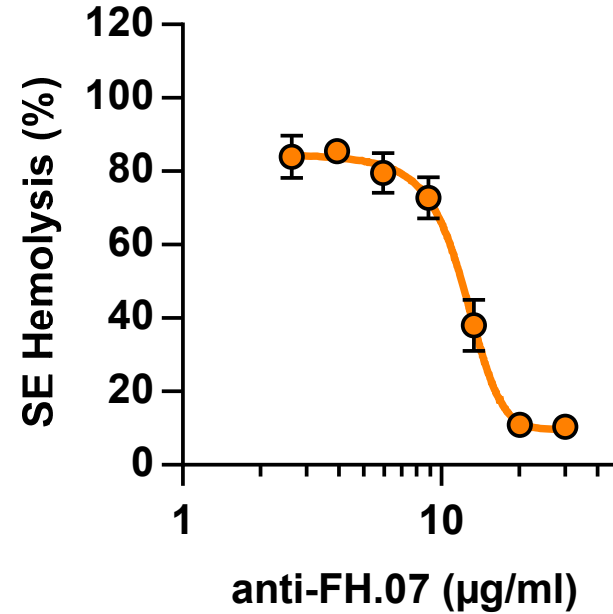
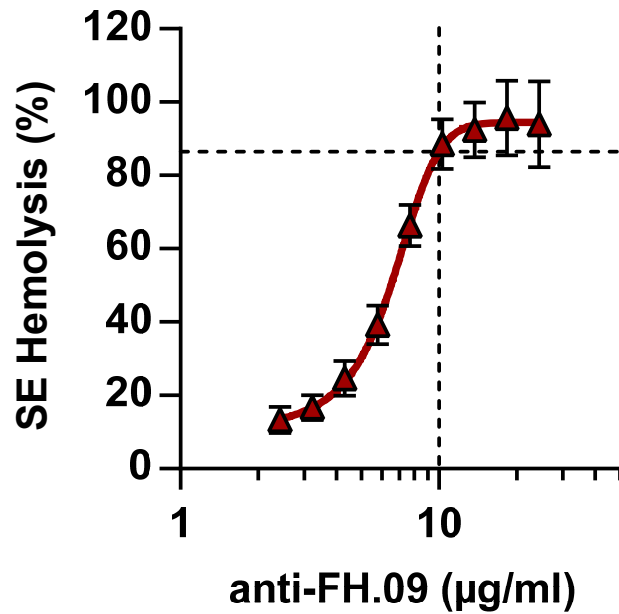
Potentiating FH is as potent in preventing hemolysis as blocking C5



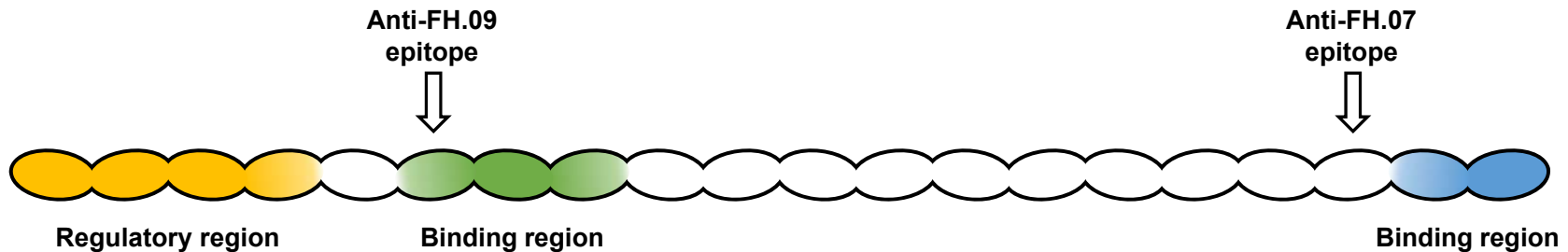
Of note; [C5] \approx 0,4 μ M, [FH] \approx 2 μ M in NHS



