Q32 BIO

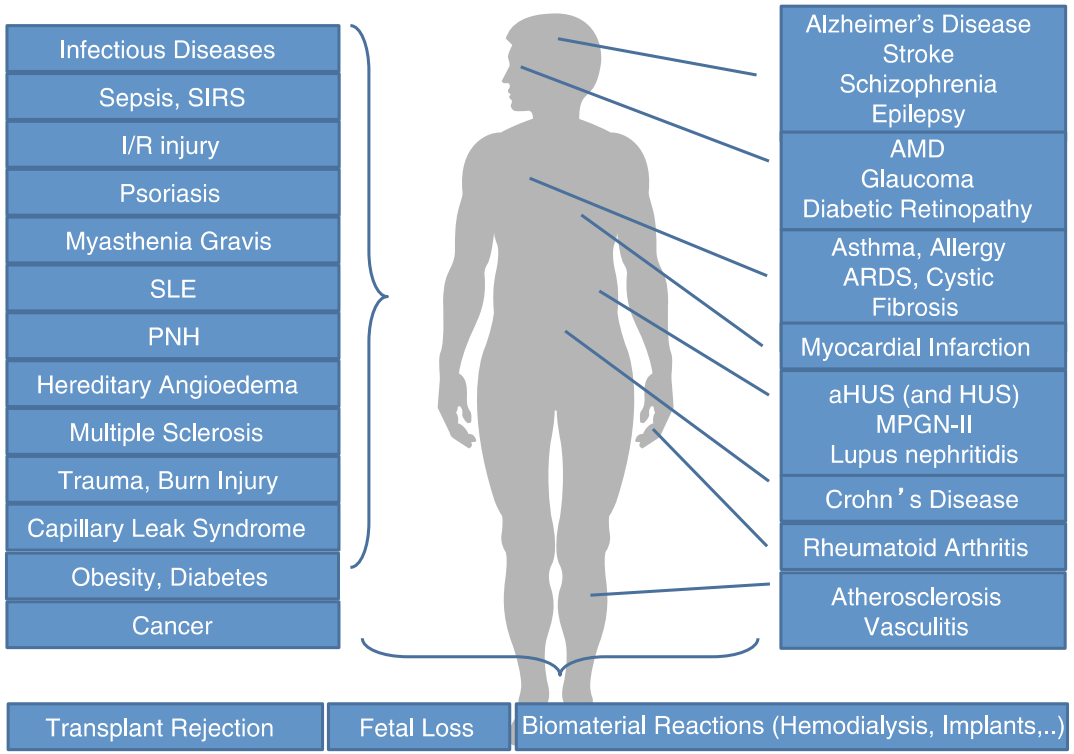
The Clinical Promise of Tissue Directed Complement Therapeutics

Jason A Campagna MD, PhD

'For extreme diseases, extreme strictness of treatment is most efficacious’

Hippocrates of Kos, Aphorisms

The complement system is now understood to causally contribute to a growing list of immune, inflammatory and age-related conditions

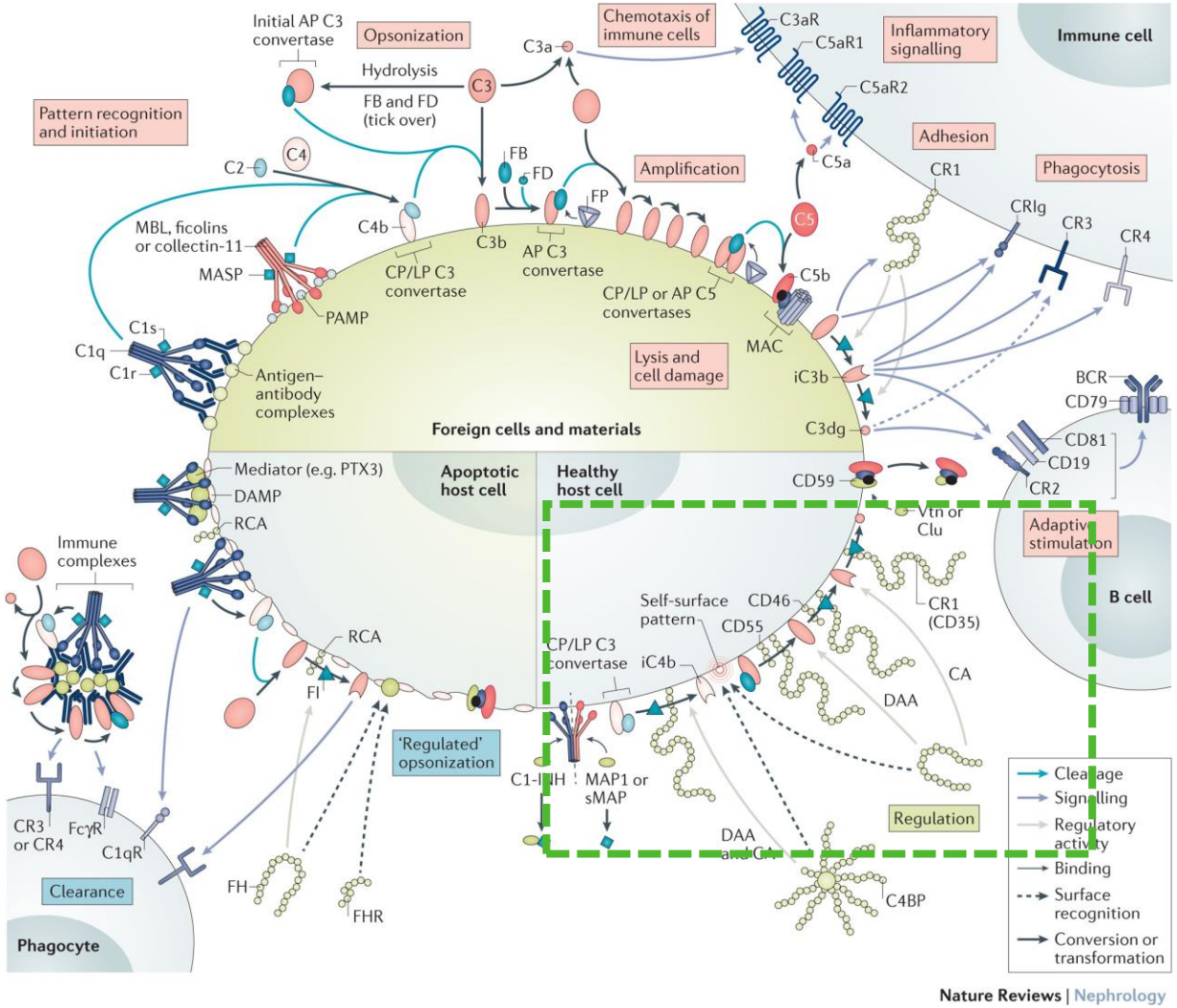


Adapted from D. Ricklin and J.D. Lambris 2013

- The modern picture of complement is one of **a powerful surveillance system** that can be triggered and cause damage to injured, stressed or immune targeted cells.
- **Excessive or dysregulated activation is linked to the pathogenesis** of myriad disorders ranging from acute inflammatory to chronic, including cancer, autoimmune, and age-related neurodegenerative, diseases.

Successful therapeutic modulation of the complement system across a broad array of diseases requires maximal inhibition of inappropriate activation at specific sites injury while limiting impairment of systemic protective functions

Modulators of complement in circulation and on cell surfaces are essential to protect healthy cells and to adjust the response of the system to insults



Ricklin, D. *et. al.* (2016) *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2016.70

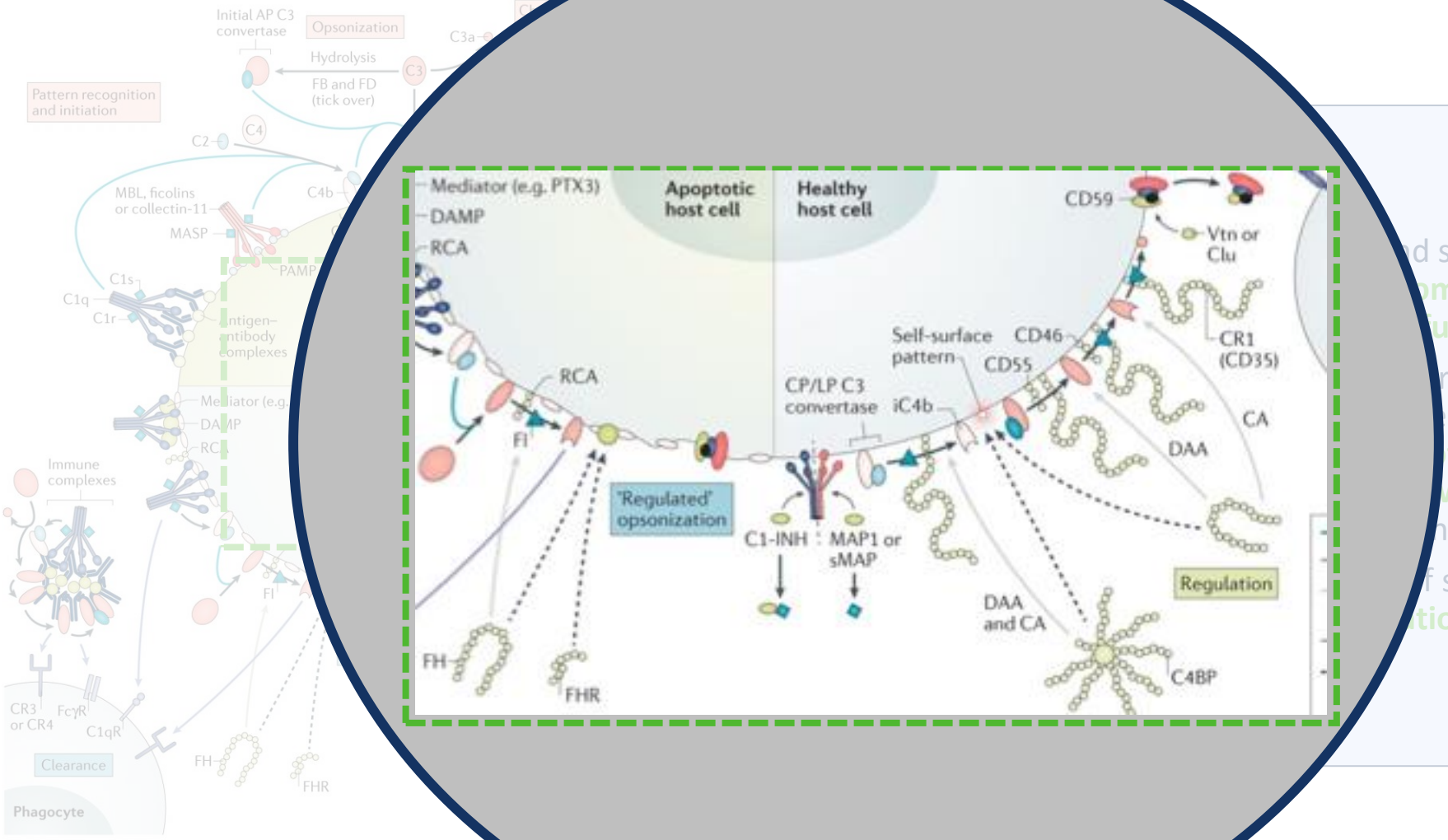
Health

- When fluid-phase and surface-directed complement regulation is intact, **complement maintains immunosurveillance function by sparing healthy cells**.
- The severity and outcome of complement response to distinct triggers must be **carefully tuned and depends on the context-specific interplay** of some 50 different proteins.

