ADX-097, a tissue targeted complement inhibitor

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3rd Rare and Genetic Kidney Disease Drug Development Meeting

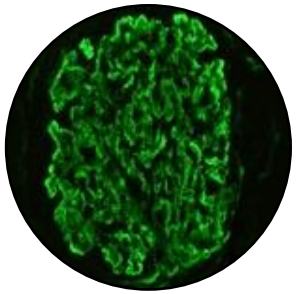
Boston, MA

13 Sept. 2023

Complement is an important driver of disease…

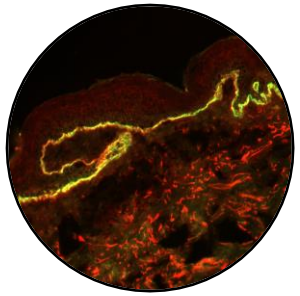
…but complement is also an immune & homeostatic mediator

Dysregulated local complement drives autoimmune diseases



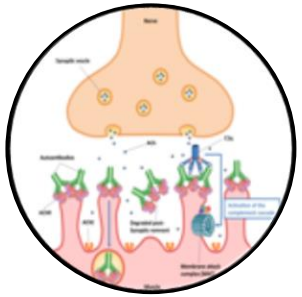
Kidney

- aHUS
- PNH
- Lupus Nephritis
- IgA Nephropathy



Skin

- Bullous Pemphigoid
- Hidradenitis suppurativa (HS)
- Discoid Lupus Erythematosus (DLE)



Neurodegenerative

- Myasthenia Gravis
- Multiple Sclerosis

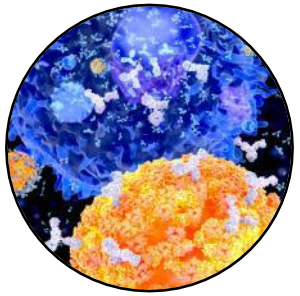
Eye

- Geographic Atrophy
- Autoimmune Uveitis

Complement mediates homeostatic and immune functions

Osmotic lysis of microbes

Phagocytosis (microbes & dead cells)



Recruitment and activation of leukocytes

Q32 BIO

Systemic/non-targeted complement inhibition has inherent limitations

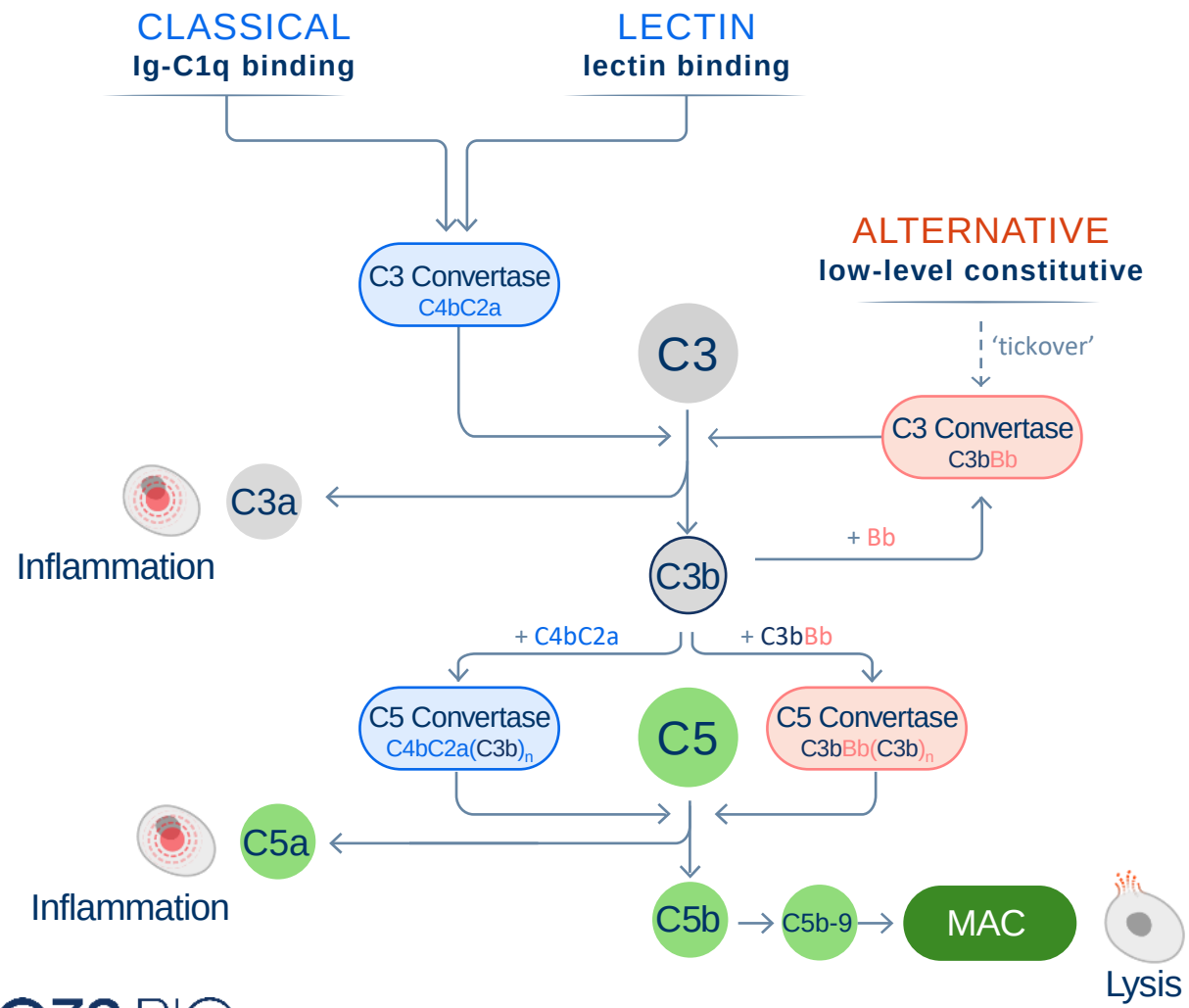
Complement contributes to pathology of myriad diseases. However, few drugs have made it to the final regulatory approval. **Why?**

- Large target sinks (e.g., circulating C3 levels are >1.0 mg/mL)
  - Some targets upregulated in disease (e.g. factor D, factor B)
- Rapid target turnover
  - Half-lives ranging from hours to a few days
- Need to maintain the protective roles of complement
  - Infection clearing
  - Shaping of adaptive immune response
  - Cross talk with coagulation and other systems

Q32 Bio is generating tissue-targeted complement inhibitors to address the limitations of systemic blockade