aHUS phenotype can be mimicked by inhibiting FH

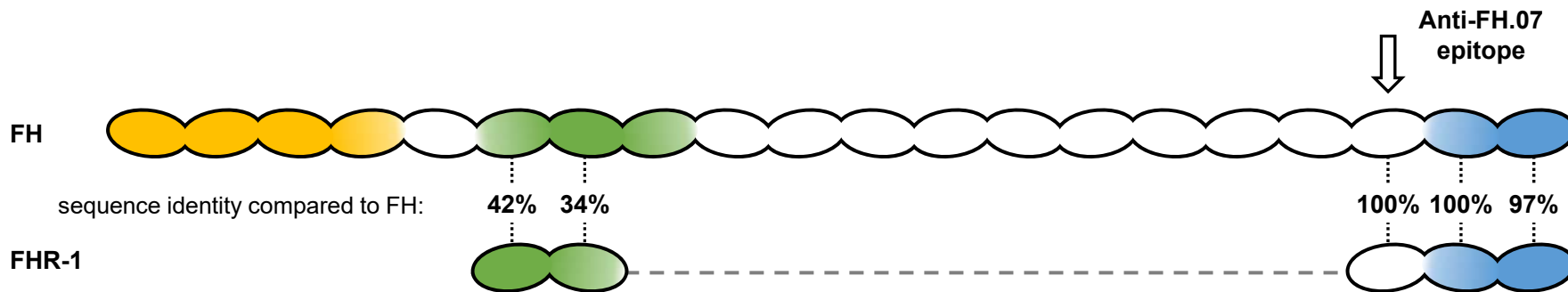
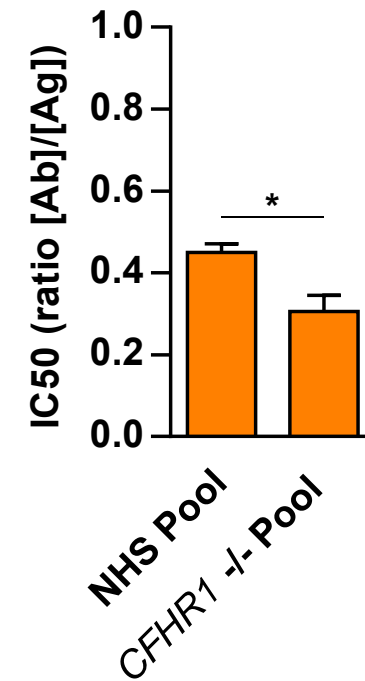
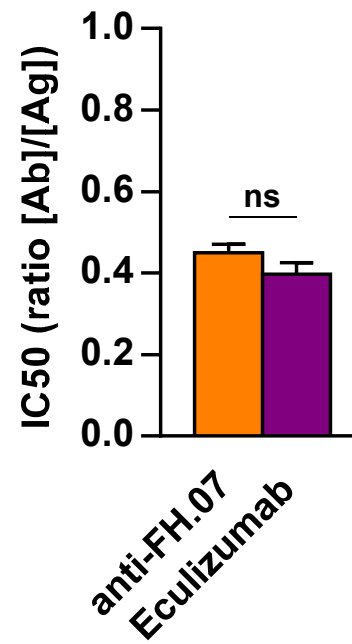
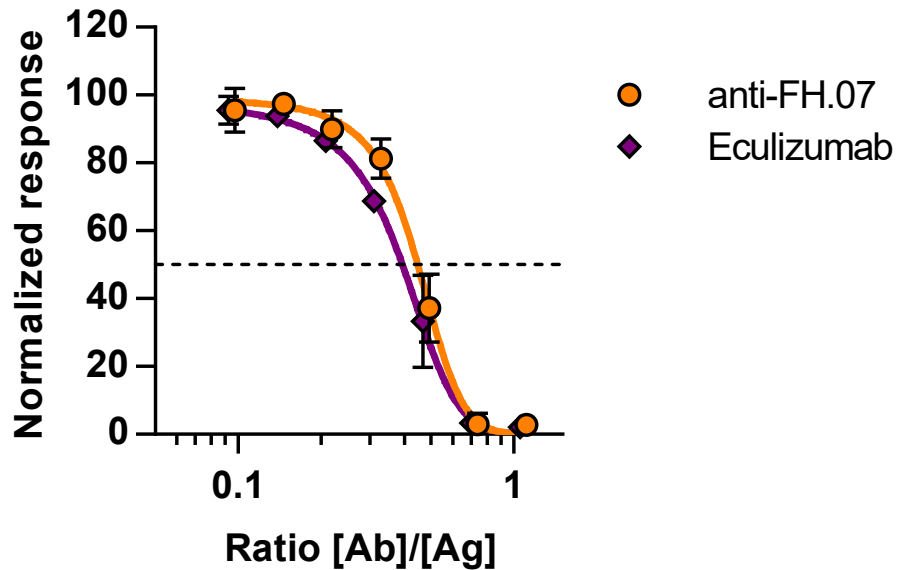


