

Therapeutic efficacy of a bi-functional C5 mAb-FH1-5 fusion protein in a mouse model of rapidly progressing lethal C3 glomerulopathy (C3G)



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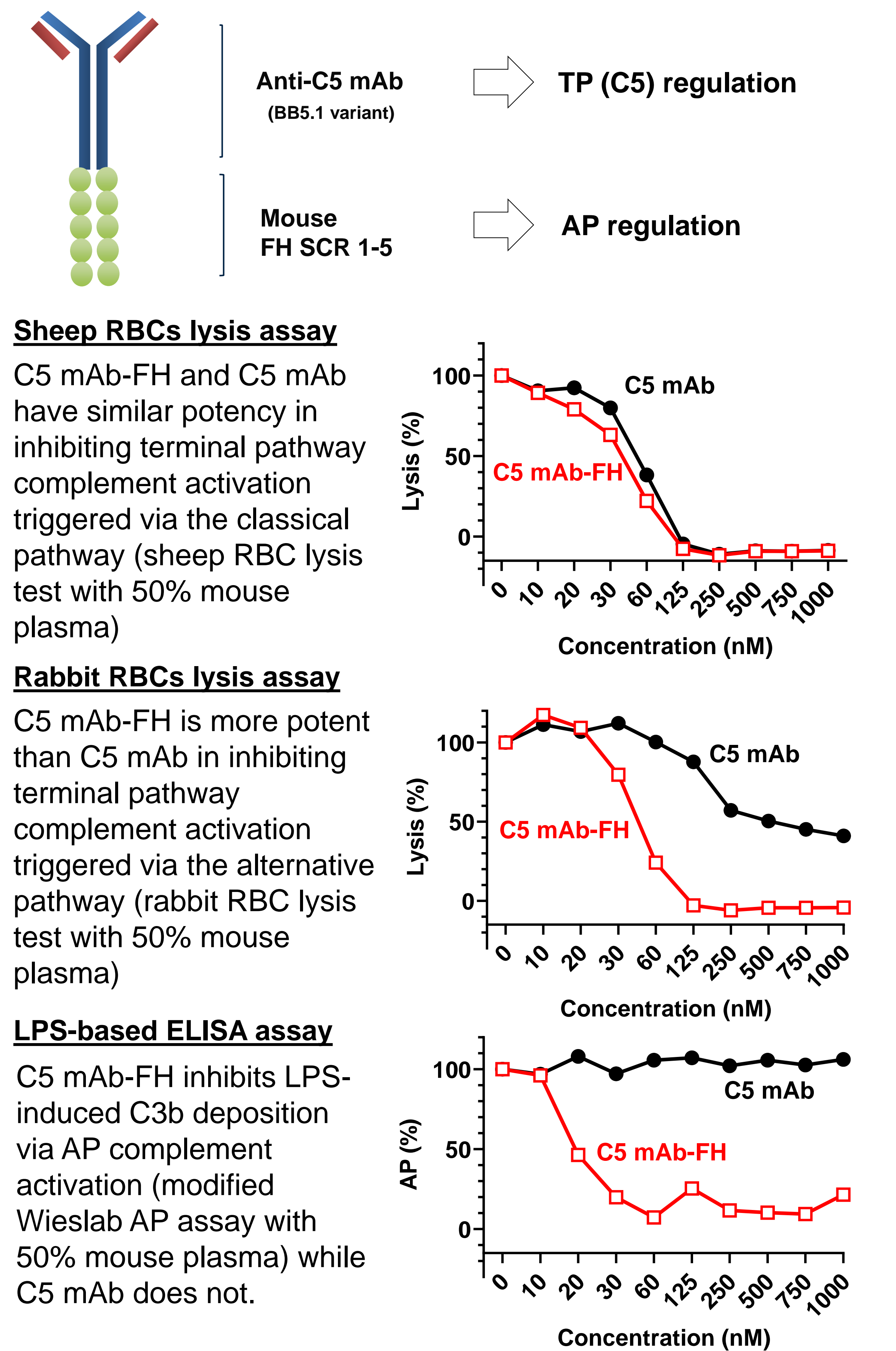
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Introduction