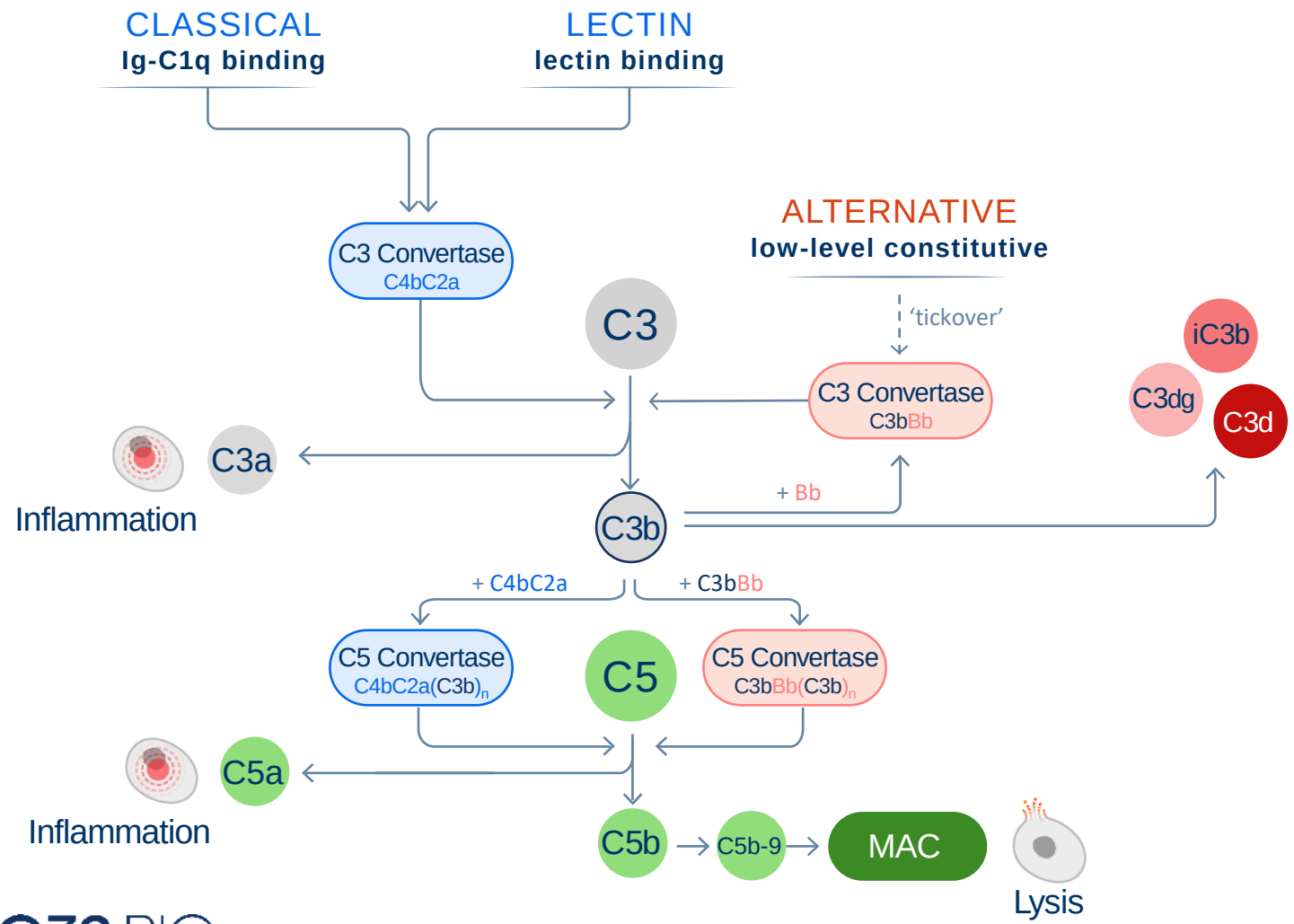
Q32 BIO

Complement is regulated by C3 and C5 convertases

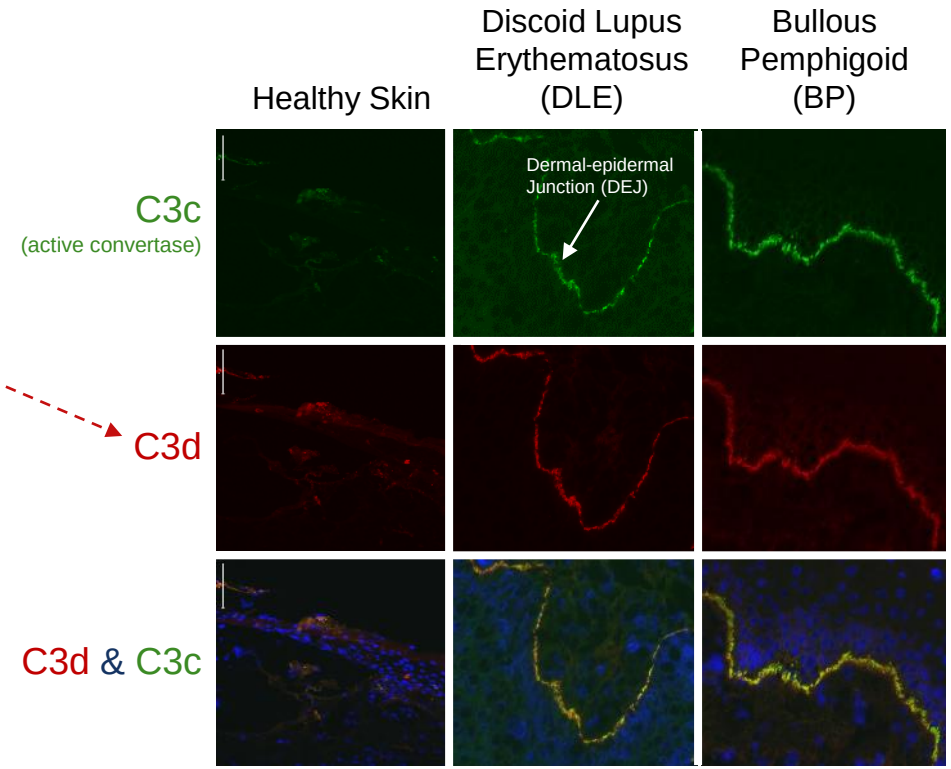


Q32 BIO

C3d is locally deposited where complement is active



C3d-containing fragments at skin sites of active complement



Shuyun Yu, Christine Lian
Brigham & Women's Hospital

Q32 BIO

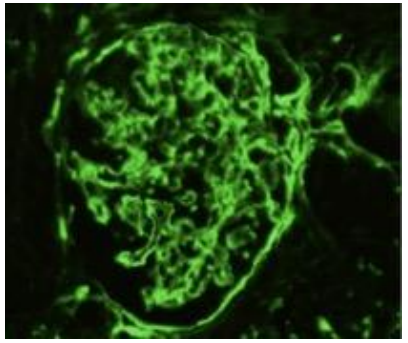
High density C3d deposition is observed in numerous complement-associated kidney diseases

anti-C3d immunofluorescence

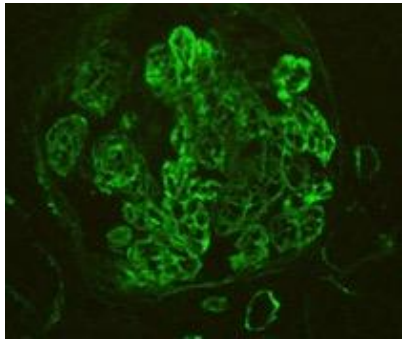
Negative controls

Disease

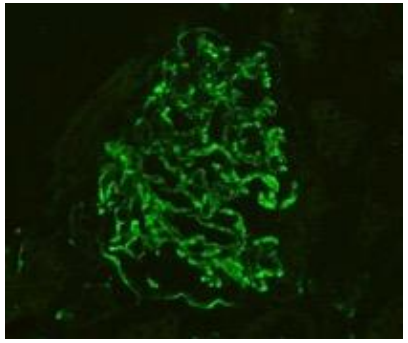
Acute Tubular Necrosis



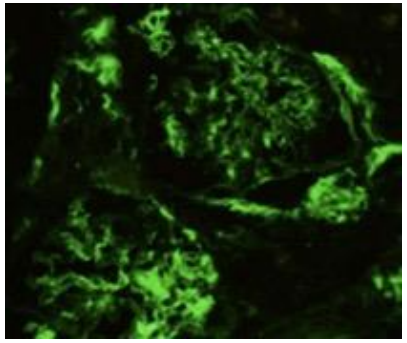
IgA Nephropathy



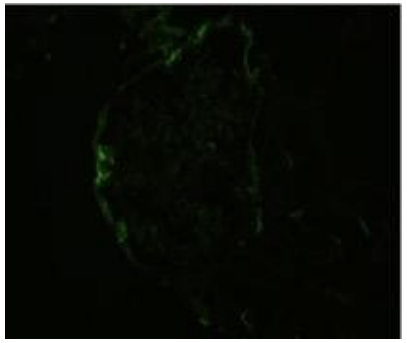
Lupus Class IV



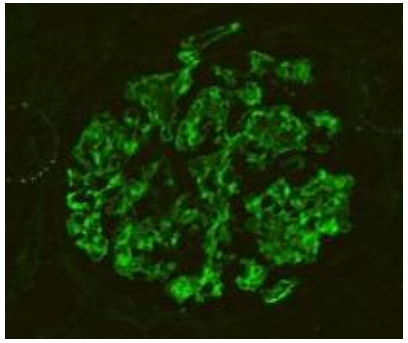
Lupus Class V



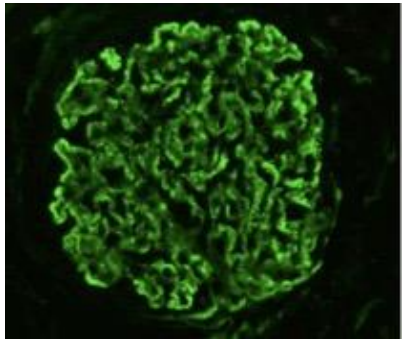
Minimal Change Disease



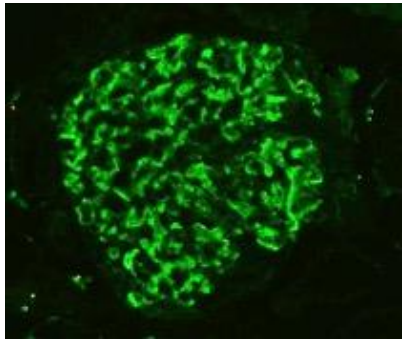
Thin Glomerular BM



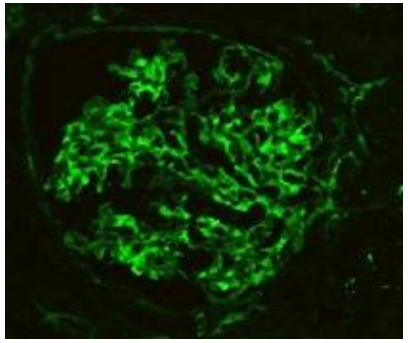
MPGN



Membranous (PLAR2+)