Up to ~60% FH blocked



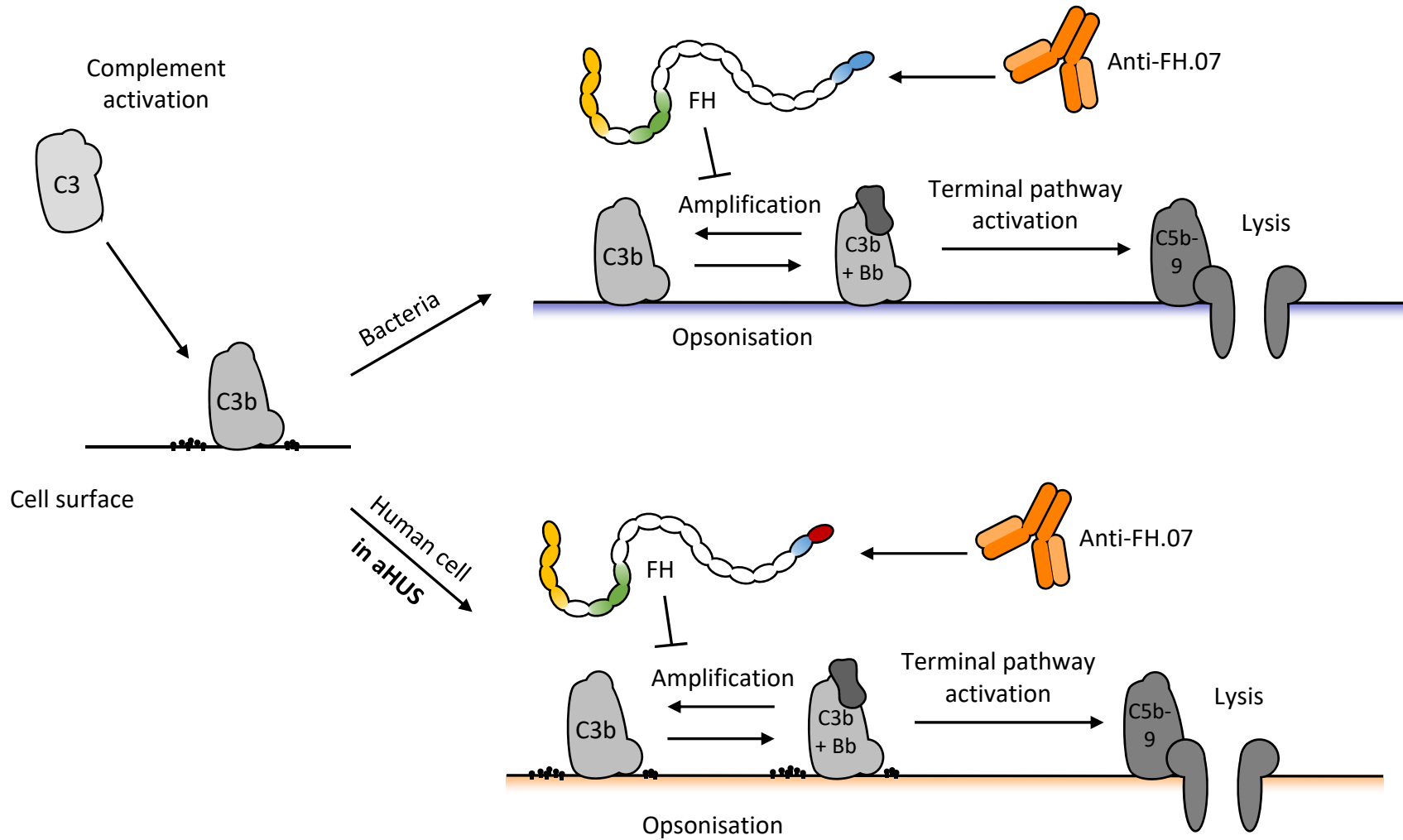


FH potentiation is as effective as Eculizumab and independent on FH-related protein-1