Disease

- When damaged cells, artificial surfaces or host surfaces are **not sufficiently protected by regulatory molecules that drive the C3b breakdown process and inhibit AP amplification,** non-linear C3 fragment accumulation occurs, **driving convertase assembly**
- Persistent assembly of **surface-bound** C3 and C5 convertases **fuels** effector generation **and inflammatory tissue damage**.

Modulators of complement in circulation and cell surfaces are essential to protect healthy cells and to adjust the response of the system to insults



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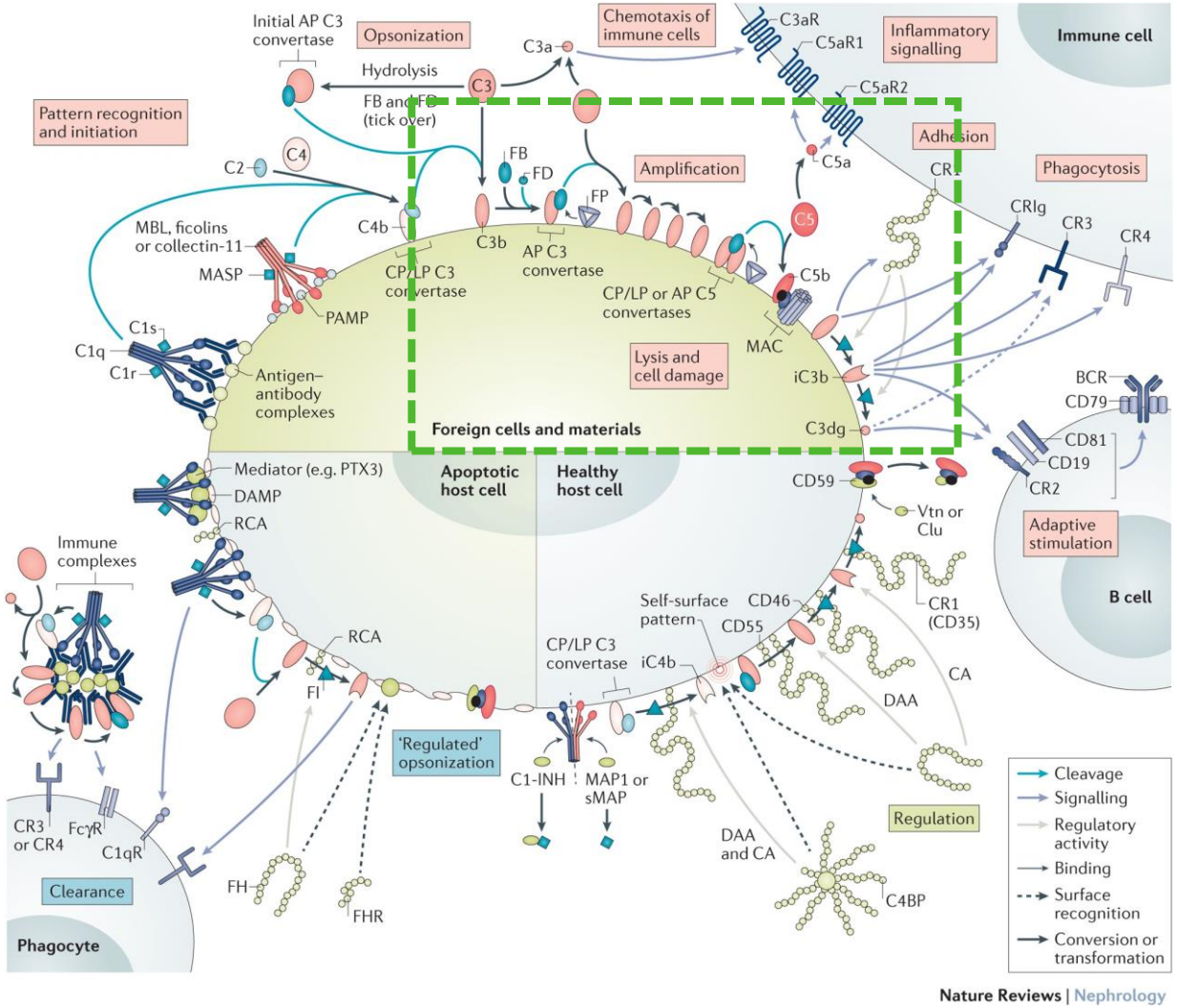
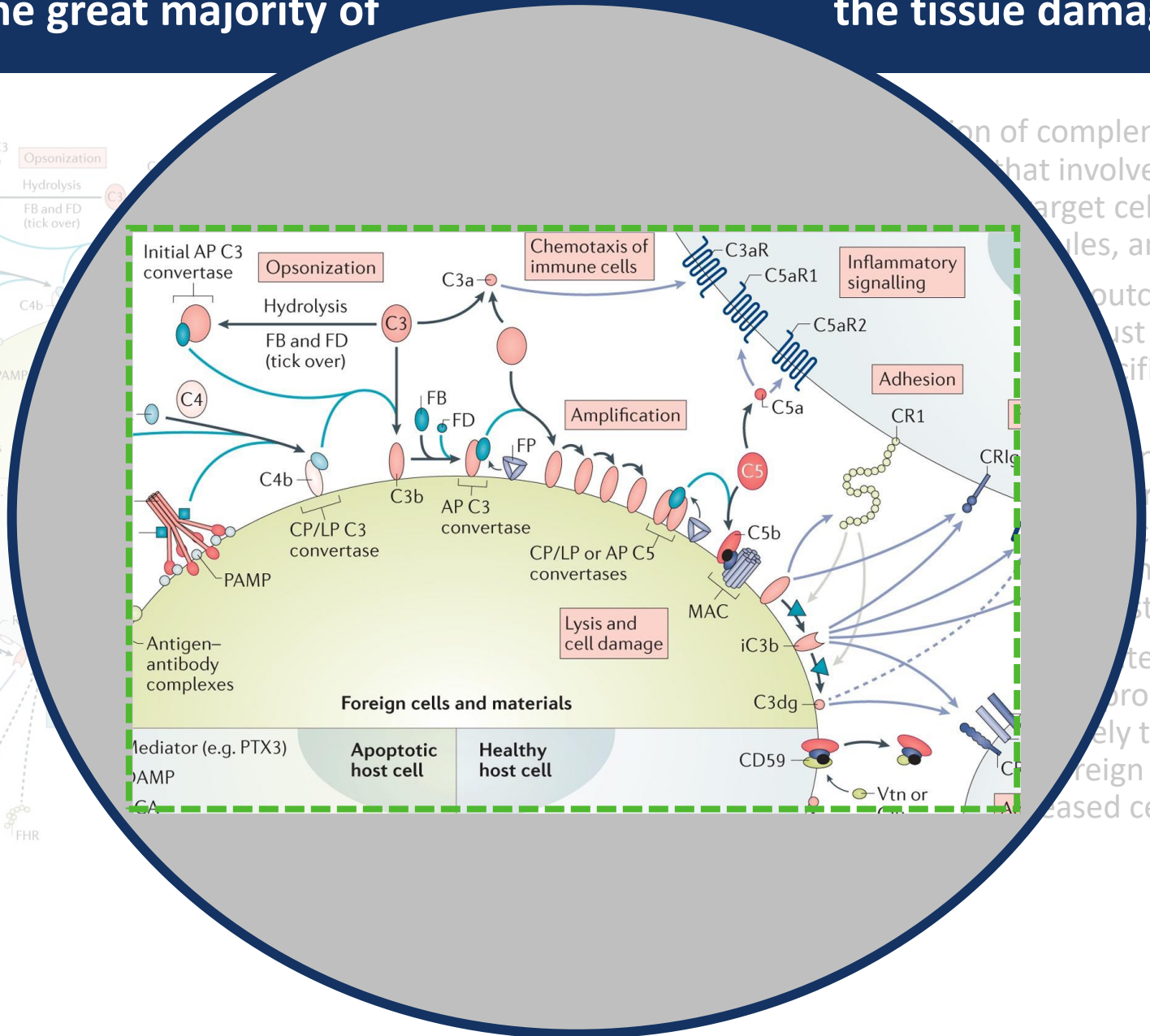


Nature Reviews | Nephrology

- Activation of complement typically follows a simple sequence that involves **surface recognition and opsonic tagging of a target cell,** self-amplification, generation of effector molecules, and induction of immune signaling.
- In complement-related disorders, detrimental activation and amplification process **occurs directly on surfaces that inappropriately trigger the defensive actions of complement:** foreign biomaterials, transplanted cells or organs, or diseased cells and tissues.
- Independent of initiation route, **amplification of response by the AP, via formation of C3 convertases** that cleave the central component C3 into C3a and an C3b (opsonin) fragment, **cause most of overall complement activation.**

Under most circumstances, C3-mediated surface amplification by the alternative pathway contributes the great majority of the tissue damaging effector response