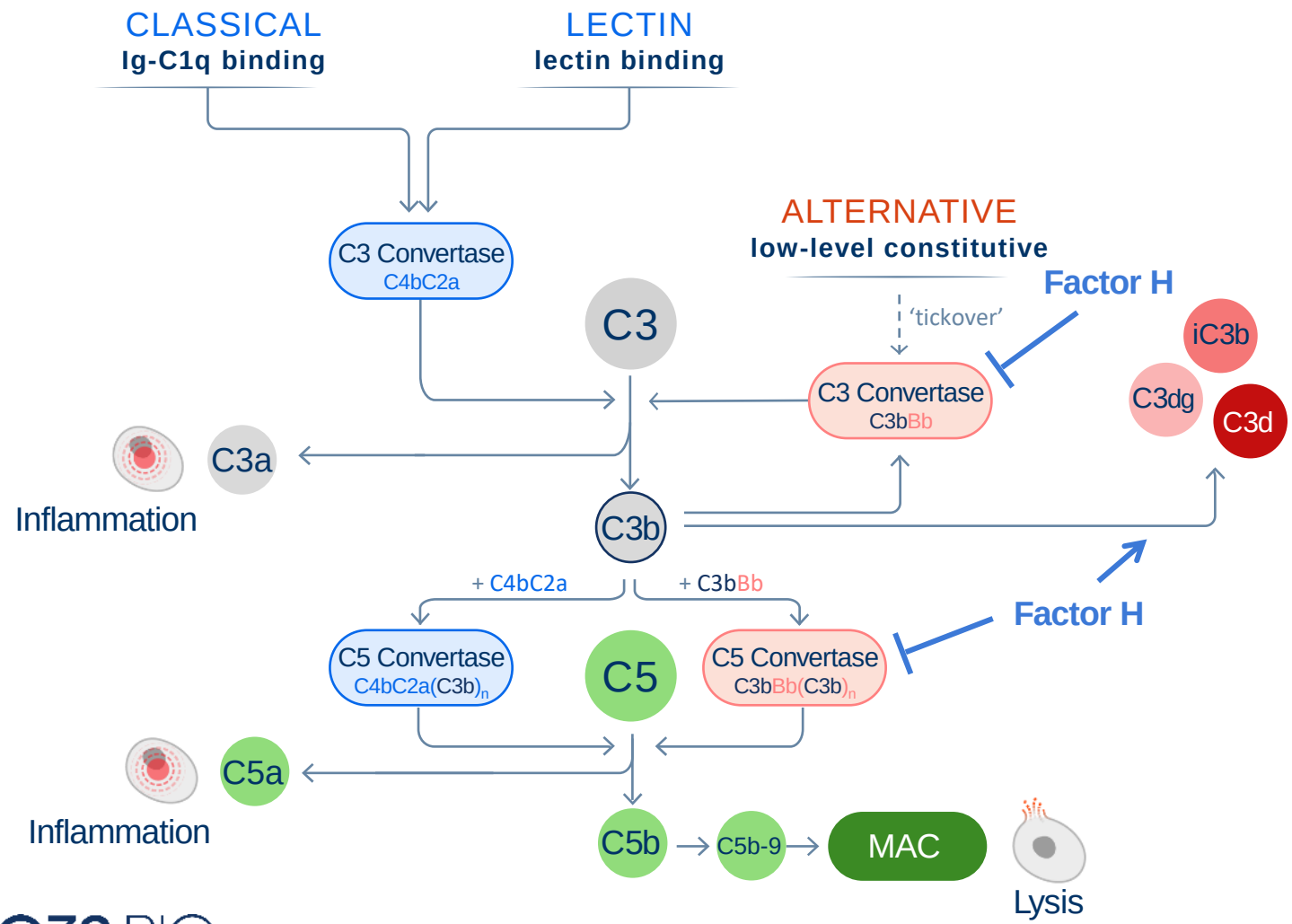


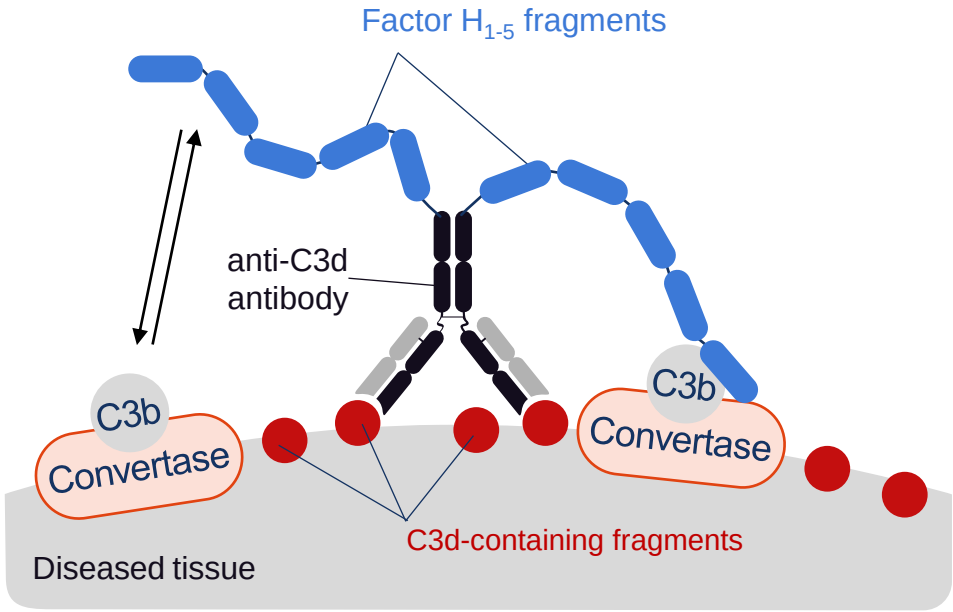
C3 Glomerulopathy



Diabetic Nephropathy

ADX-097 binds C3d and localizes factor H to complement in tissues





Q32 BIO

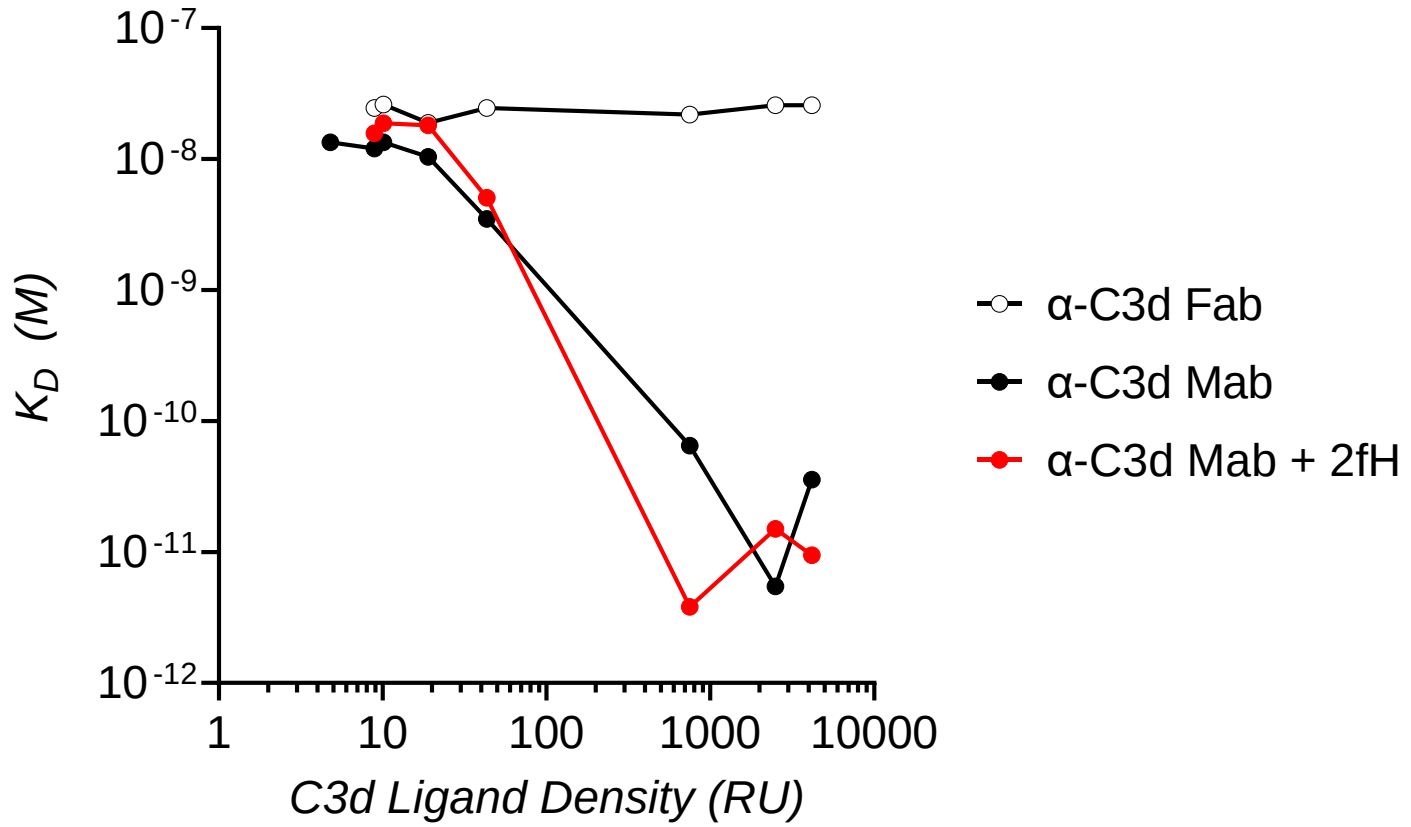
ADX-097 binds high-density C3d with high affinity

ADX-097 binds high-density C3d with greater affinity than to low density C3d

Affinity measurements (SPR) with increasing C3d density

Lower affinity

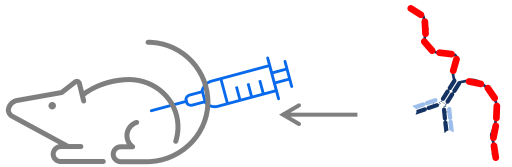
Higher affinity



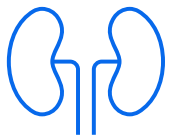
C3d mAb-fH$_{1-5}$ potently and durably reduces glomerular complement while avoiding systemic complement inhibition

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

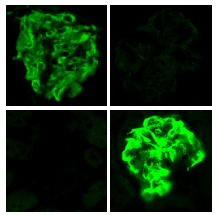
Loss of factor H leads to uncontrolled complement



