C3d-Targeted Factor H Achieves Potent Tissue-Directed Complement Inhibition and Disease-Modifying Efficacy Without Affecting Systemic Complement

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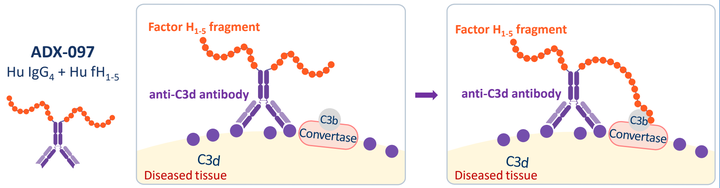
INTRODUCTION

While systemic complement blockade is a therapeutic strategy for complement-driven diseases, effective inhibition is challenging due to high circulating concentrations and rapid turnover of complement effector proteins. Furthermore, because of complement's essential role in innate and adaptive immunity, systemic blockade leads to increased infection risk. Consequently, substantial unmet need remains for more effective and safer anti-complement therapies, particularly for chronic diseases. **ADX-097, a humanized anti-C3d monoclonal linked to five N-terminal consensus repeats (SCR) of the complement AP inhibitor factor H (fH_{1-5}),** is designed to inhibit complement in diseased tissue while minimizing systemic blockade. After evaluating in vivo ADX-097 tissue targeting in skin, liver, and kidney diseases, we extensively characterized circulating and tissue PK and PD of a mouse ADX-097 surrogate, ADX-118, in CfH-/- mice that exhibit robust glomerular complement activation. We then examined ADX-097 efficacy in the rat Passive Heymann Nephritis (PHN) model of membranous nephropathy. We have further characterized C3 complement activation and C3d deposition by immunostaining in patient samples of renal, liver and skin diseases.

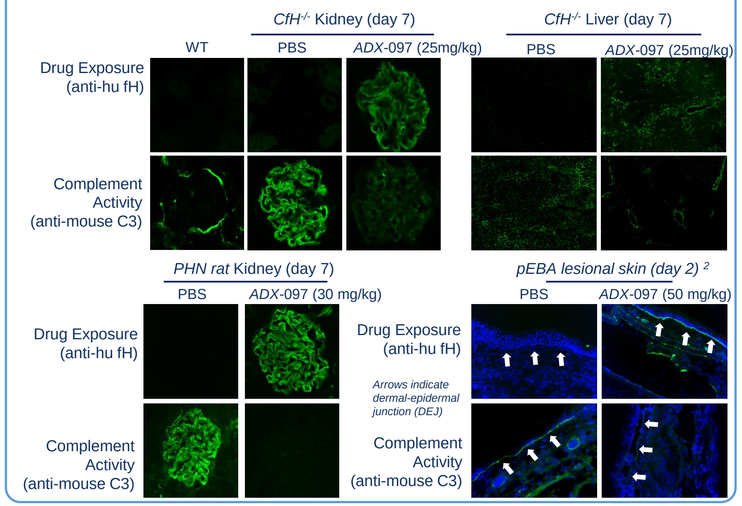
TISSUE-TARGETING FUSION PROTEIN DESIGN [1]

ADX-097 targets tissue-deposited C3d, thus delivers fusion protein to disease tissue sites and inhibits pathogenic complement activation locally at disease tissue sites.



METHODS & RESULTS

ADX-097 Biodistribution and Complement Inhibition in Rodent Disease Tissues

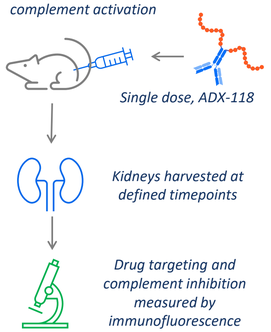


METHODS & RESULTS

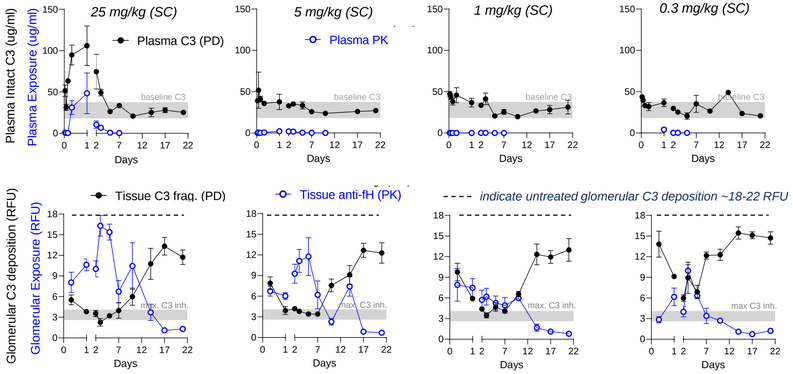
- A dose-response PK/PD study in CfH-/- showed that a single subcutaneous (SC) dose of >1 mg/kg ADX-118 (mouse surrogate of ADX-097) achieves >75% glomerular complement inhibition for at least 7 days without systemic complement blockade, while a 0.3 mg/kg dose still achieves approximately 50% glomerular inhibition.