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Fluid phase targeting of complement has inherent limitations

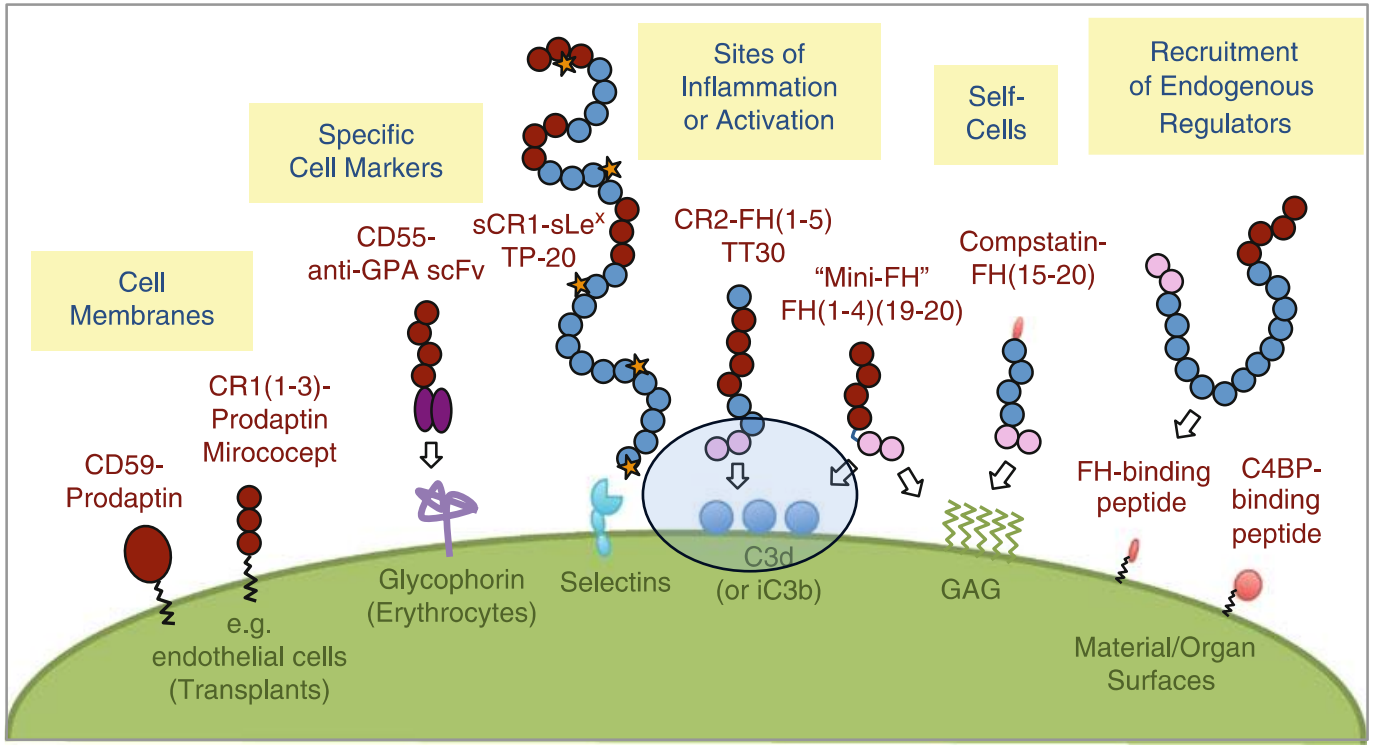
The complement system is known to contribute to the pathology of myriad diseases and is an active area of drug development. However, despite a wealth of knowledge, very few drugs have made it to the final regulatory approval. **Why?**

- Poor bioavailability
- Large levels of target proteins (e.g., circulating C3 levels are >1.0 mg/mL)
- Rapid target turnover with half-lives ranging from hours to only a few days
- Need to control locally synthesized factors and increased systemic sinks in inflammatory disease.
- Need to maintain the protective roles of complement (infection clearing, shaping of adaptive immune response, cross talk with coagulation and other systems)

If these limitations could be overcome and control of the *full system could be achieved*, dosing for circulatory compartment inhibition would also address local, tissue specific amplification and injury

Q32 Bio approach to addressing these limitations is *via* tissue localization and sequestration

Approaches to target complement inhibitors to various surfaces



Adapted from D. Ricklin and J.D. Lambris 2013

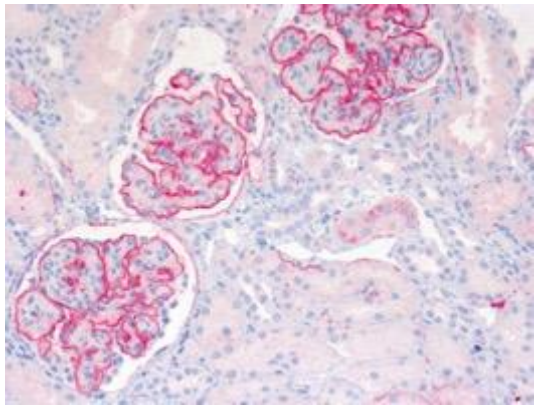
- Through the three major processes which initiate the complement system, **convergence upon the centrally important C3 protein occurs when multi-component C3 convertases are formed and C3 is cleaved and covalently attached to targeted sites**.
- These **C3 fragments irreversibly "mark" the targets as immunologically different** and allows the subsequent cleavage of C3b to the iC3b/C3dg/C3d forms and binding of the complex to specific C3 fragment receptors.
- **C3 activation is followed by the formation of a C5 convertase**, resulting in C5 cleavage and activation, coincident release of soluble anaphylatoxins C3a and C5a, and formation of the pore-like membrane attack complex (MAC)

It is the deposition of tissue-localized C3 fragments and their subsequent processing to fragments with altered receptor-binding characteristics that underlies the tissue-specific targeting of Q32 Bio therapeutics

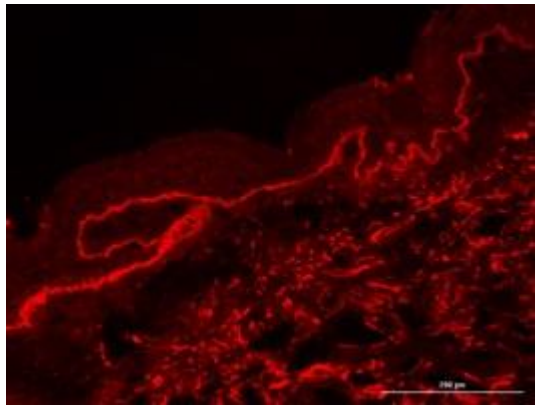
Unique therapeutic approach to restore complement regulation in diseased tissue is achieved via targeting C3d

- C3d is a validated ubiquitous biomarker of complement activation
- C3d is a clinical biomarker of tissue level complement activation
- C3d is deposited and covalently linked at sites of complement activation in diseased tissue; directly adjacent to C3 convertase complexes
- C3d is expressed in a wide range of diseases