Single dose, IV or SC ADX-118



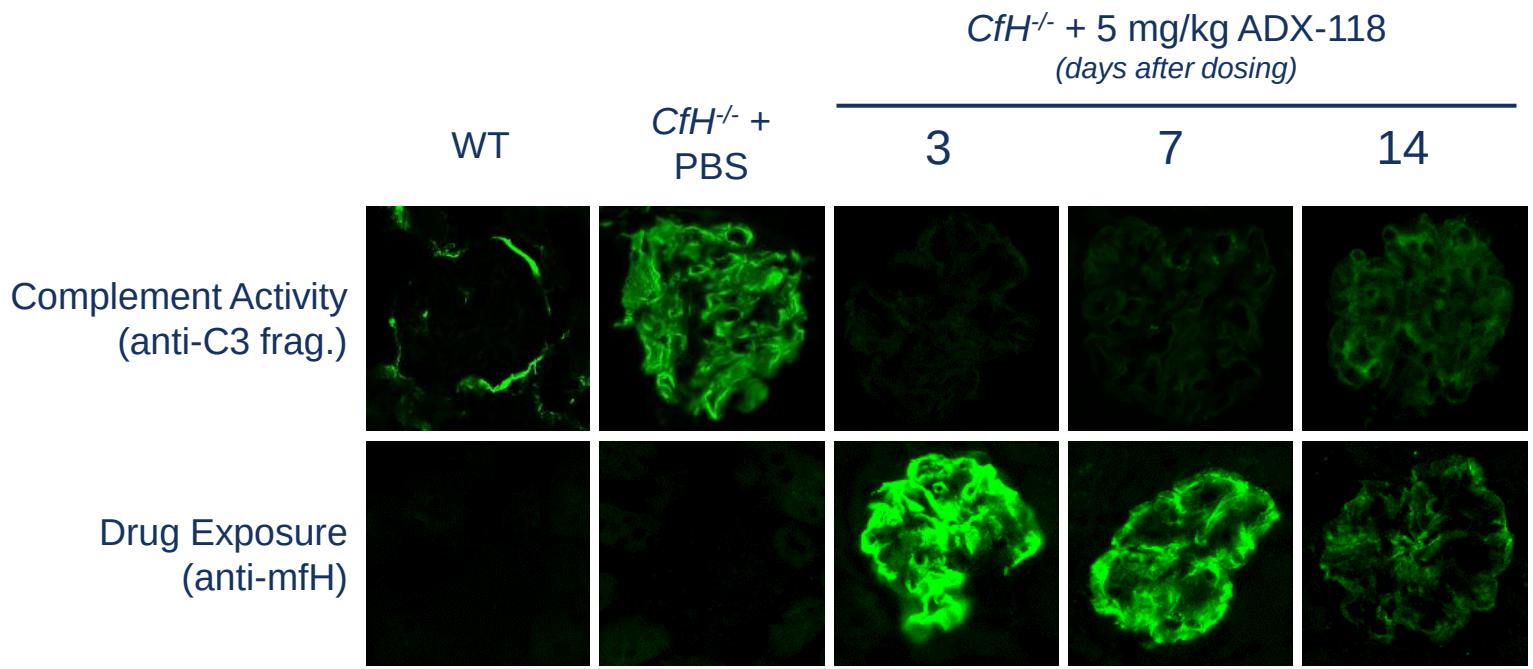
Kidneys harvested at defined timepoints



Tissue drug targeting and complement inhibition measured by immunofluorescence

ADX-118 localizes to kidney and inhibits complement

Single subcutaneous administration



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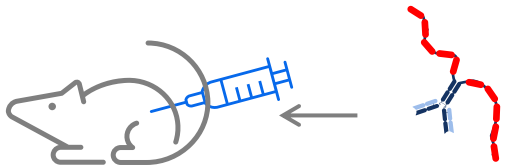
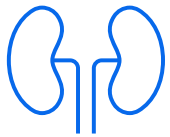
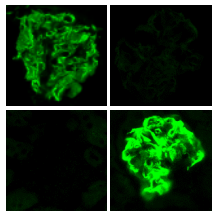


Single dose, IV or SC ADX-118



Kidneys harvested at defined timepoints

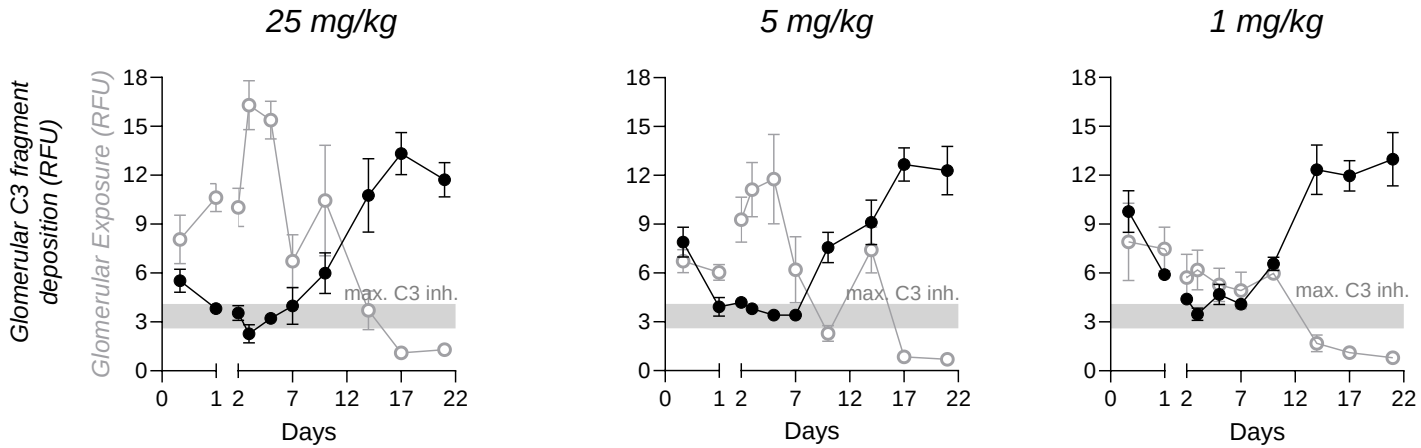


Tissue drug targeting and complement inhibition measured by immunofluorescence

Durable tissue complement inhibition without systemic blockade

Single subcutaneous administration of mouse C3d mAb – fH$_{1-5}$ (ADX-118)

Tissue PK/PD



● Glomerular C3 Fragment

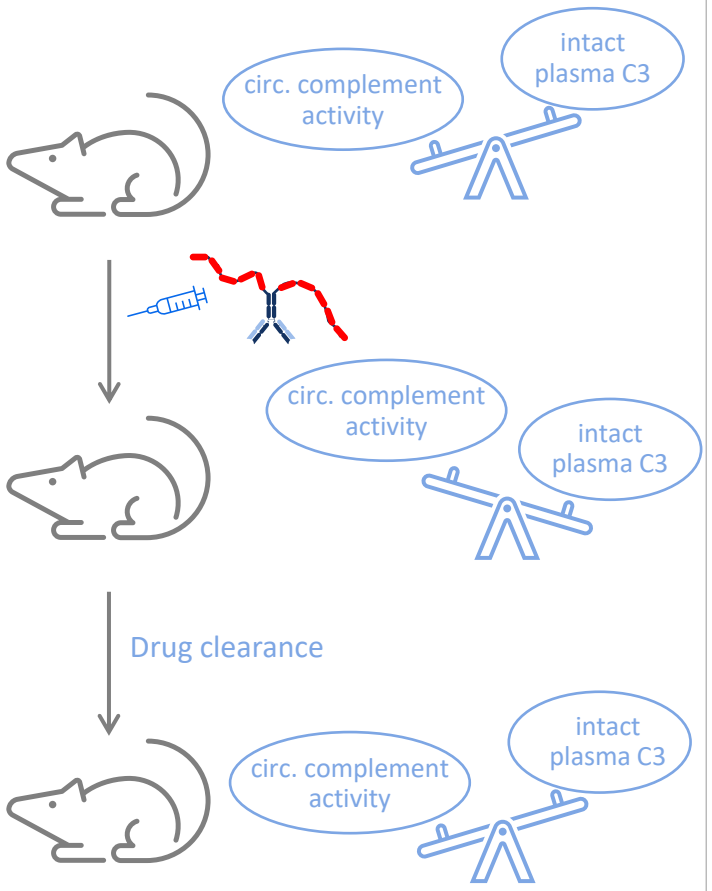
○ Glomerular Drug Exposure

Q32 BIO

C3d mAb-fH$_{1-5}$ potently and durably reduces glomerular complement while avoiding systemic complement inhibition

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

Loss of factor H leads to low plasma C3



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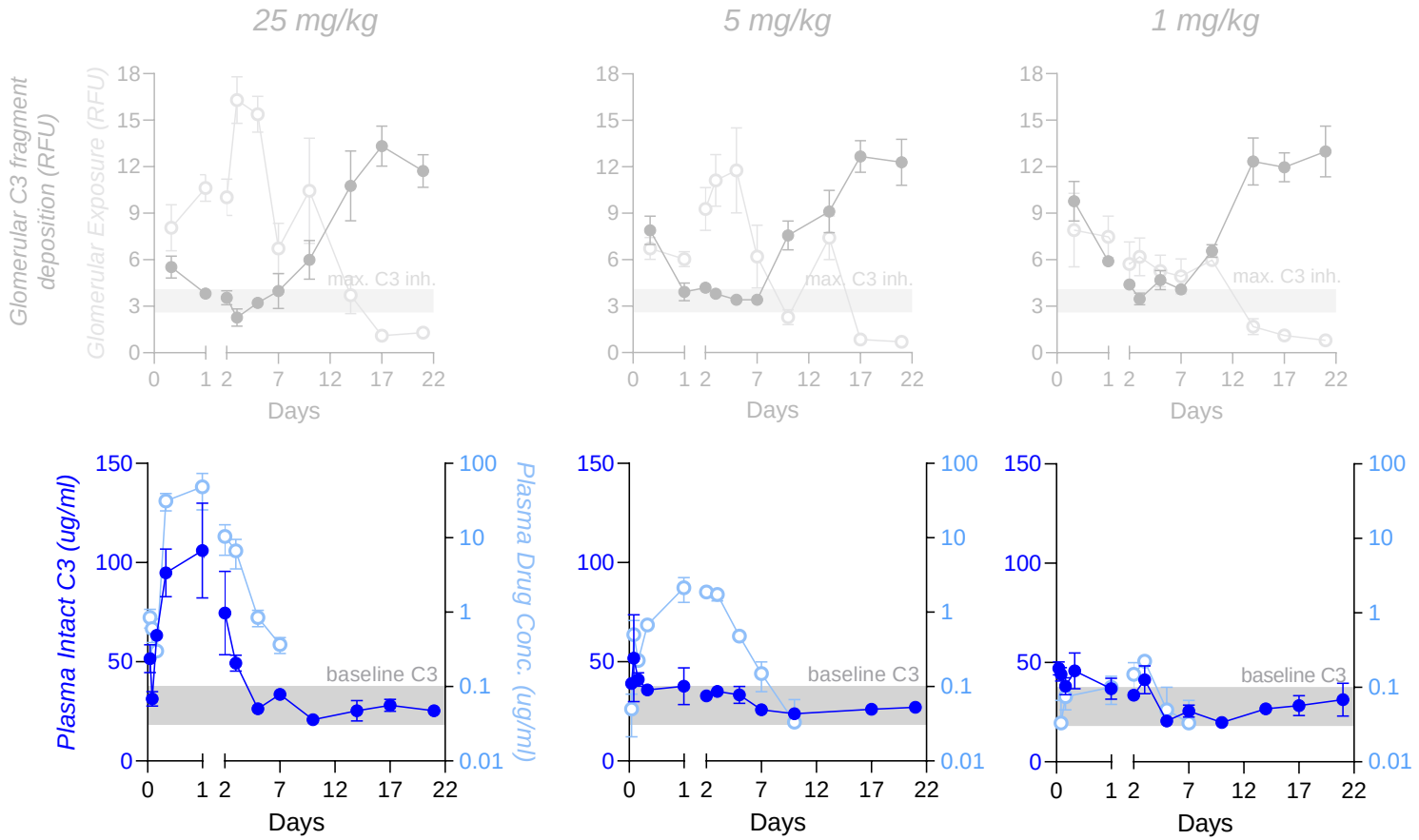
Tissue PK/PD