C3 glomerulopathy (C3G) is a rare kidney disease caused by dysregulated alternative pathway (AP) complement activation. It is characterized by glomerular C3 deposition, proteinuria, crescentic glomerulonephritis and renal failure. The anti-C5 mAb drug Eculizumab has shown therapeutic effect in some but not all C3G patients and no approved therapy is currently available. We previously characterized a lethal murine model of C3G (FH^{m/m}P^{-/-} mice) and demonstrated an anti-C5 mAb to be completely effective in preventing disease but only partially effective in treating established disease. We have recently humanized factor D (FD) in FH^{m/m}P^{-/-} mice by crossing with a human FD knock-in mouse (hFD). Unexpectedly, hFD-FH^{m/m}P^{-/-} mice not only recapitulated the C3G phenotype but also developed a more aggressive form of C3G, with 100% mortality occurring before 7 (instead of 12-14) weeks of age. In this study, we used this newly developed, rapidly progressing C3G mouse model to test the therapeutic efficacy of an anti-mouse C5 mAb and a bi-functional anti-mouse C5 mAb/mouse FH1-5 fusion protein. hFD-FH^{m/m}P^{-/-} mice aged 3-6 weeks were screened by proteinuria and only those that had developed 3+ proteinuria/hematuria were enrolled in this therapeutic study. The C5 mAb-FH tested in this study is a murine surrogate of KP104, a bi-functional complement inhibitor under clinical development by Kira Pharmaceuticals. Please visit poster/abstract #132, #126 for more details on KP104.

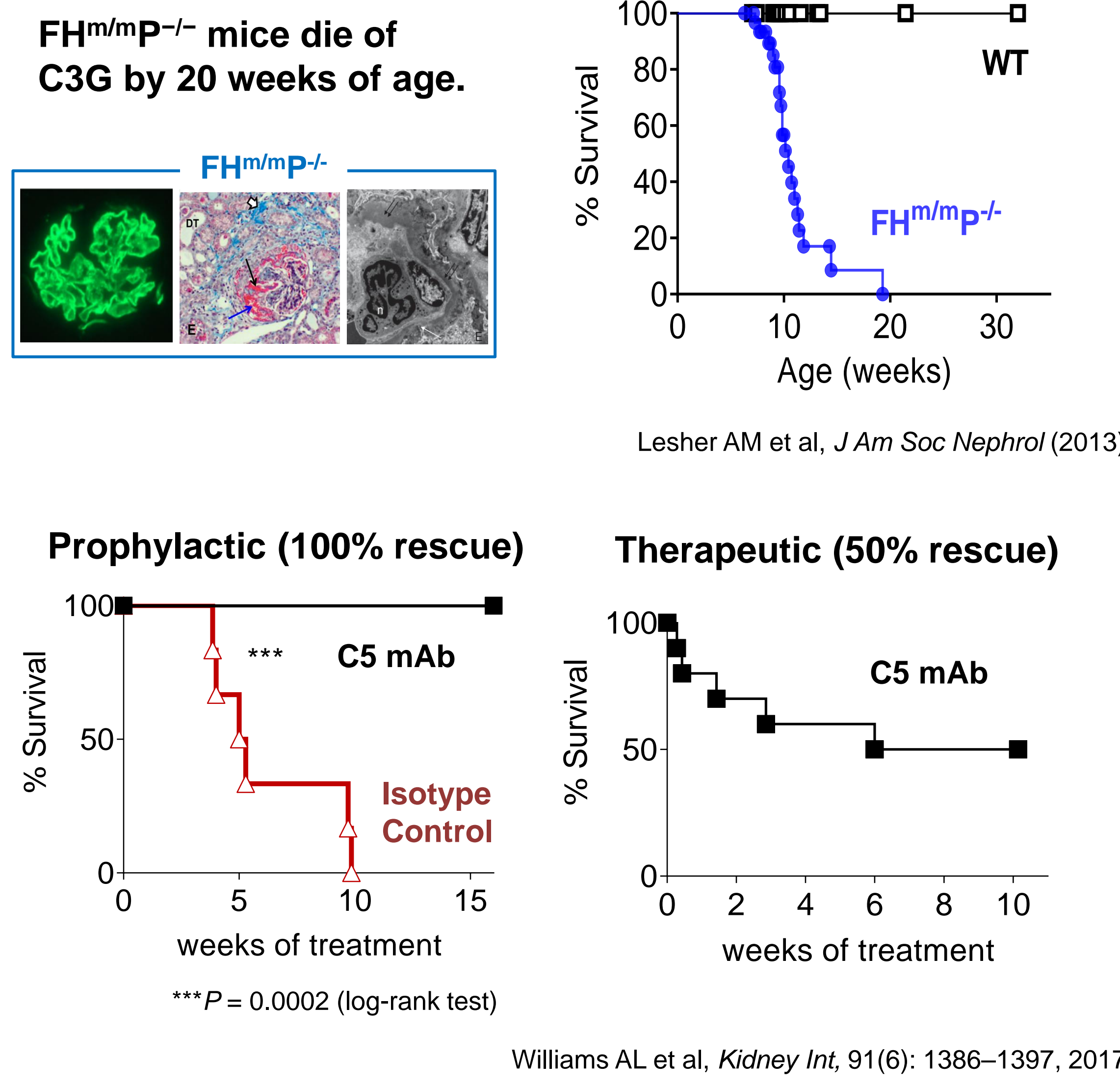
3 Novel bi-functional complement inhibitor: anti-C5 mAb and FH1-5 fusion protein