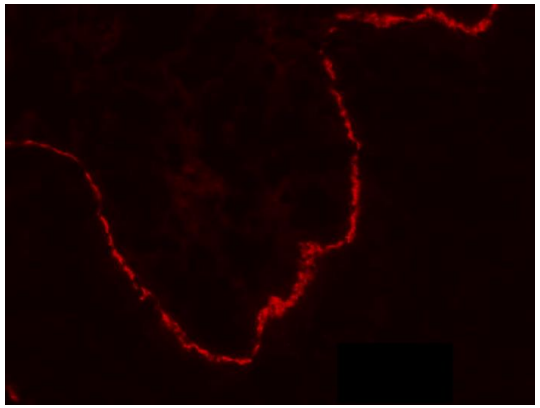
Human Disease C3d Immunostaining



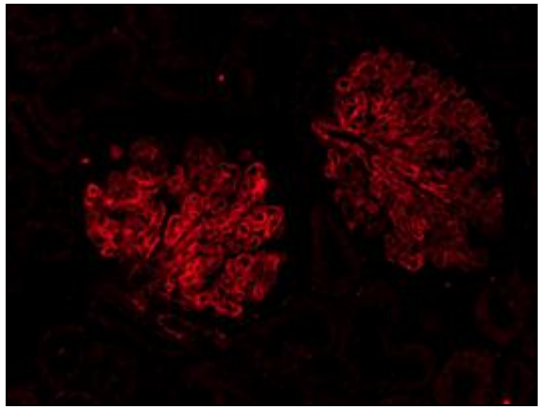
C3G kidney Glomeruli



Bullous Pemphigoid



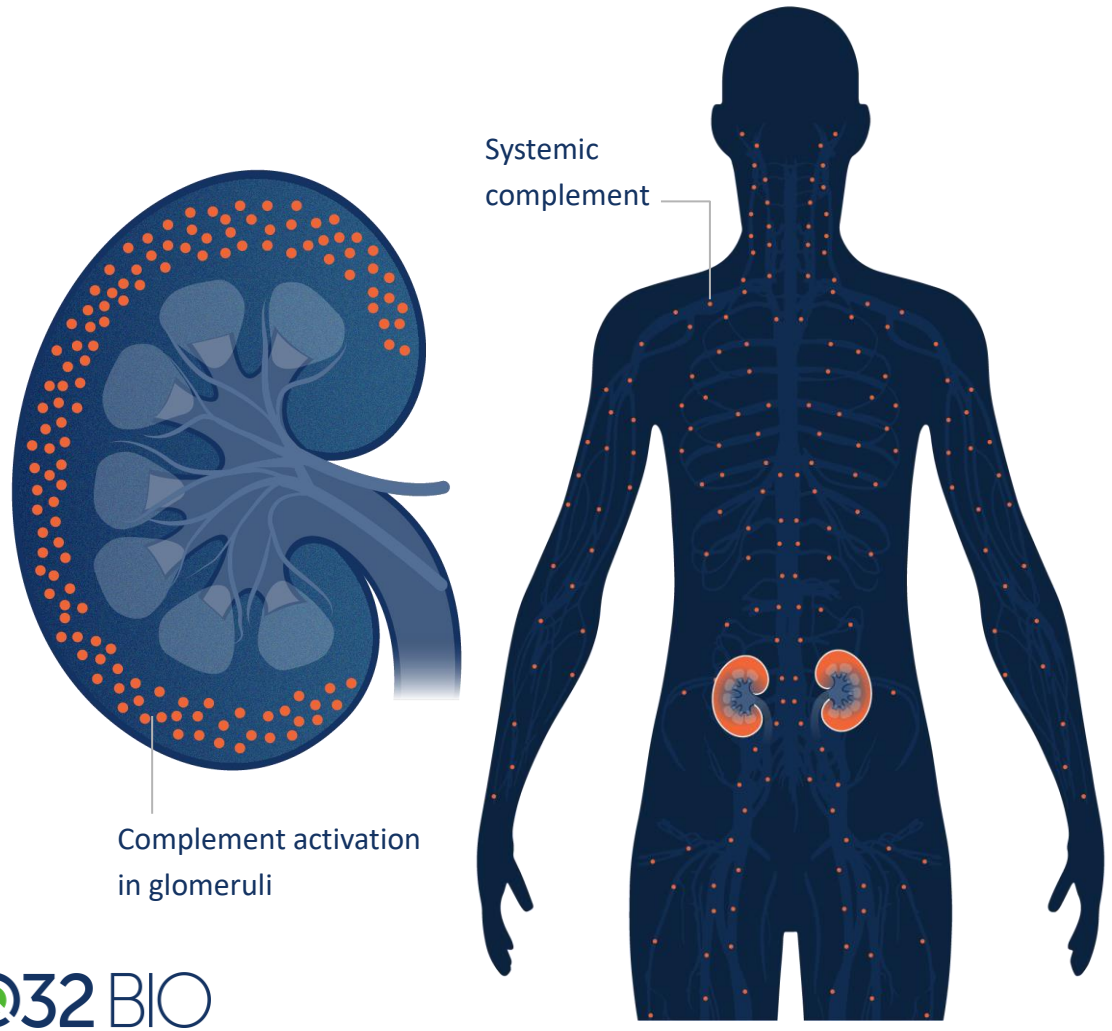
Discoid Lupus Erythematosus



Lupus Nephritis Glomeruli

ADX-097 Unique MOA: Localized, Multi-Nodal Complement Re-Regulation

Complement activation in diseased tissue



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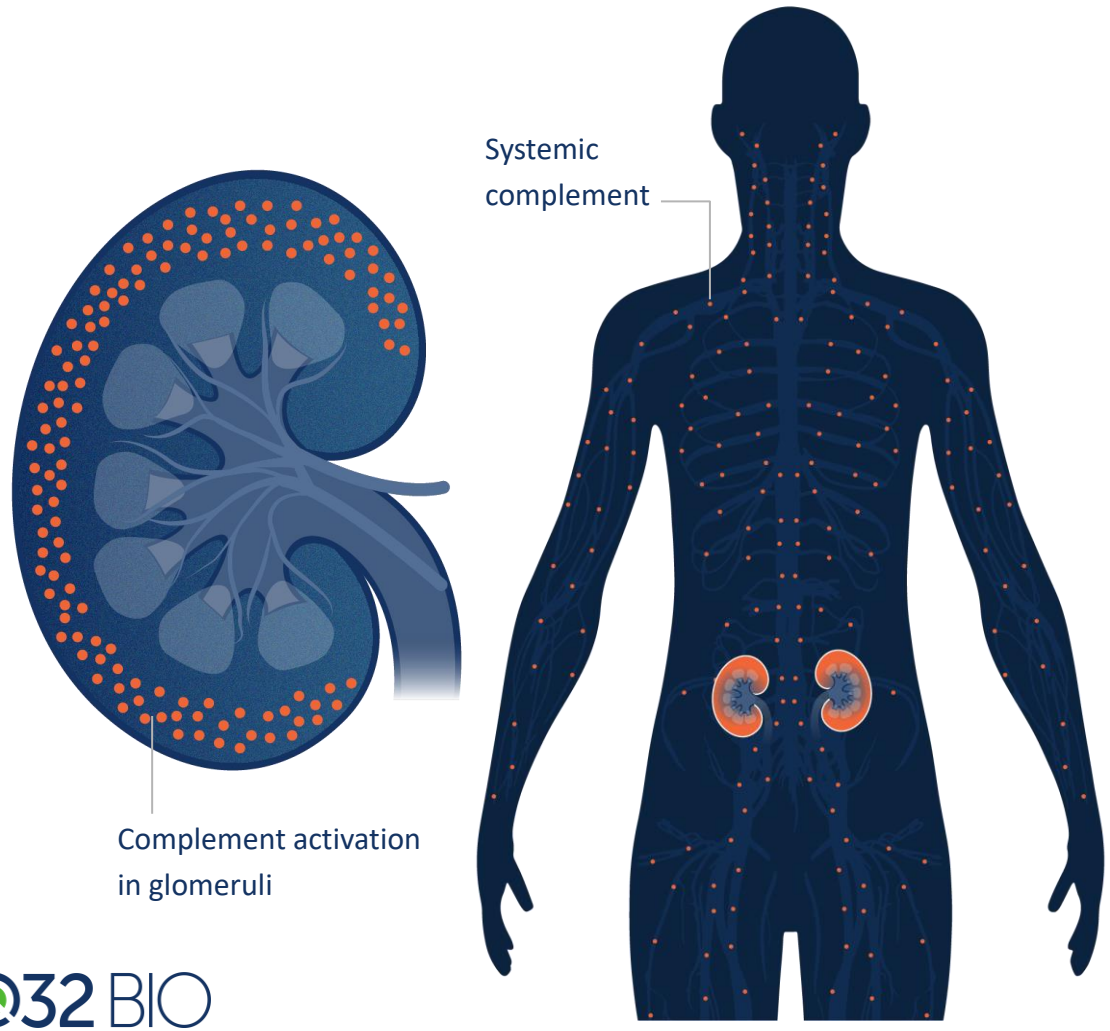
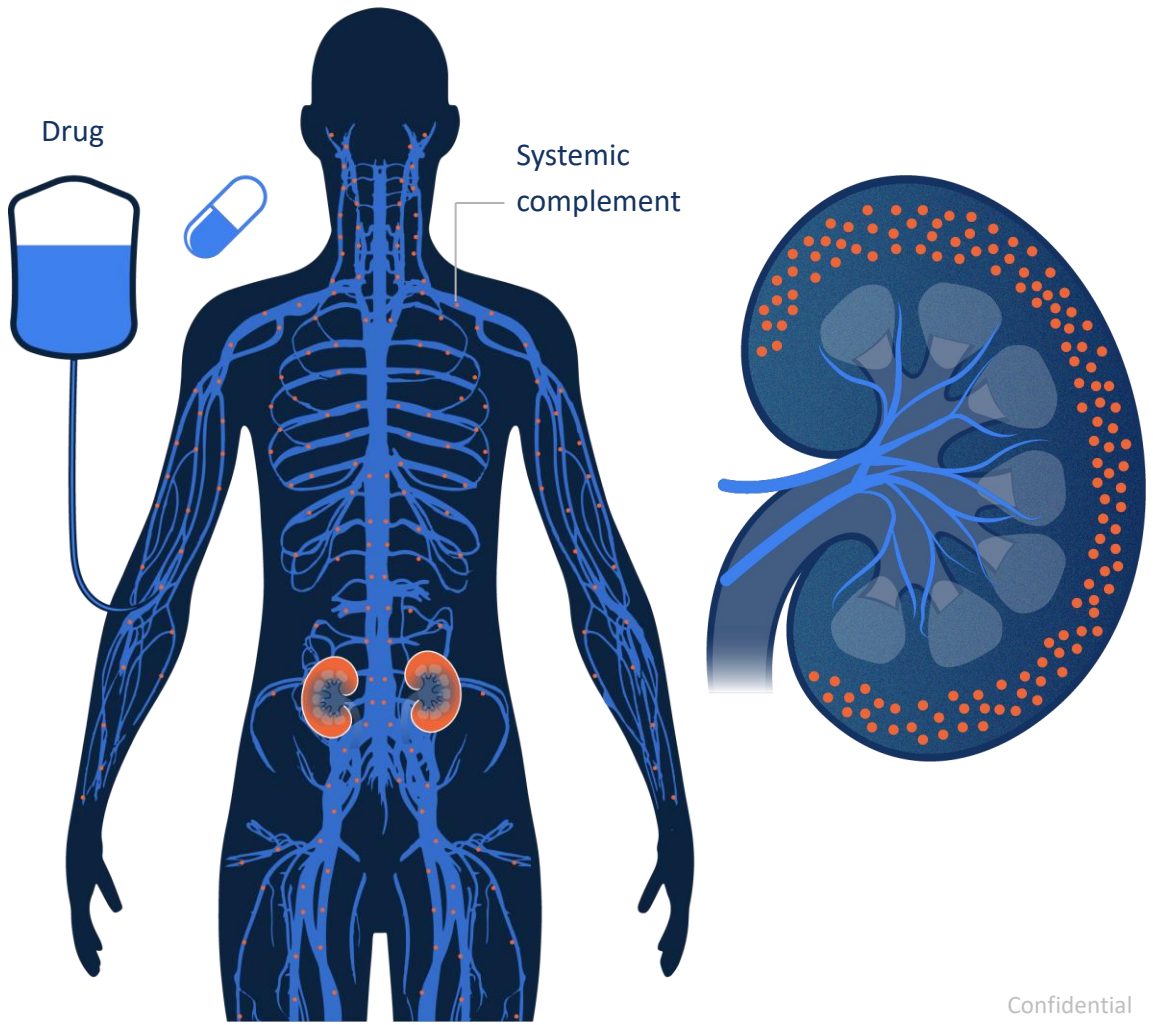