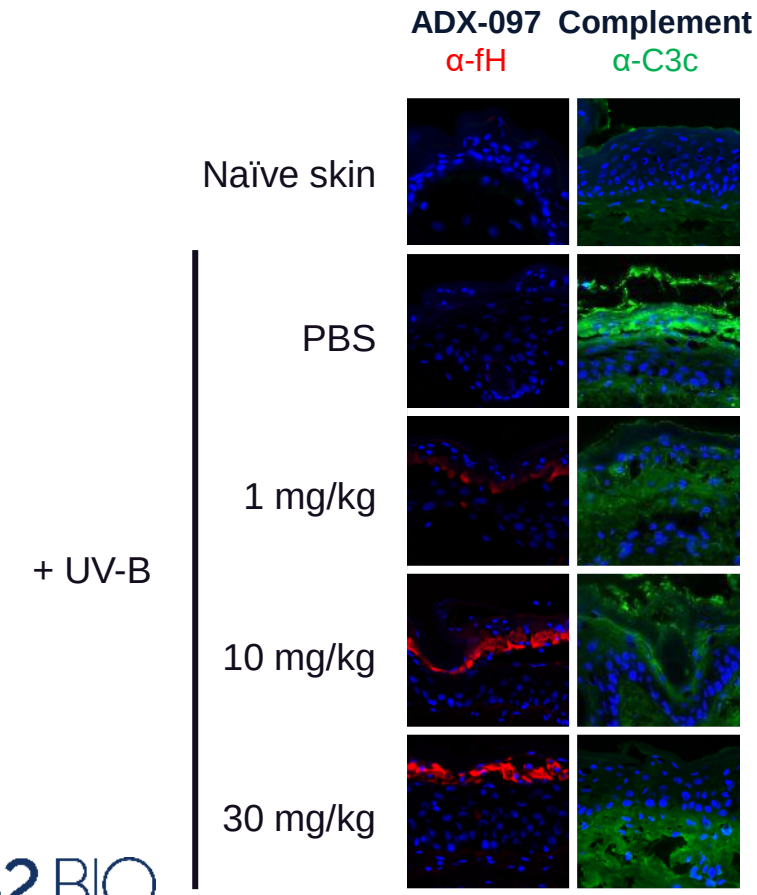
Circulating PK/PD



ADX-097 inhibits NHP skin complement activation at doses that do not affect systemic complement activity

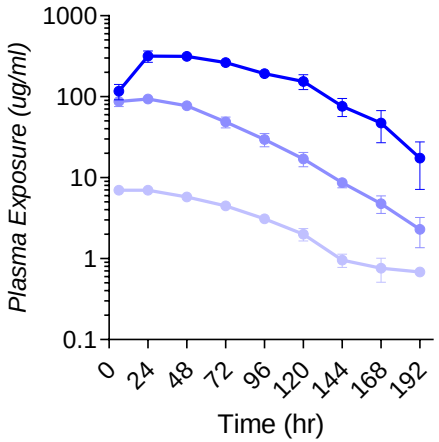
Immunostaining of ADX-097 and Inhibition of Complement Activation

48h post-dose

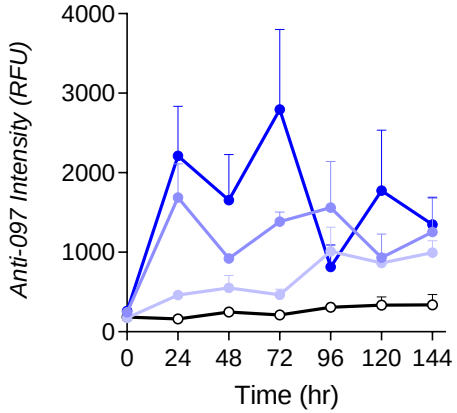


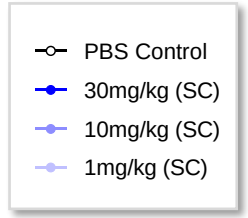
Quantitation of Tissue and Circulating PK/PD

Circulating drug exposure

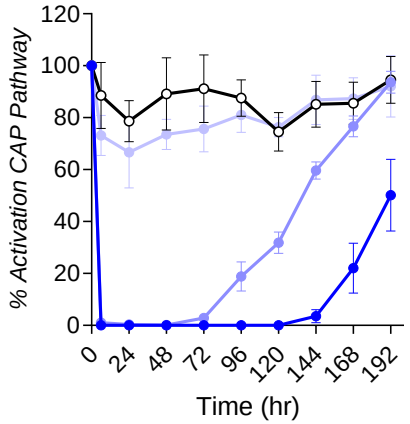


Tissue drug exposure

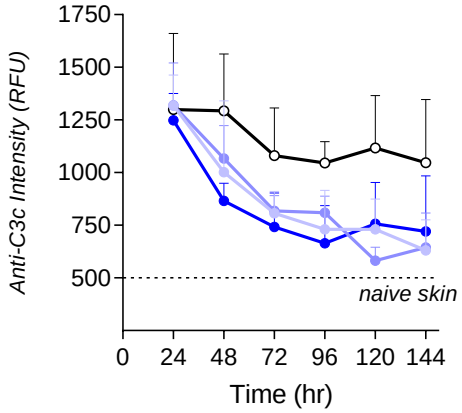




Circulating complement activity



Tissue complement activity



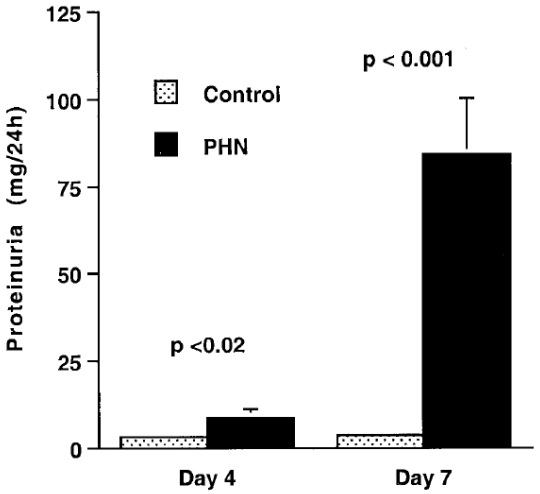
ADX-097 reduces disease progression by locally inhibiting tissue complement

- ADX-097 homes to local complement through C3d binding
- Subcutaneous delivery at doses that do not affect systemic complement

Passive Heymann Nephritis (PHN) is a complement-driven model of Membranous Nephropathy in rats

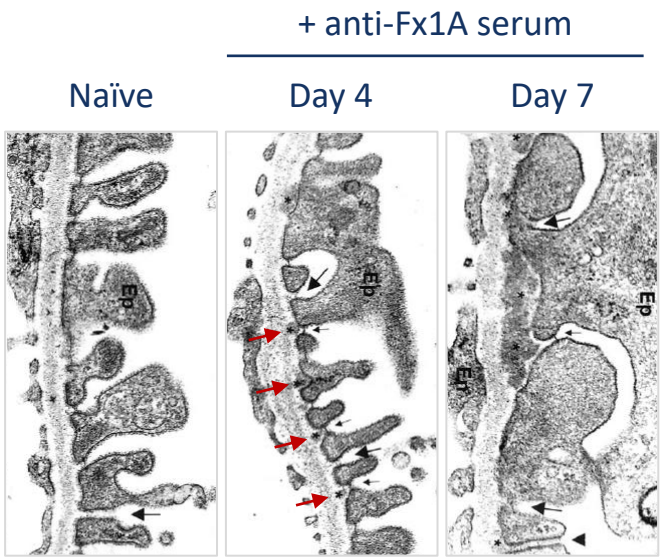
Passive Heymann Nephritis (PHN): Injection With Sheep anti-GBM Serum Induces Rapid, Immune Deposit-Driven Renal Injury

Proteinuria
mg/24 hr volume (ml)