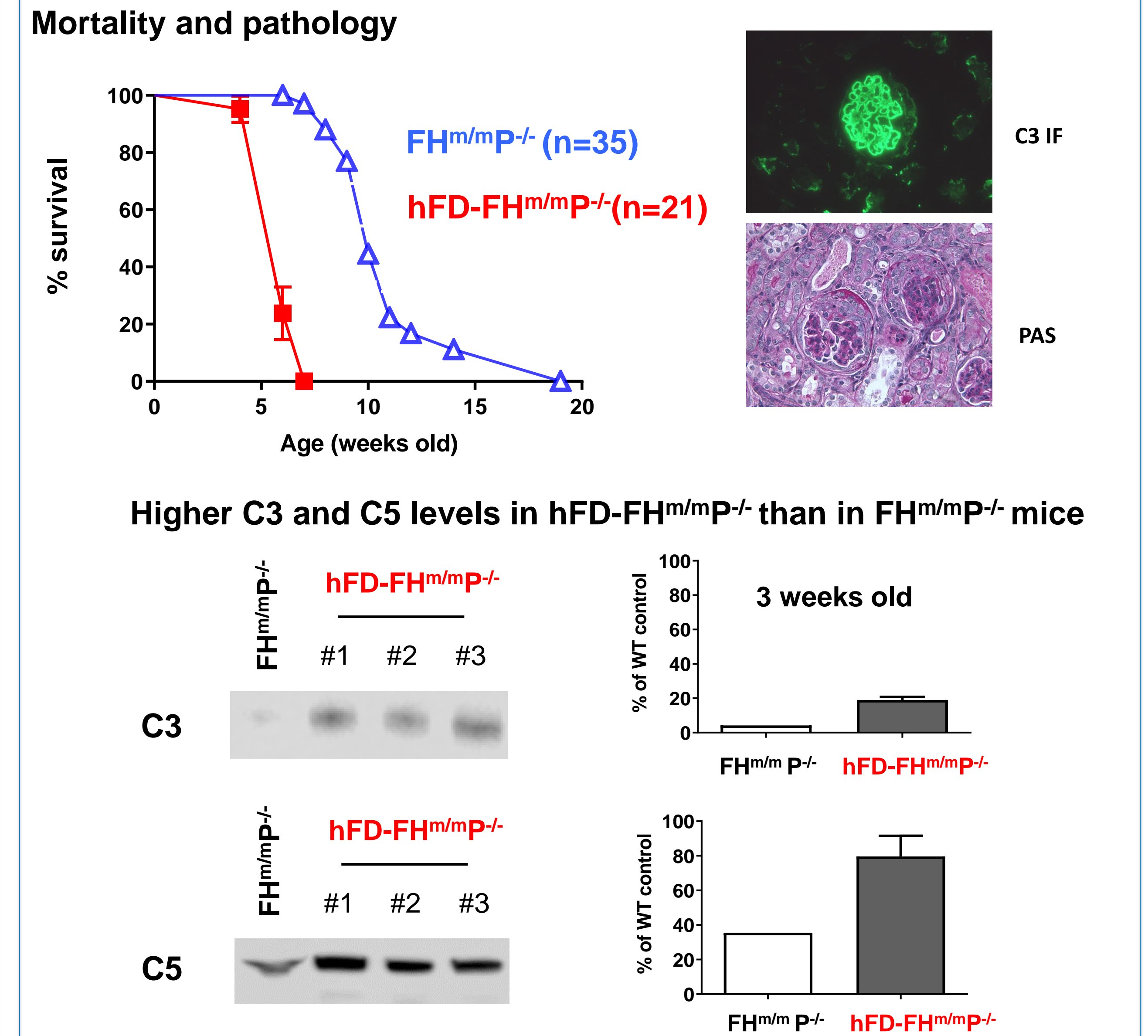
Result Summary and Conclusions

- Humanization of FD in FH^{m/m}P^{-/-} mice exacerbated C3G, likely due to higher plasma C3 and C5 levels in this strain.
- hFD-FH^{m/m}P^{-/-} mice developed severe and rapidly progressing C3G, with 100% mortality by 7 weeks old.
- hFD-FH^{m/m}P^{-/-} mice were screened and those showing 3+ proteinuria/hematuria (age ranging 3-6 weeks) were treated with either a murine anti-C5 mAb or the same mAb fused with mouse FH SCR1-5 for 30 days (n=6)
- All mice treated with C5 mAb-FH survived the 30-day treatment whereas only 50% treated with C5 mAb did.
- Treatment with C5 mAb-FH but not C5 mAb prevented systemic AP activation and C3, FB consumption.
- C5 mAb-FH prevented glomerular C3 and C9 deposition whereas C5 mAb prevented glomerular C9 deposition only.
- Both drugs significantly ameliorated mesangial hypercellularity over baseline, and crescent/fibrin deposition, mesangial hypercellularity over non-treated group, but only C5 mAb-FH significantly reduced proteinuria, hematuria and glomerular endocapillary hypercellularity over baseline.