Systemic inhibition: Non-targeted



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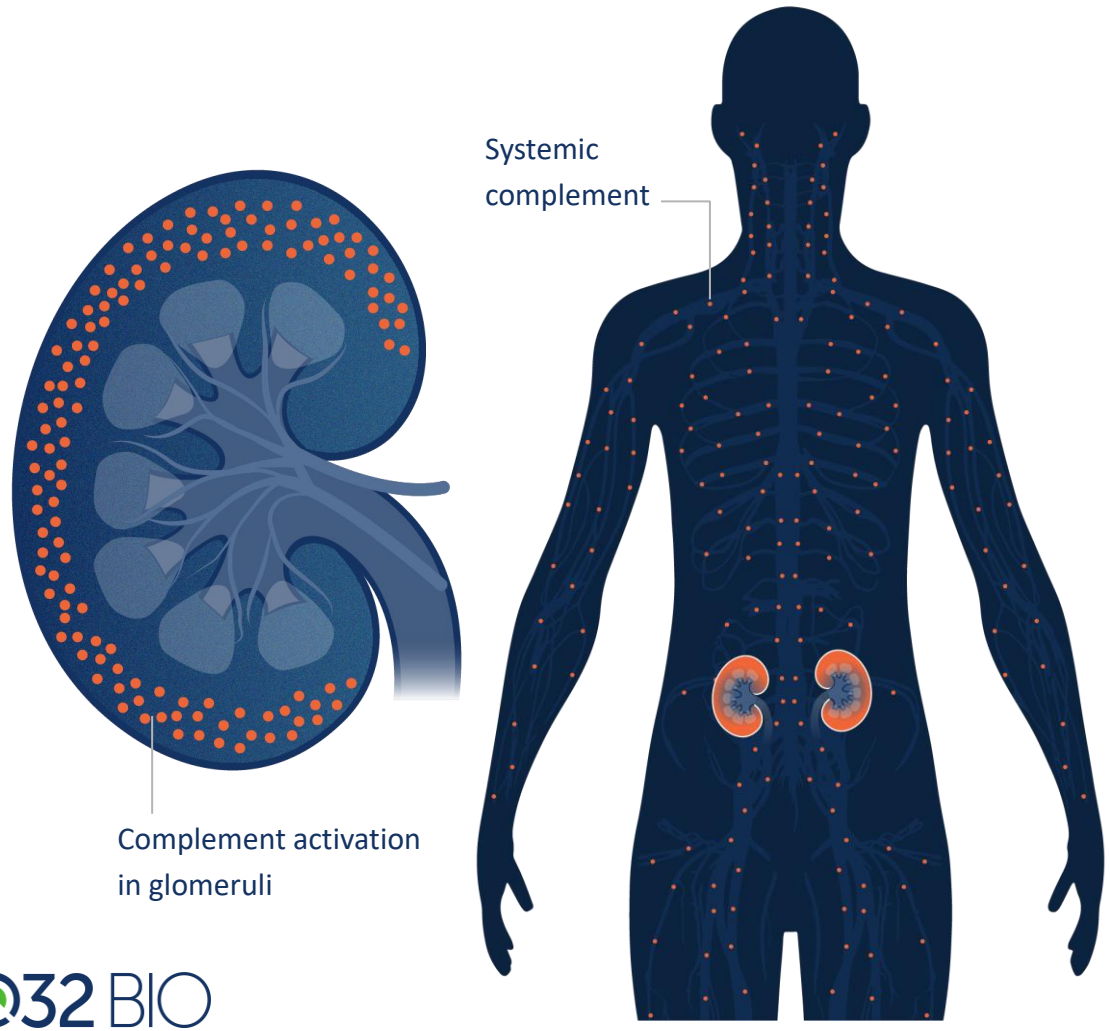

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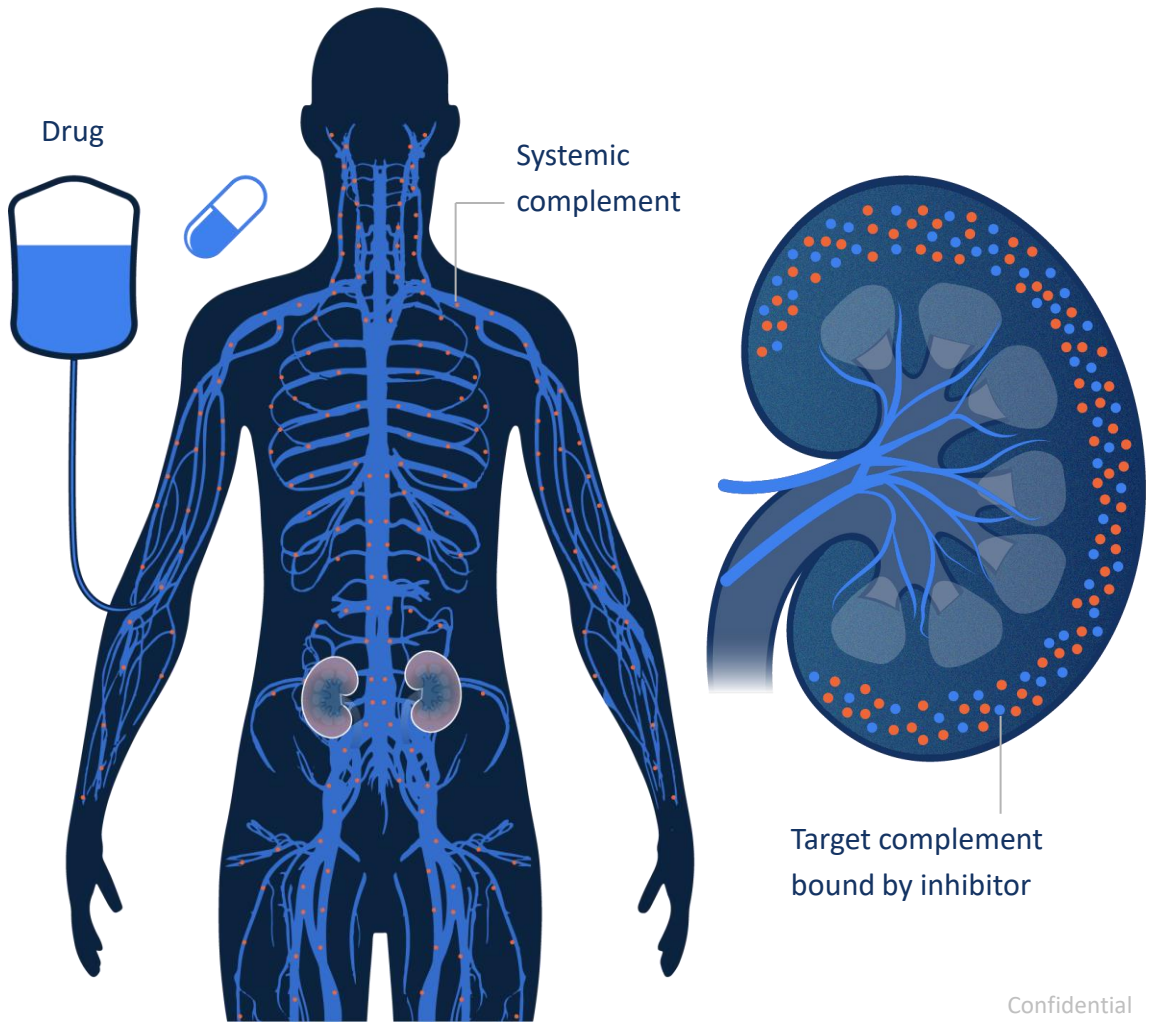