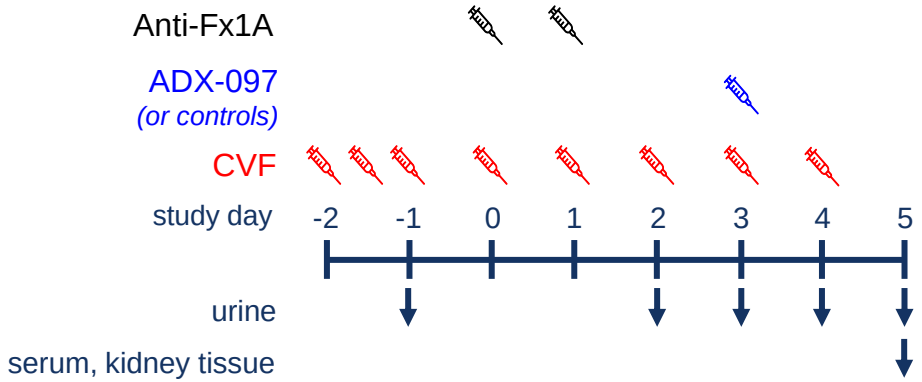
Yuan et al., JASN 2002

Podocyte Effacement and GBM Alteration
Transmission EM



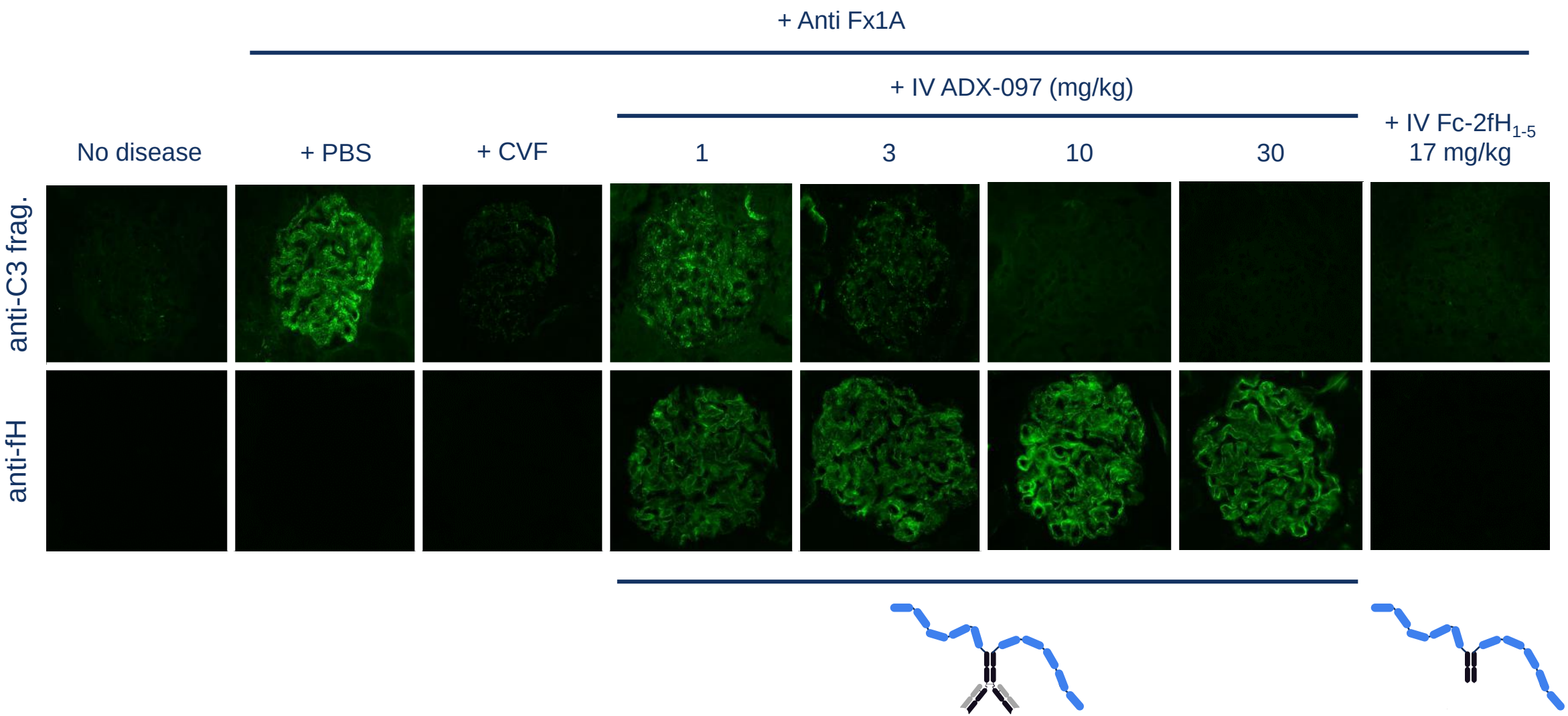
Yuan et al., JASN 2002

Study Design: Evaluation of ADX-097 in PHN



Q32 BIO

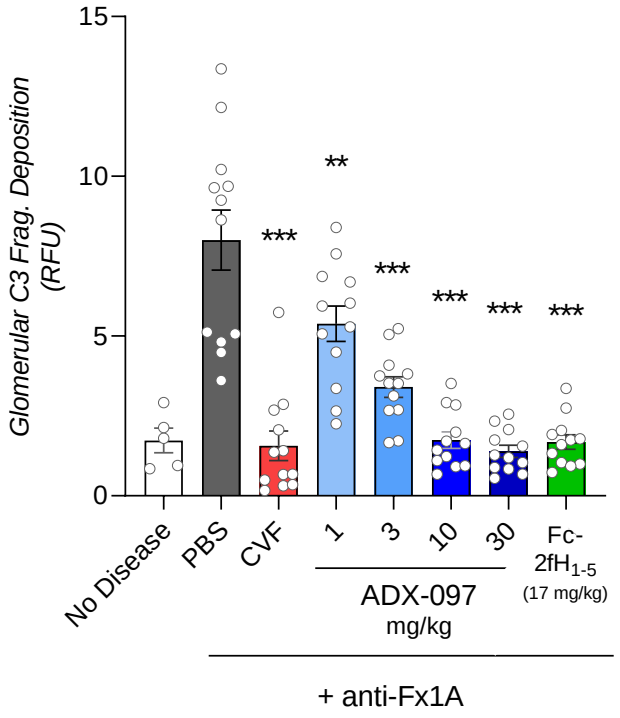
ADX-097 homes to PHN glomeruli and inhibits local complement activation



ADX-097 reduces proteinuria and inhibits glomerular complement at doses that do not block systemic complement activity

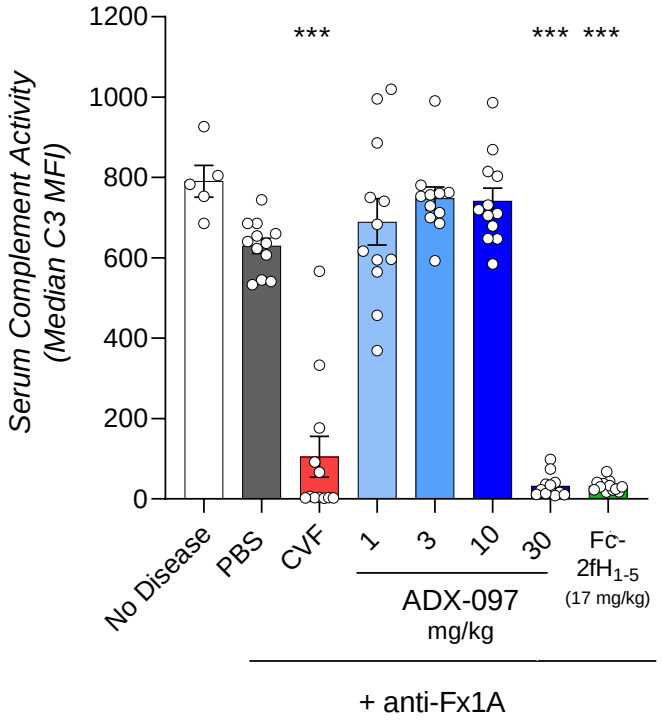
ADX-097 Inhibits Tissue Complement at Doses ≥ 1 mg/kg

Glomerular Complement – anti-C3 frag. IHC



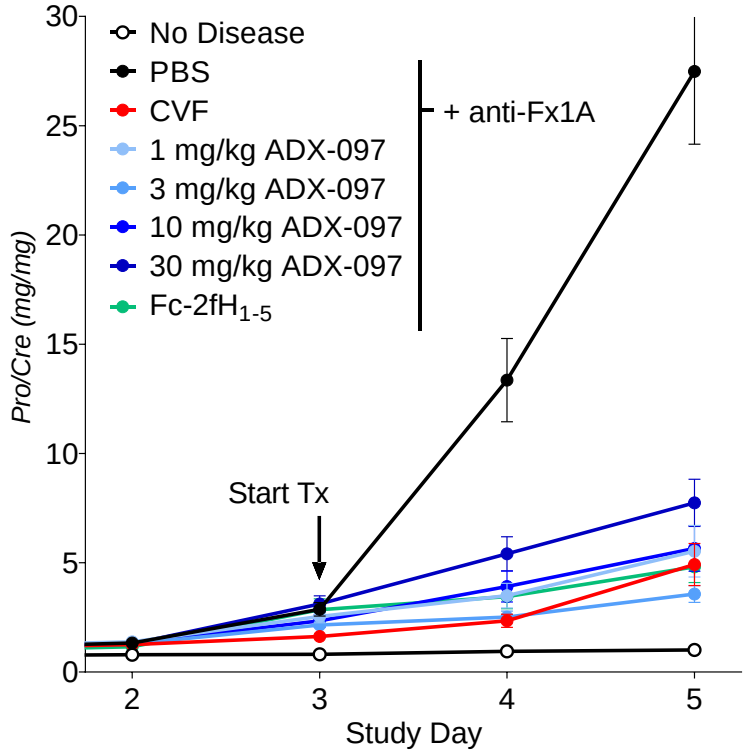
Low Doses of ADX-097 Do Not Inhibit Systemic Complement

Serum Complement Activity - Zymosan Assay



ADX-097 Reduces Renal Injury (Proteinuria) at Doses ≥ 1 mg/kg

Urine Protein/Creatinine Ratio



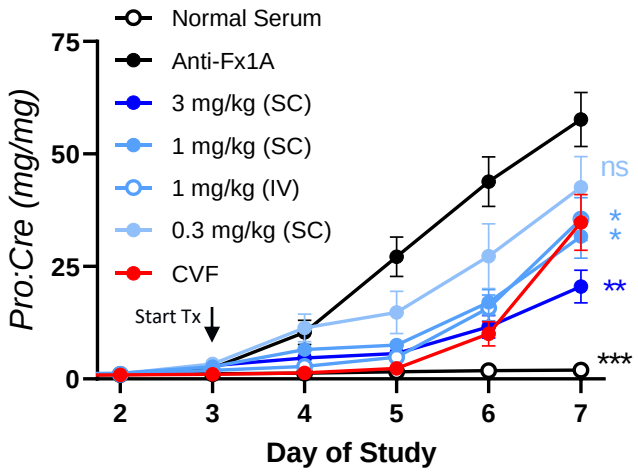
* P < 0.01, ** P < 0.005, *** P < 0.0001 (vs. PHN + PBS)