1 FH^{m/m}P^{-/-} mouse: a lethal mouse C3G model, and mixed efficacy of a murine anti-C5 mAb



2 Factor D humanization in FH^{m/m}P^{-/-} mice further exacerbates C3G due to higher C3 and C5

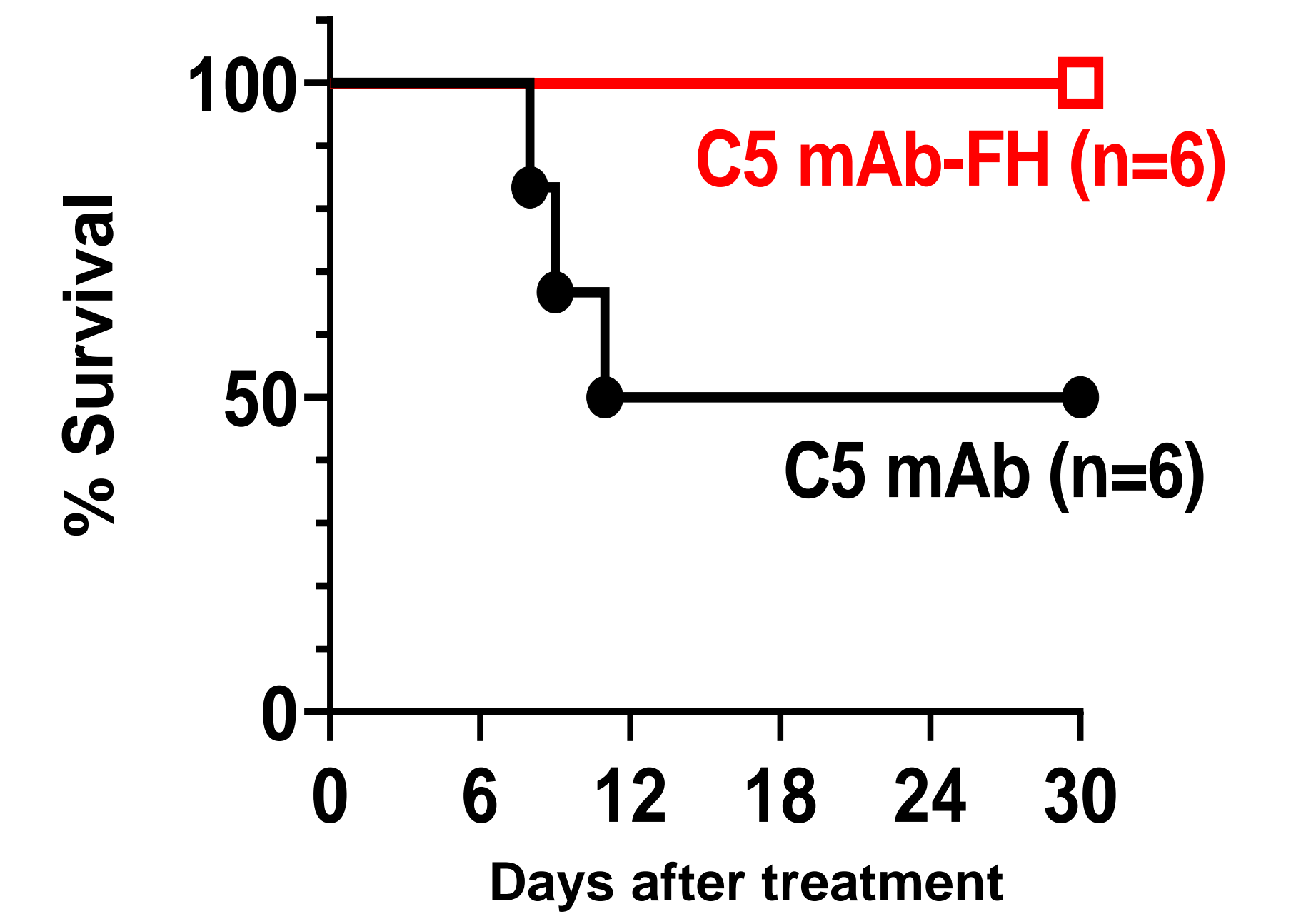


4 Anti-C5 mAb-FH is therapeutically more efficacious than anti-C5 mAb in hFD-FH^{m/m}P^{-/-} mice

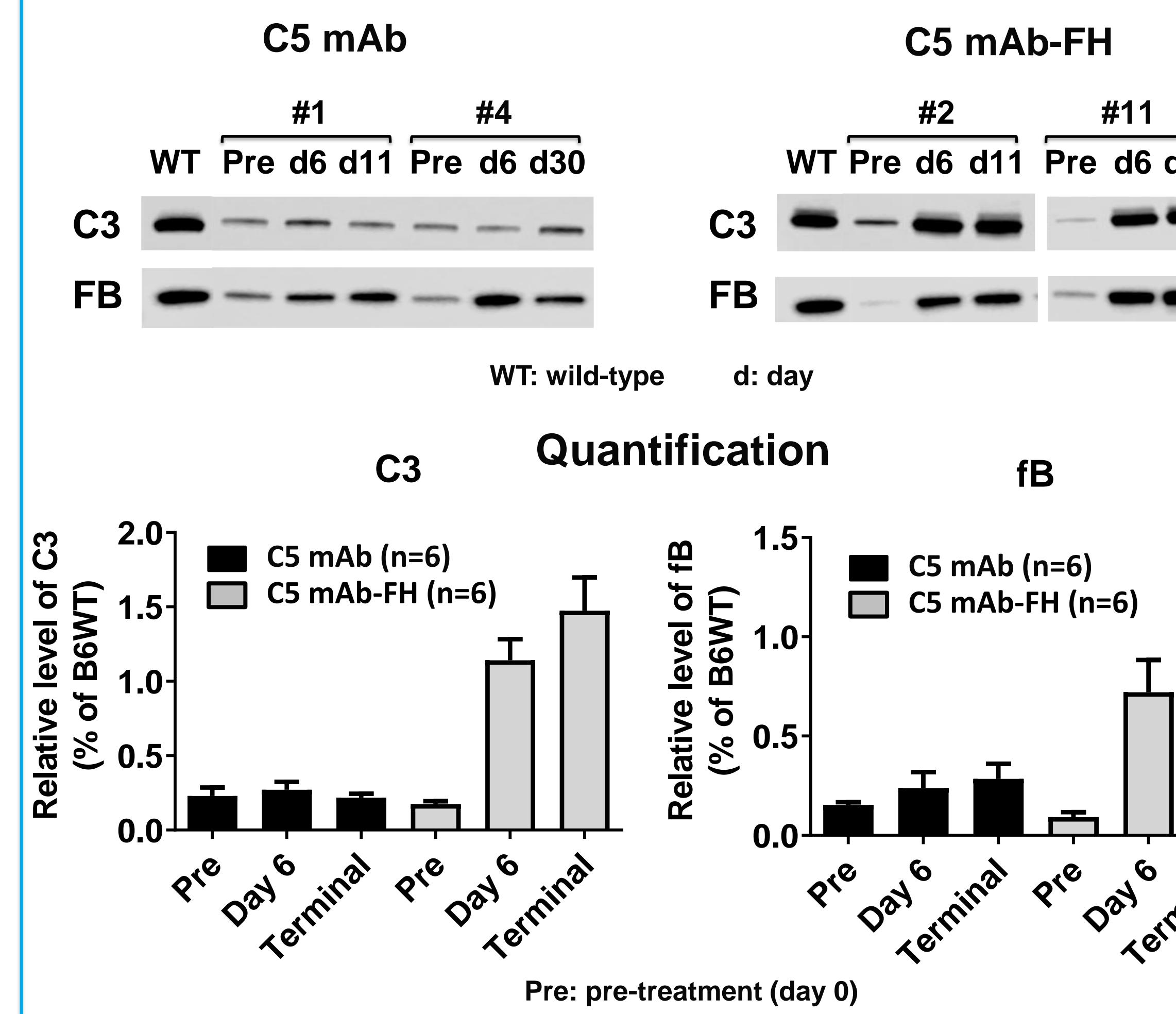
a Study Objective and Experimental Protocol

- Compare C5 mAb and C5 mAb-FH therapeutically
- Use the new and rapidly progressing hFD-FH^{m/m}P^{-/-} model
- Screen mice with 3+ proteinuria/hematuria for enrollment
- C5 mAb (enrolled n=6 male mice, 4-6 weeks old)
- C5 mAb-FH (enrolled n=6 male mice, 3-6 weeks old)
- 40 mg/kg, i.p., every 3 days x 10 doses (30 days treatment)