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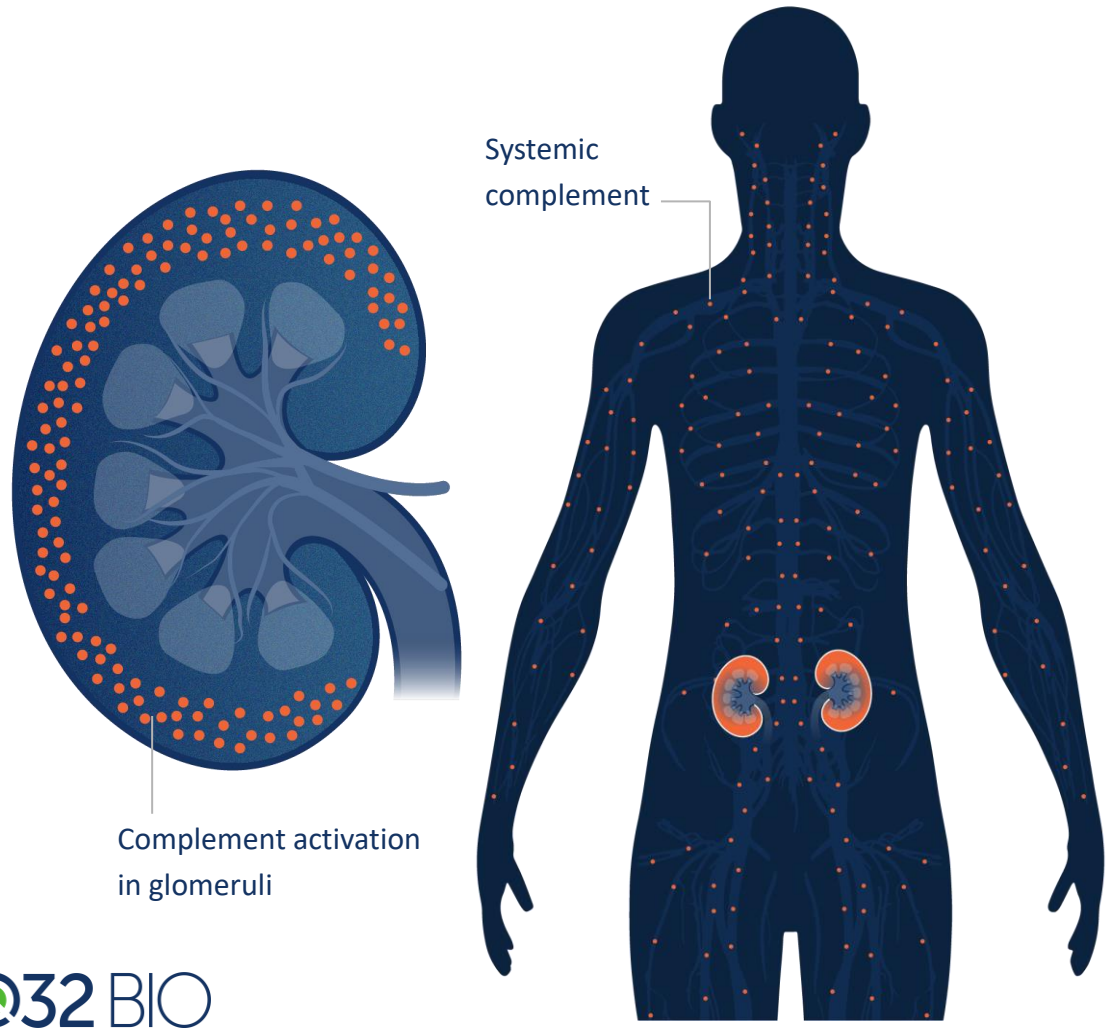
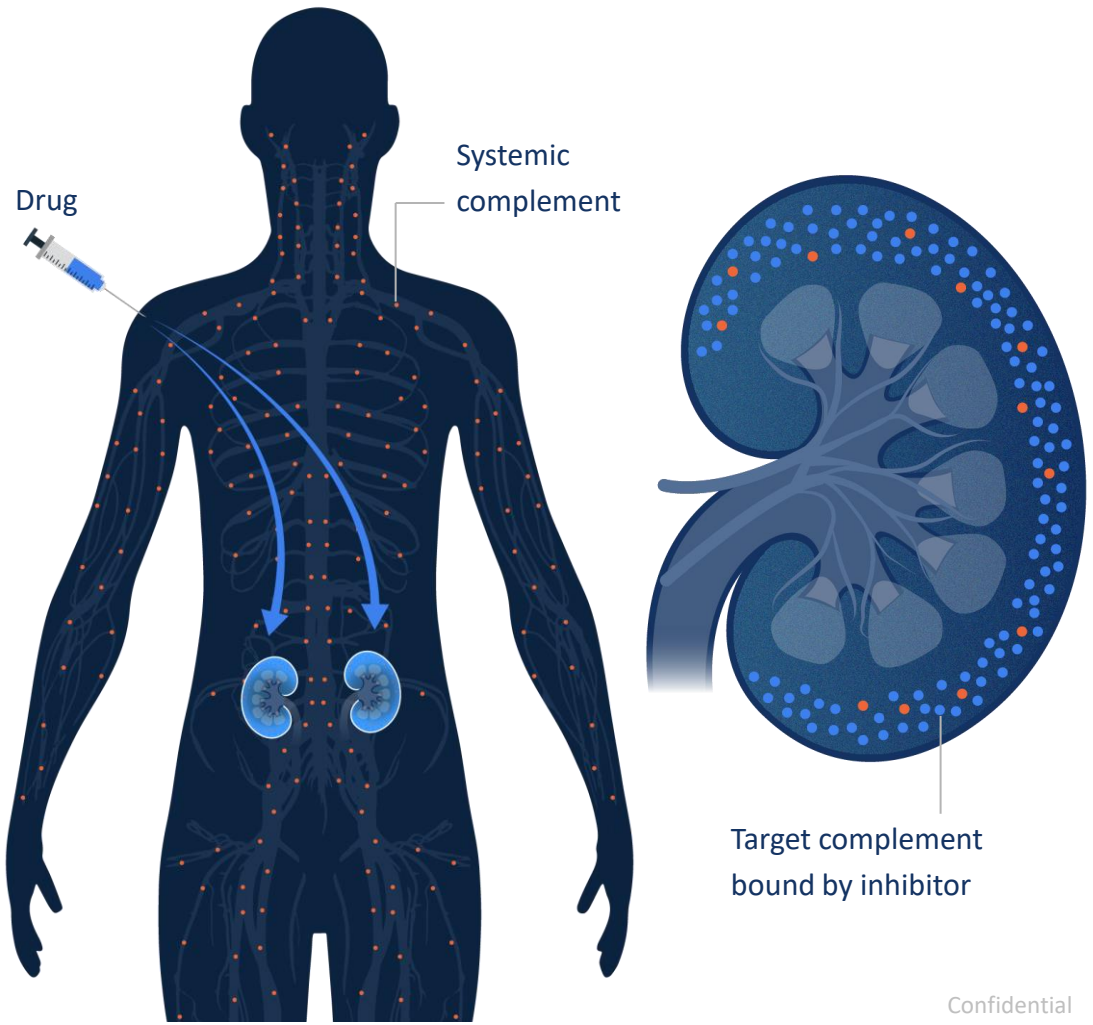


Q32: Tissue-targeted inhibition



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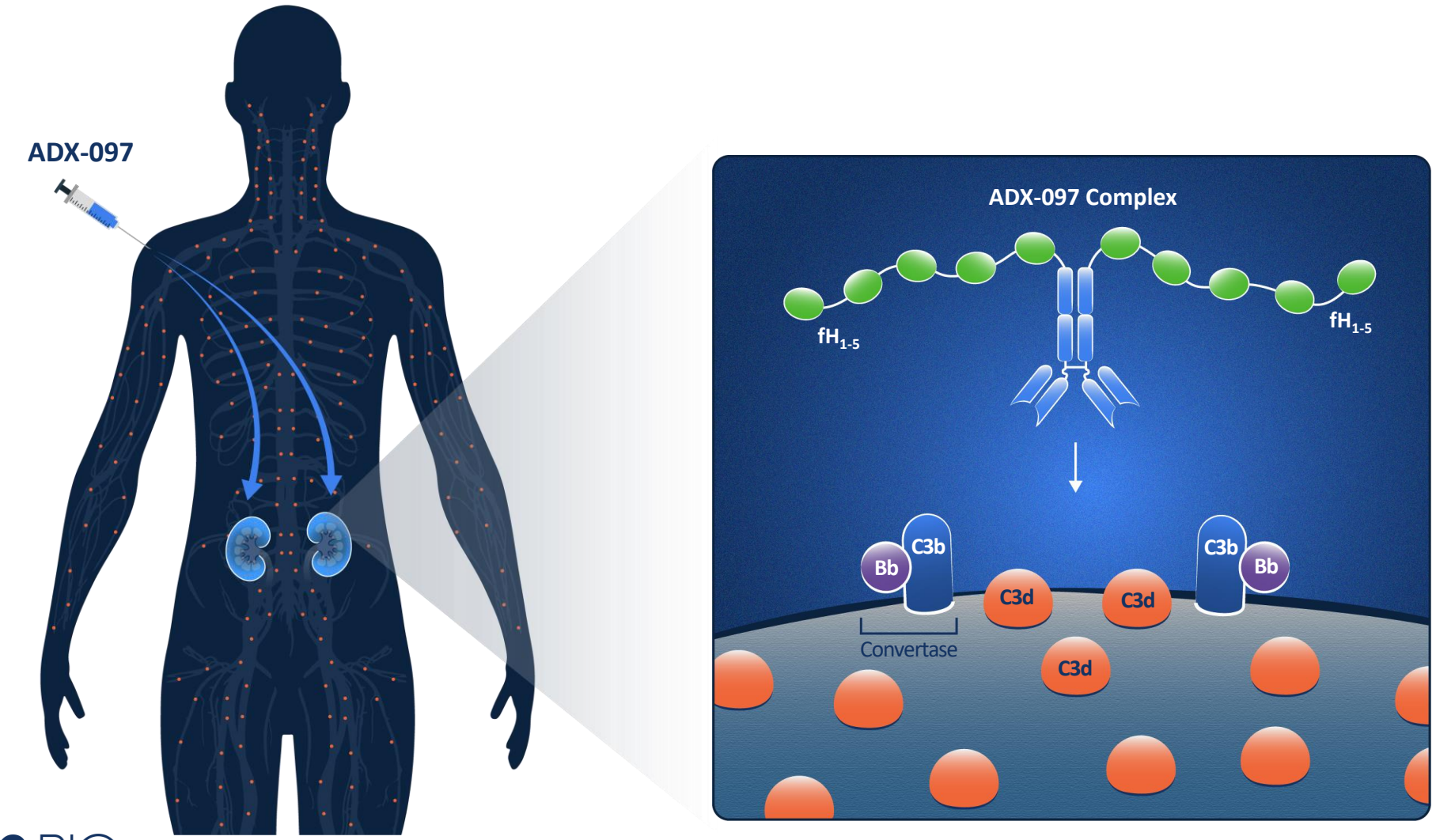

- FH binds to C3 fragments, thereby controlling both tick-over activation and the amplification loop.
- The N-terminus of FH provides catalytic convertase decay activity and enables FI-mediated degradation of C3b to iC3b/C3d.
- This mode of action creates additional ADX-097 binding sites and increases local retention.

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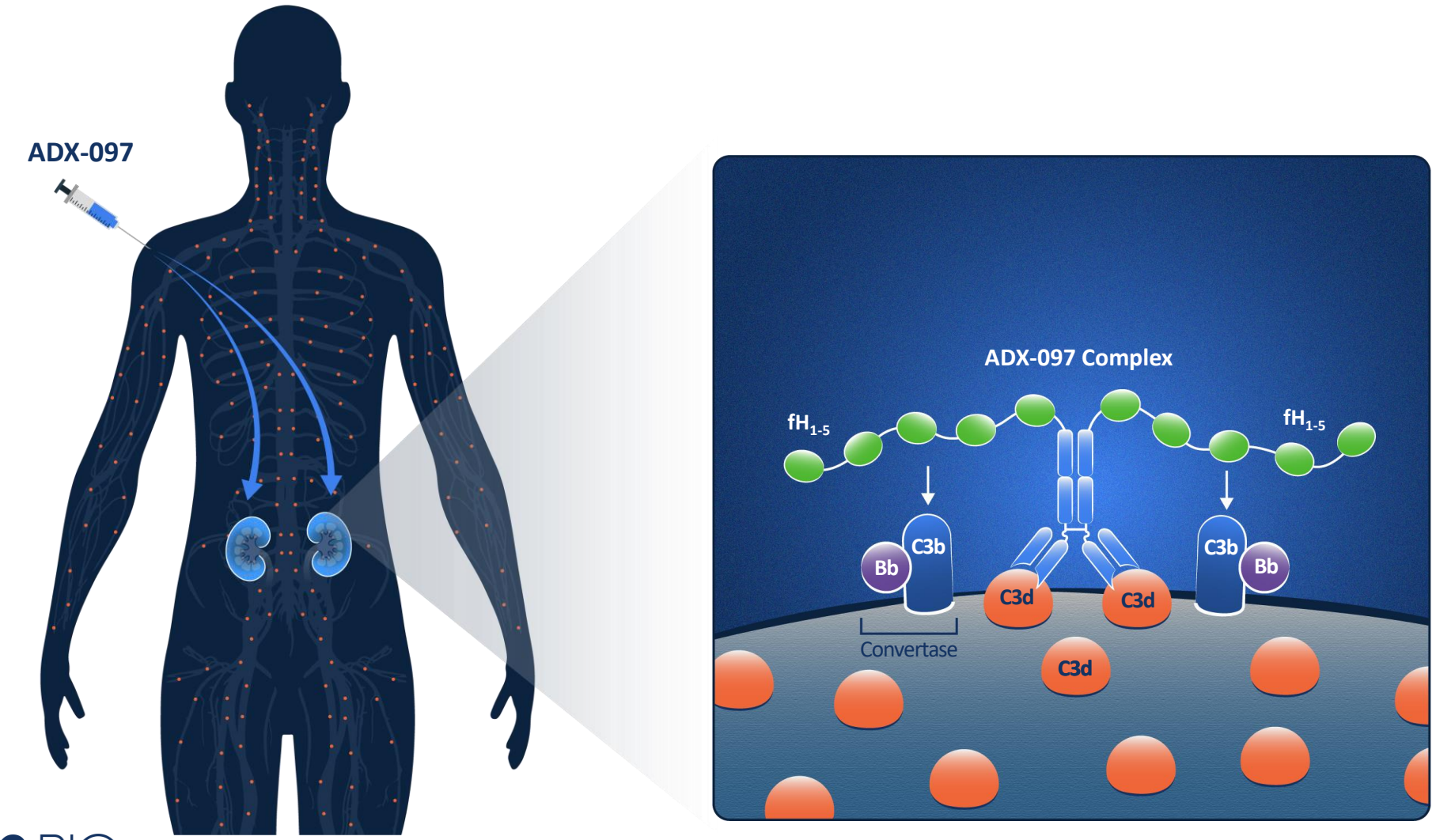