CVF = Cobra Venom Factor (systemic complement inhibitor)

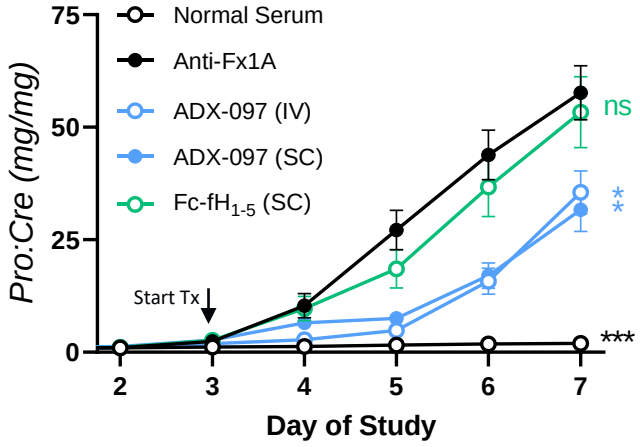
Q32 BIO

Tissue targeting improves renal potency in Passive Heymann Nephritis rats

ADX-097 dose-dependently attenuates proteinuria

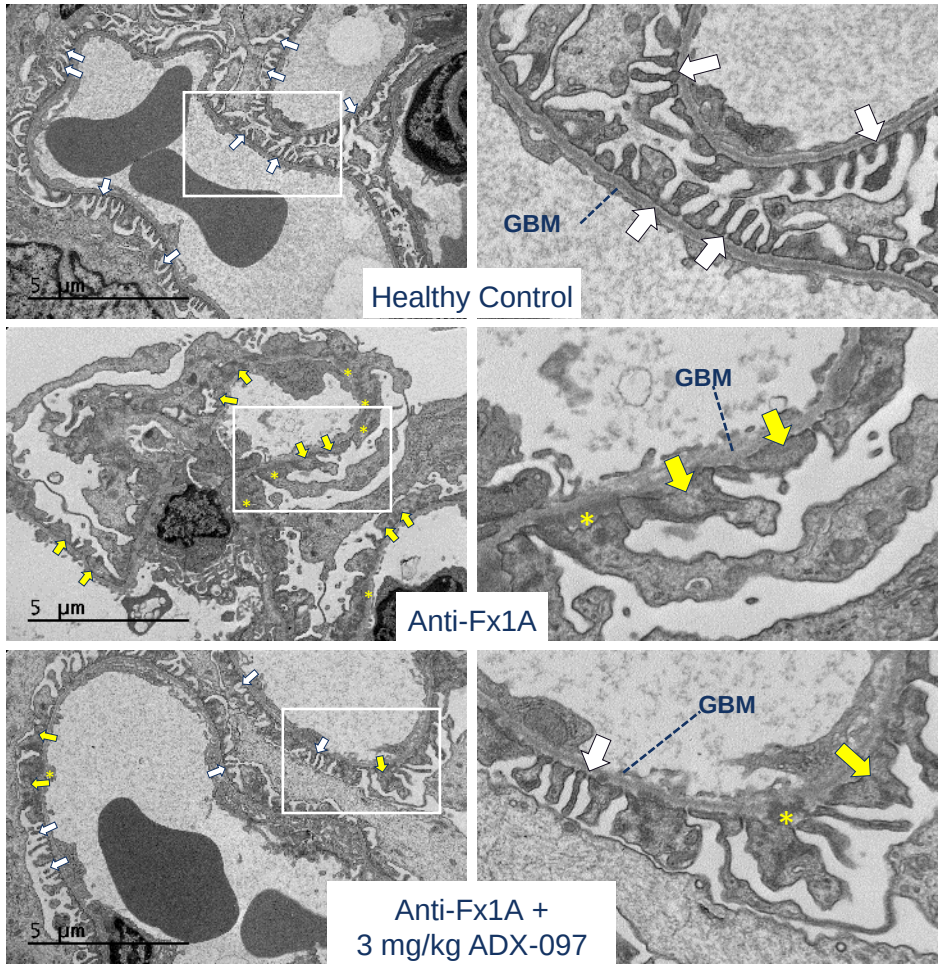


Tissue targeting drives potency of ADX-097



** P < 0.01, ** P < 0.005, *** P < 0.0001 (AUC vs. anti-Fx1A + PBS)*

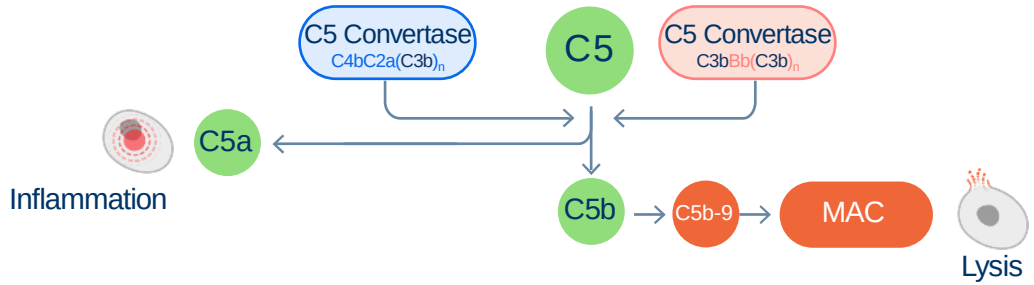
ADX-097 preserves podocyte ultrastructure



Hui Chen, Joel Henderson
Boston University Medical School

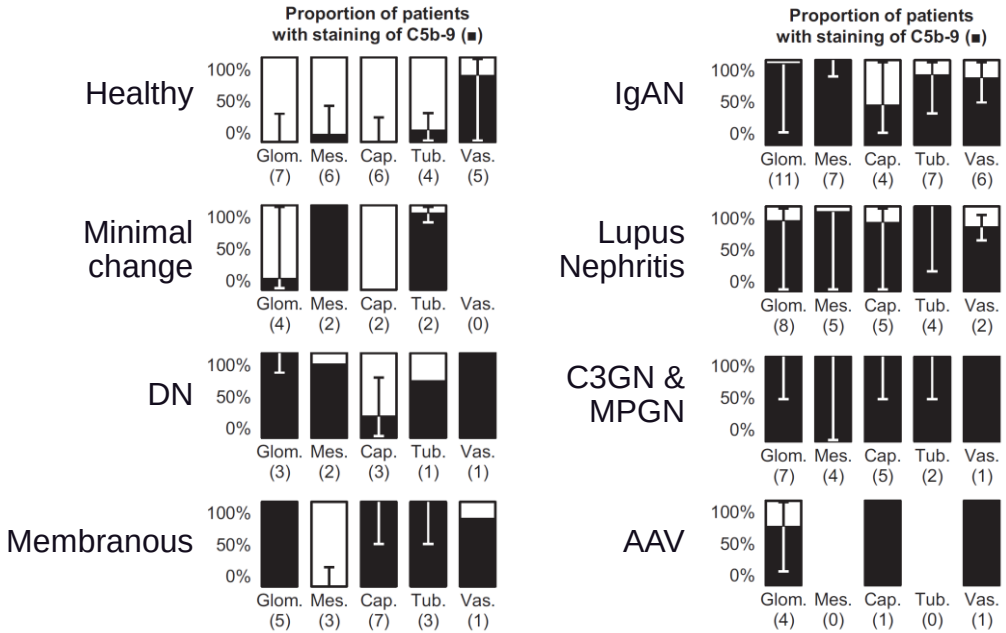
Changes in C5b-9 are associated with complement-driven disease

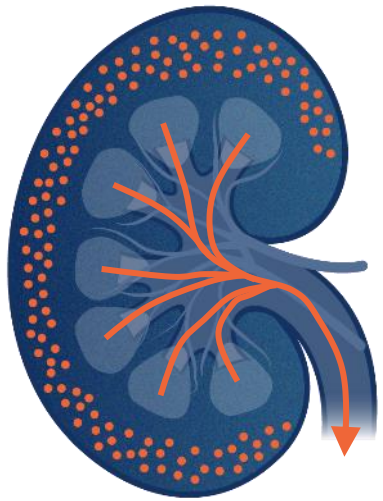
Terminal C5b-9 complement complex mediates cell lysis



C5b-9 is deposited in diseased kidney tissue

meta-analysis by Koopman et al., Front. Immunol., 2021



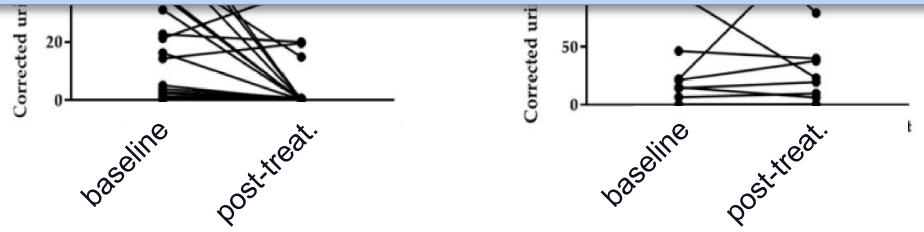


C5b-9 can be detected in urine and can be a marker of treatment response in IgAN

data from Yu et al., J. Clin Med. 2022

steroid response | steroid non-response

Key question:
How does urine C5b-9 relate to tissue C5b-9?