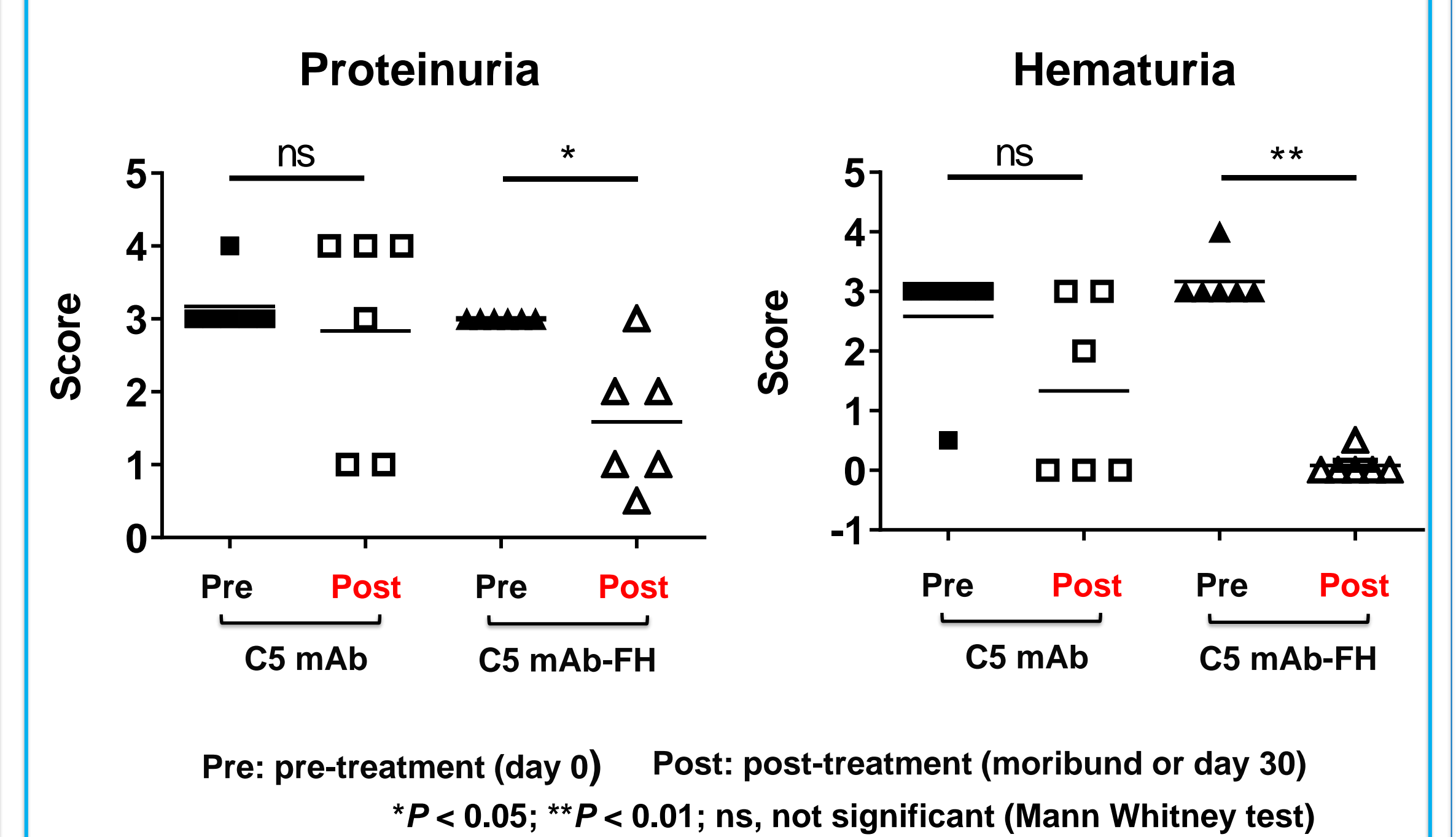
b Survival curves



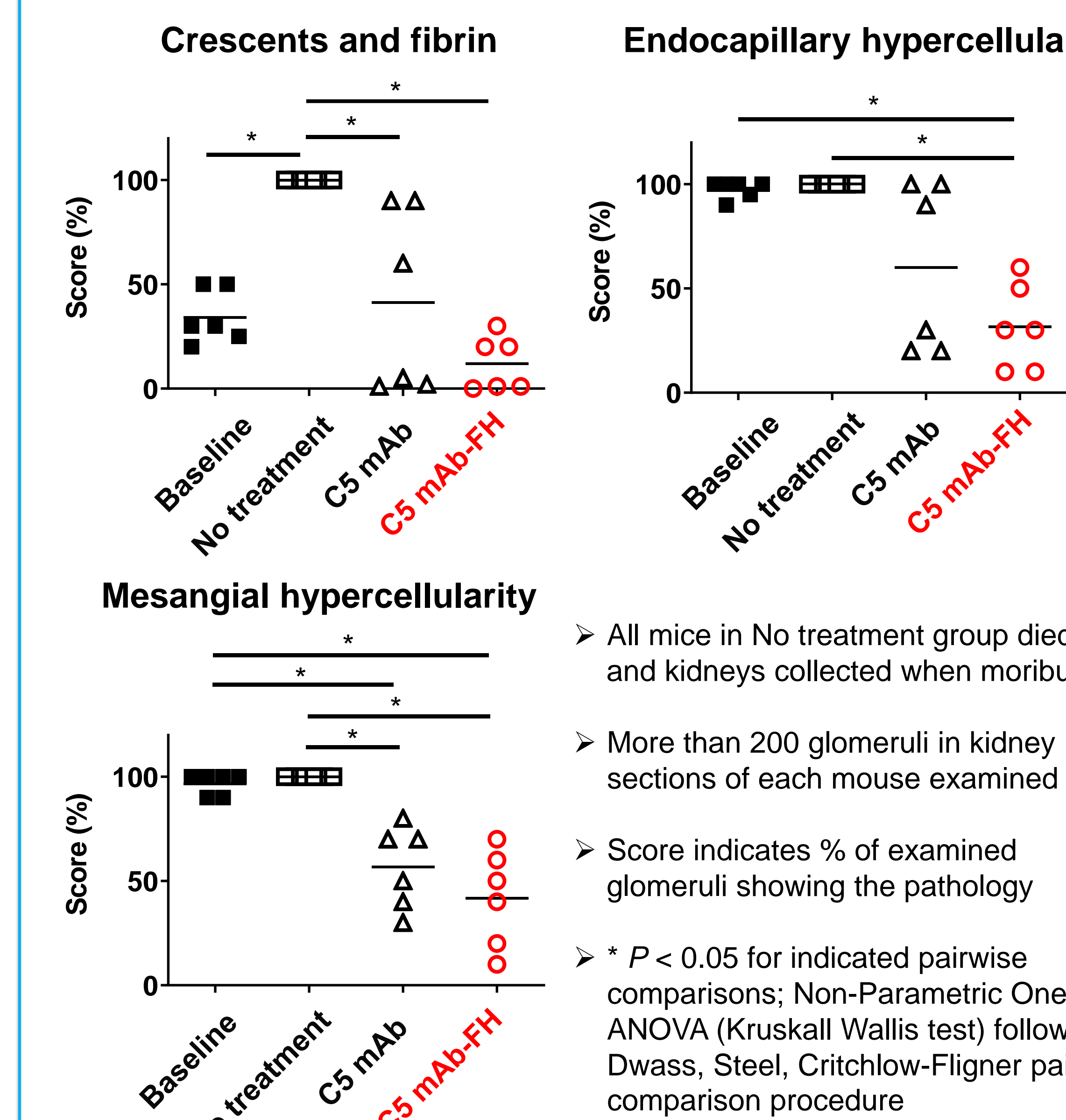
c C5 mAb-FH but not C5 mAb inhibited systemic C3 and Factor B consumption



d C5 mAb-FH improved renal function to a greater degree than C5 mAb



e C5 mAb-FH treatment significantly ameliorated renal pathology



f C5 mAb-FH eliminated both C3 and C9 deposition in glomeruli