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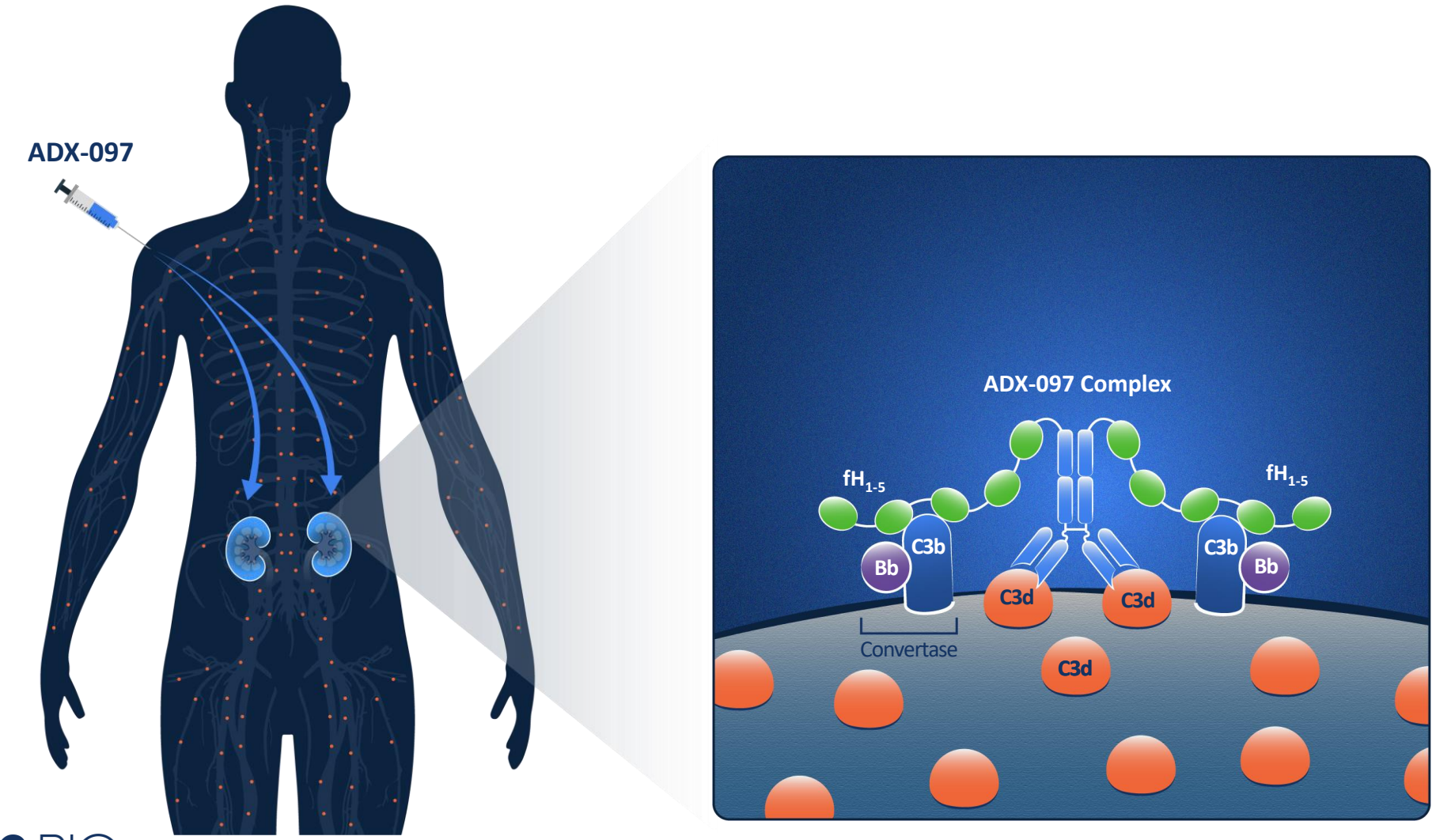

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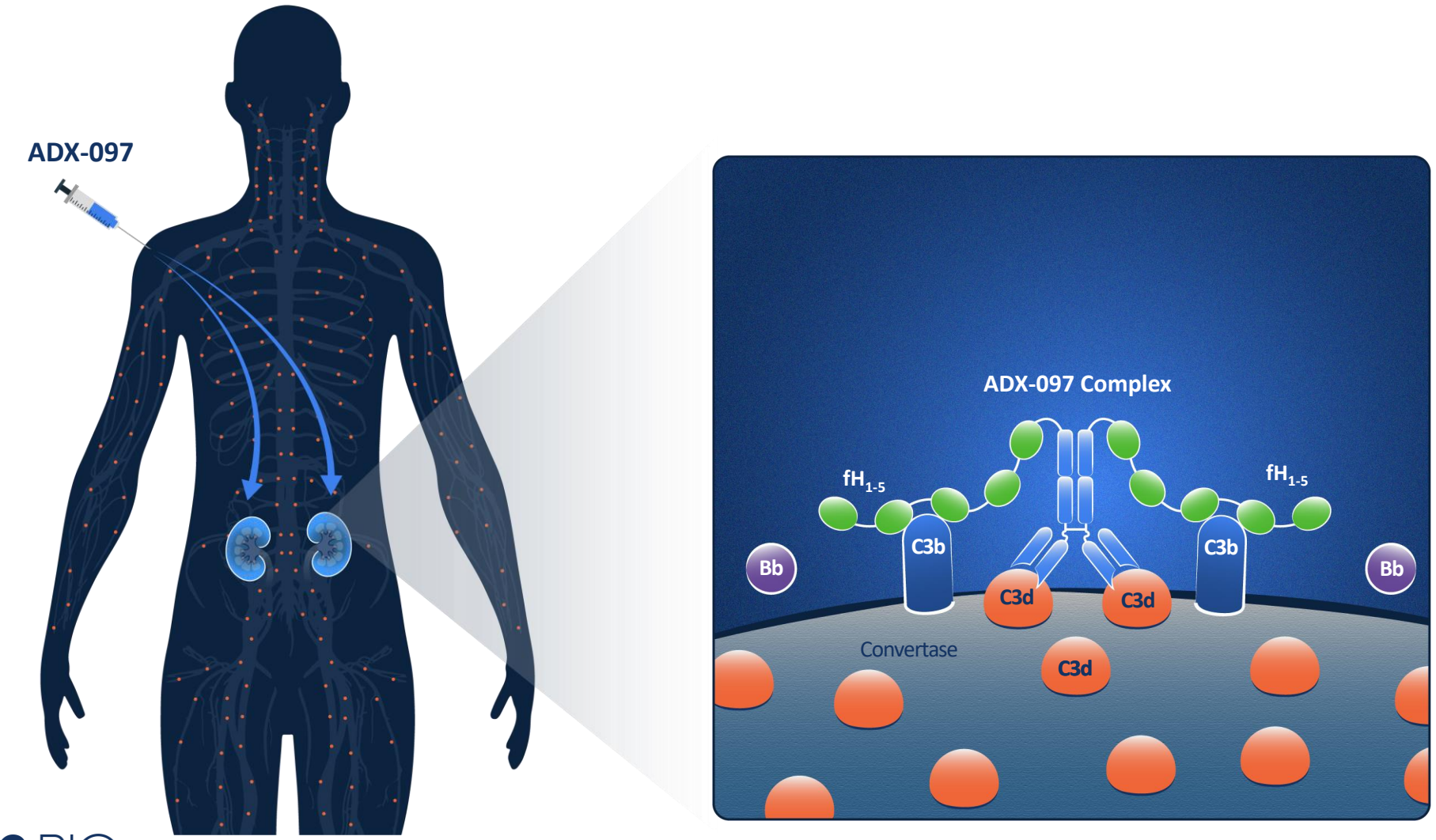