Samples from studies of ADX-097 in PHN allow evaluation of relationship between tissue complement and urine C5b-9

ADX-097 Inhibits Tissue Complement at Doses ≥ 1 mg/kg

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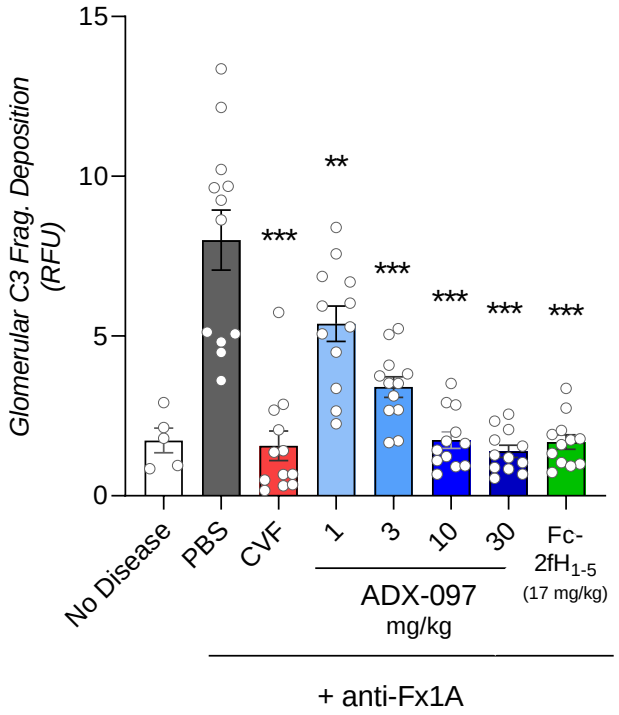
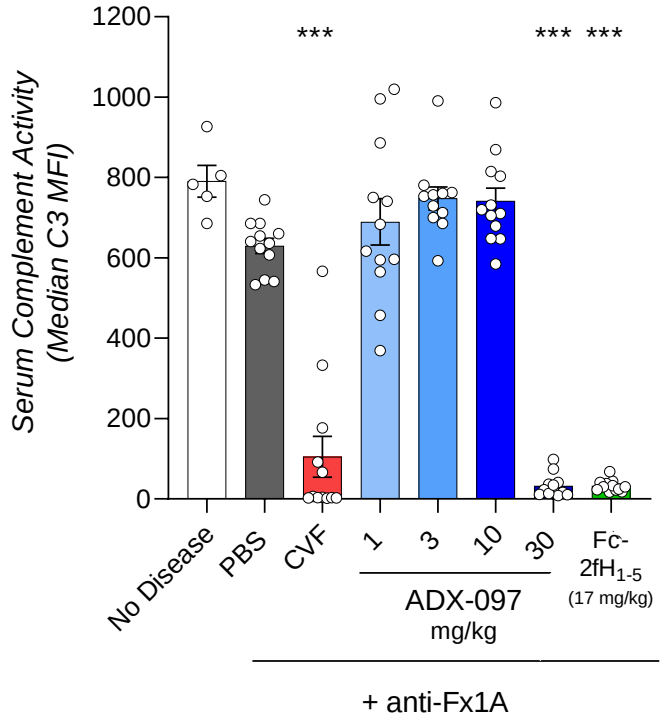


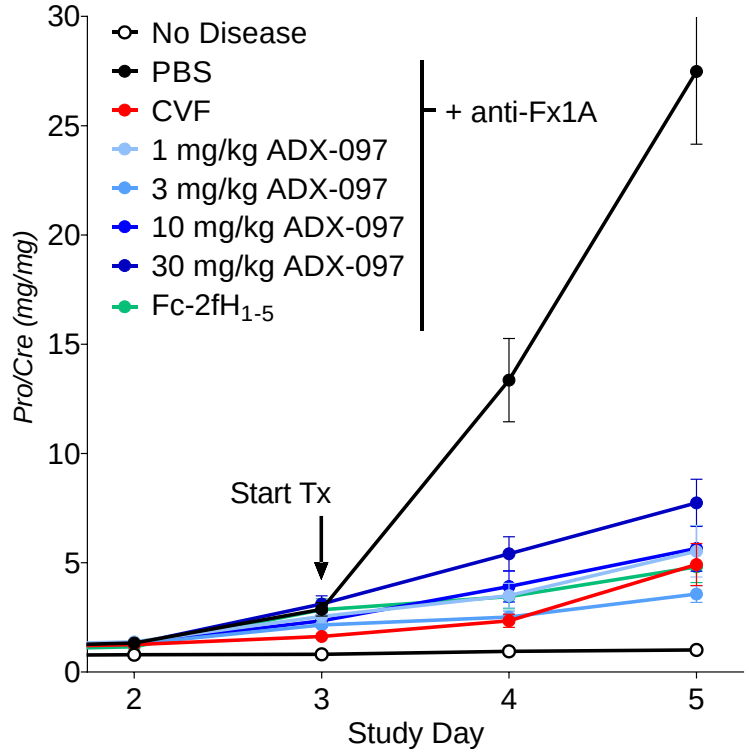
Low Doses of ADX-097 Do Not Inhibit Systemic Complement

Serum Complement Activity - Zymosan Assay



ADX-097 Reduces Renal Injury (Proteinuria) at Doses ≥ 1 mg/kg

Urine Protein/Creatinine Ratio



0.005, *** P < 0.0001 (vs. PHN
enom Factor (systemic com

Dose-dependent tissue complement inhibition

No inhibition of circulating complement

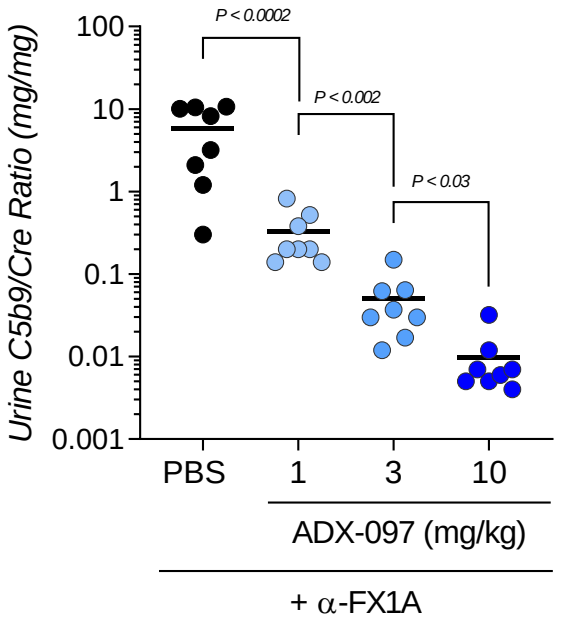
Similar proteinuria in ADX-097-treated groups

Urine C5b-9 is a biomarker of tissue complement and demonstrates kinetics of tissue target engagement

ADX-097 dose-dependently reduces urine C5b-9

Urine C5b-9/Creatinine Ratio

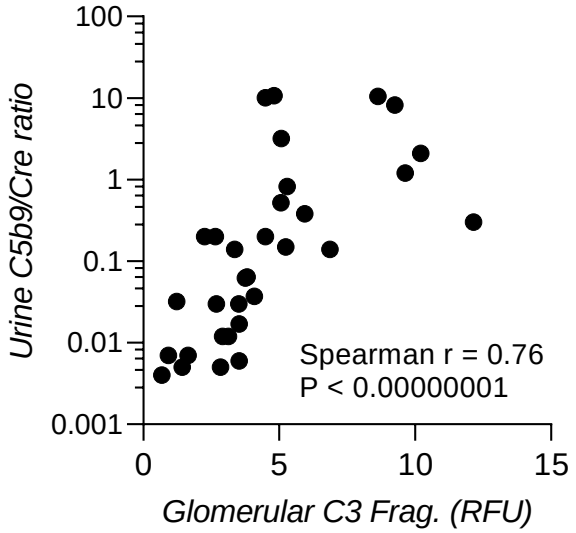
Samples collected 4 days post-dose



Urine C5b-9 closely correlates with tissue complement activity

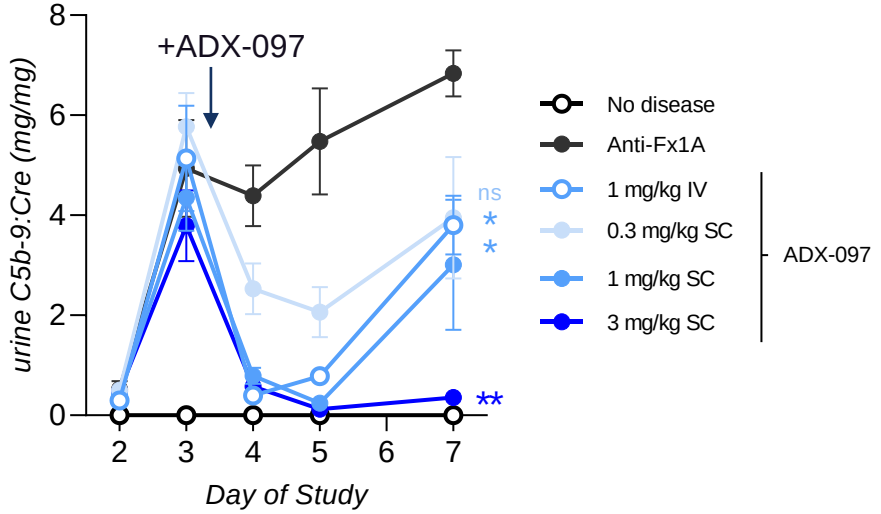
Urine C5b-9/Creatinine Ratio vs Glomerular C3 IHC

Samples collected 4 days post-dose



Urine C5b-9 reveals kinetics of tissue complement inhibition by ADX-097

Urine C5b-9/Creatinine Ratio



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ADX-097 reduces disease progression by locally inhibiting tissue complement

- ADX-097 homes to local complement through C3d binding
- Subcutaneous delivery at doses that do not affect systemic complement
- Modulates disease progression
- Soluble C5b-9: a urine biomarker of tissue complement activity
- Completing Ph1 clinical trial

Thanks!

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