Factor H knockout ($CfH^{-/-}$) mice:

- Loss *of factor H leads to uncontrolled complement activation*



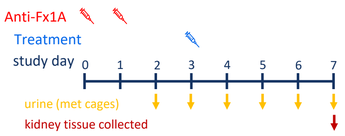
ADX-118 Circulation & Tissue PK/PD in $CfH^{-/-}$ Model



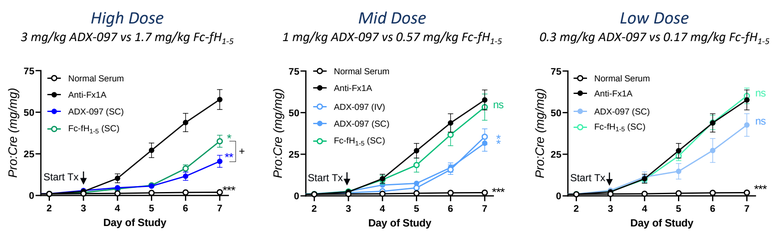
- In the rat PHN model, ADX-097 dosed as low as 1 mg/kg inhibited glomerular complement activation and significantly reduced urine protein-creatinine ratios, indicating potent disease-modifying efficacy. C3d-mediated tissue targeting drives ADX-097 potency, as tissue target engagement and efficacy in PHN are achieved without affecting systemic complement activity. Furthermore, equimolar doses of a non-targeted inhibitor (Fc-fH1-5) do not similarly reduce proteinuria.

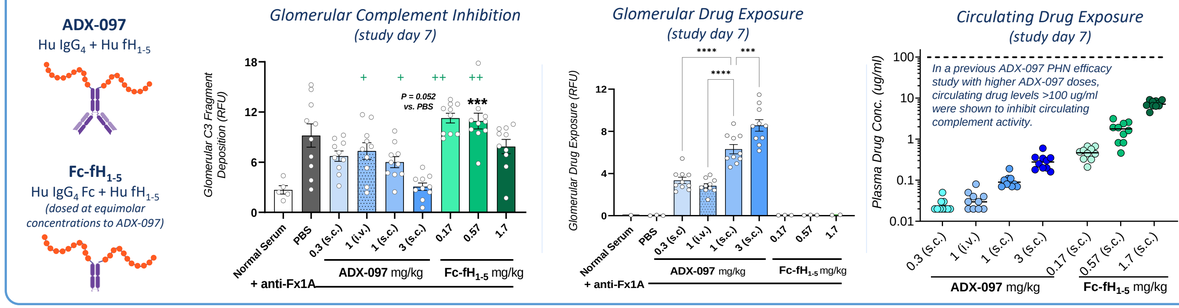
Passive Heymann Nephritis (PHN) model:

- Rats injected with 2 doses sheep anti-Fx1A serum
- Formation of immune complexes at GBM
  - Leads to complement activation & proteinuria

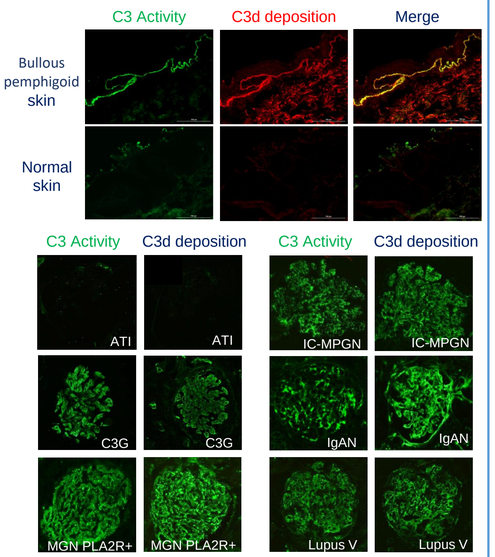


ADX-097 Efficacy in PHN Model (Proteinuria Reduction)

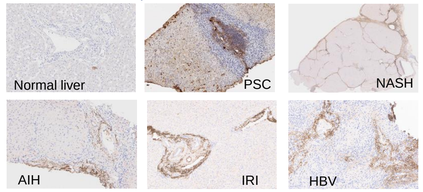




Immunostaining of C3 Active Fragment and/or C3d Deposition in Human Disease Tissues



C3d deposition in human liver diseases



ATI: acute tubular injury;
C3G: complement 3 glomerulopathy
MGN: membranous glomerulonephritis
IgAN: IgA nephropathy
IC-MPGN: membranoproliferative glomerulonephritis, immune complex type
PSC: primary sclerosing cholangitis
NASH: non-alcoholic steatohepatitis
AIH: autoimmune hepatitis
IRI: ischemia-reperfusion injury
HBV: hepatitis B viral infection

CONCLUSIONS

Our data demonstrate the therapeutic potential of ADX-097 and show that C3d-mediated tissue targeting of fH_{1-5} in preclinical models results in potent, durable, and efficacious local AP complement blockade at low doses that avoid systemic complement inhibition.

REFERENCES

1. See Poster A85 & B68 for construct design and in vitro characterizations;
2. EBA: Anti-mCol7 induced mouse model of epidermolysis bullosa acquisita;