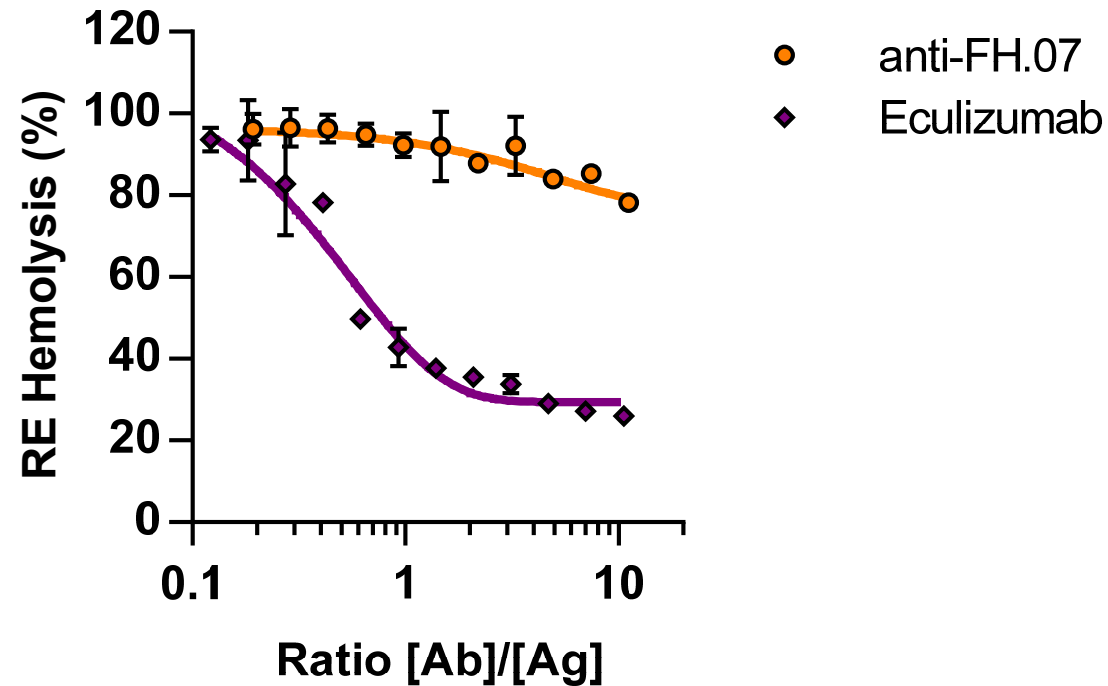


Is potentiating FH also beneficial for bacteria?





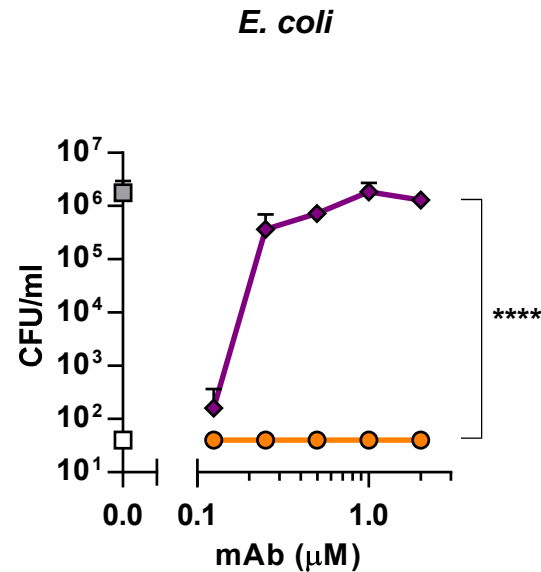
Anti-FH.07 does not effectively protect rabbit erythrocytes from AP-mediated lysis



Rabbit erythrocytes (REs) are normally not effectively protected by human FH, resulting in complement-mediated lysis.



Potentiating FH does not affect complement-mediated bacterial killing



■ HI-NHS □ NHS ● Anti-FH.07 ◆ Eculizumab

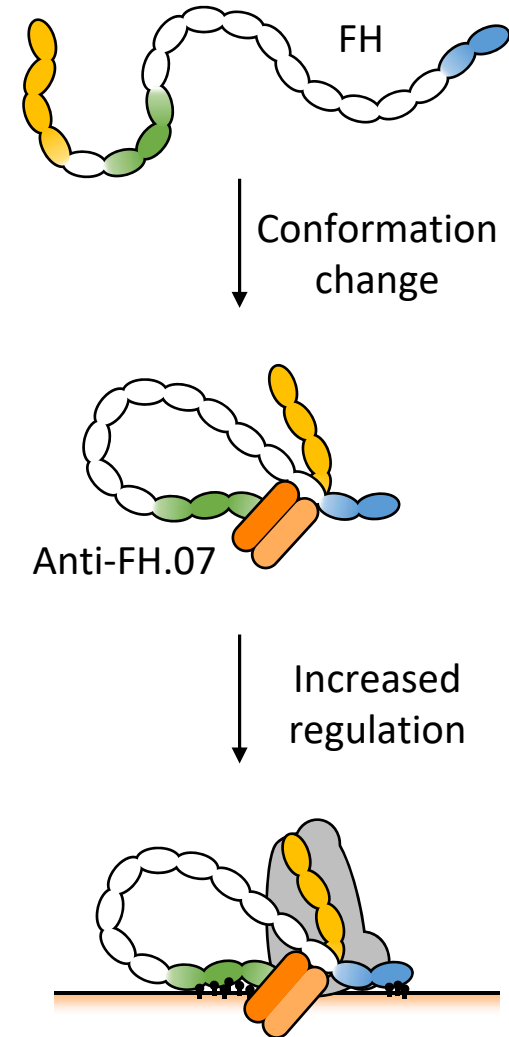
All n=3
75% NHS

Specificity of FH for host surfaces seems to be maintained



In conclusion

- FH regulation could be restored with anti-FH.07
- Potentiating FH is as effective as inhibiting C5 in preventing hemolysis
- No effect on bactericidal activity of NHS
- Specifically protects human cells from complement
- Current hypothesis: anti-FH.07 induces an “active” conformation in FH which allows for better binding to C3b on host surfaces





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