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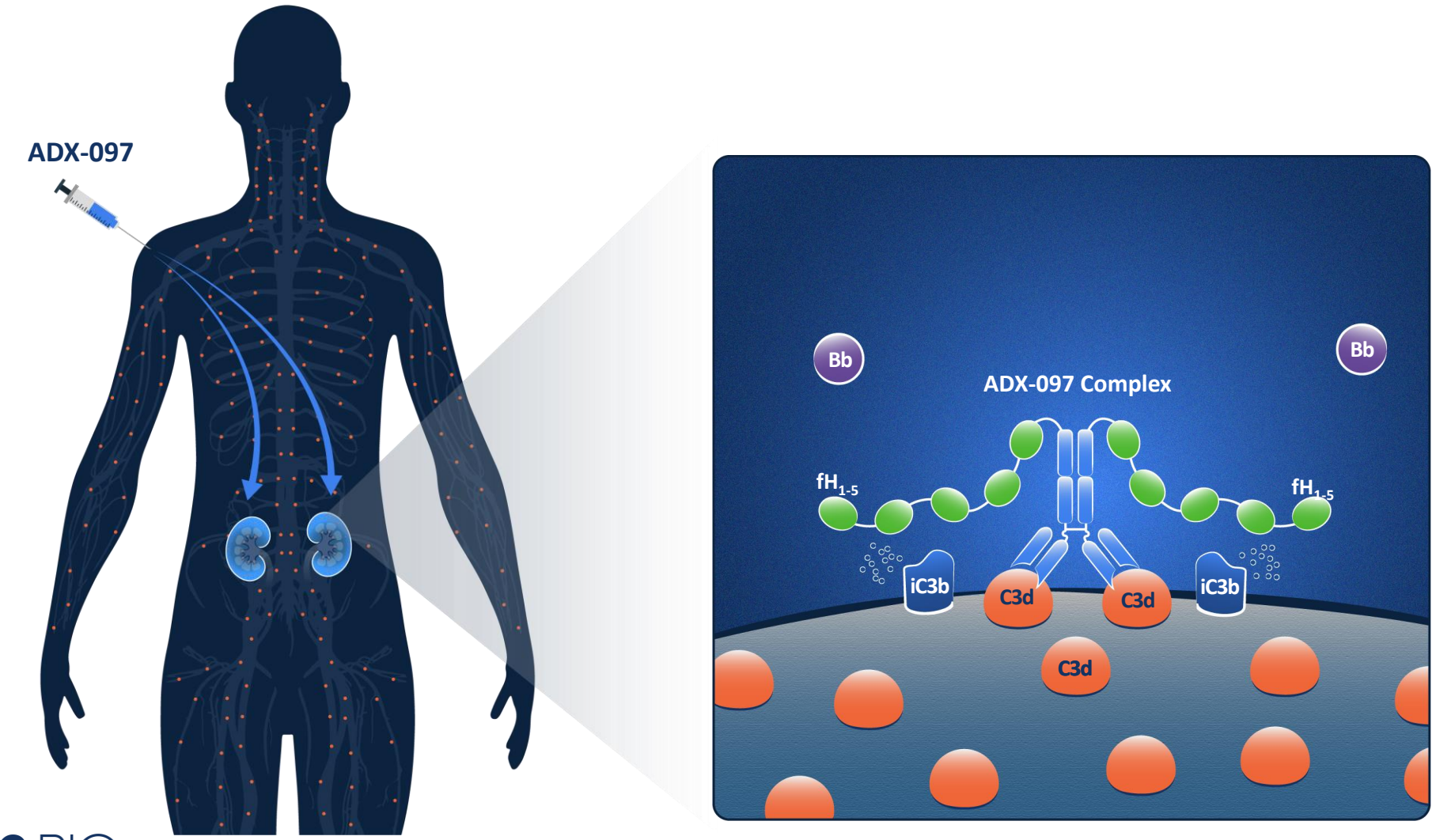

Diseased tissue surface (glomerulus)

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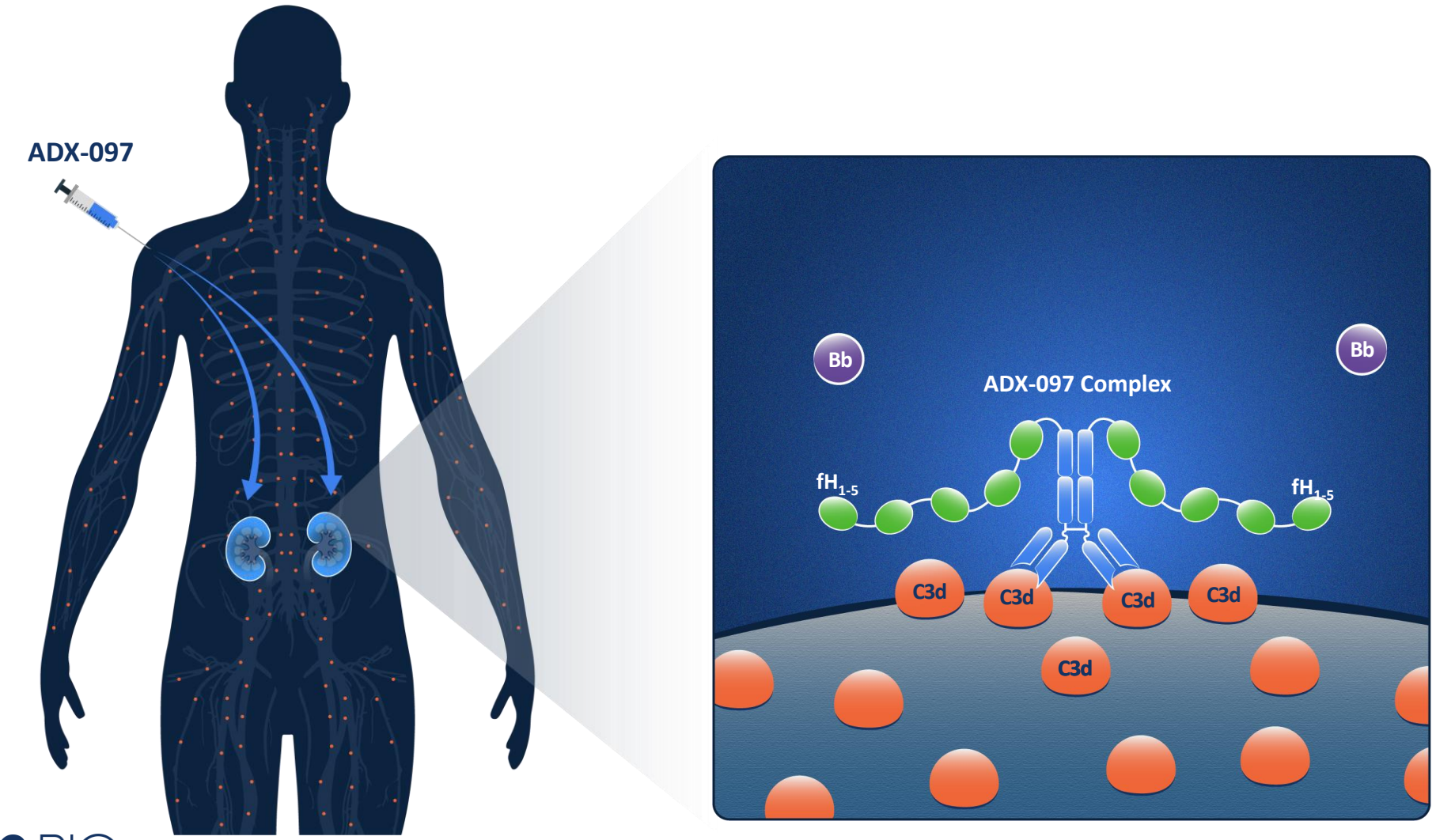

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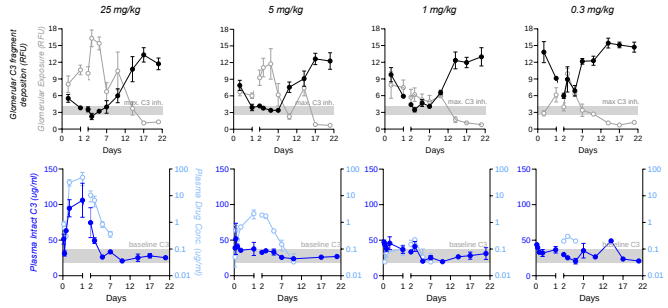
Q32 Tissue-targeted Platform Value Proposition: Designed to Enable Clinical Profile Superior to Systemic Complement Inhibitors

The Unmet Need	The Opportunity
• **Limited activity:** Reliant on systemic blockade for impact on affected organ	• **Enhanced activity through tissue targeting:** Differentiated approach to driving efficacy by inactivating convertases directly at site of destruction
• **High doses, frequent administration required:** High abundance, rapid turnover of most target complement proteins	• **Reduced treatment burden**: SC route with QW dosing; potential for Q2W
• **Infection risk:** Complement plays critical role in combating infection; systemic blockade increases risk	• **Improved risk/benefit profile**: Designed to maximize therapeutic index while maintaining intact immune surveillance; broader indication potential

Several Disease Models (Mouse, Rat and NHP) Establish Drug Levels Anticipated for Maximal Tissue PD & Activity

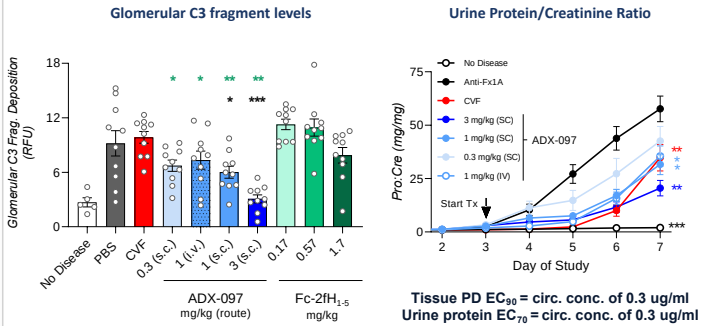
Preclinical Disease Model Studies Establishing Dose Response and PoM/PoC

fH KO mice
Relationship of Circulating to Tissue PK/PD



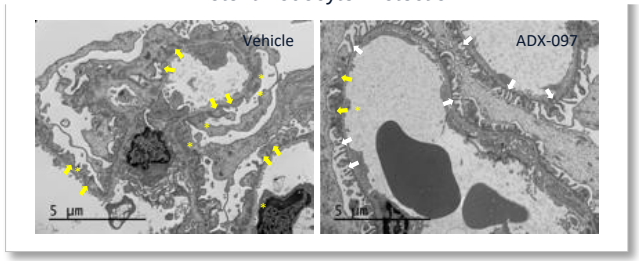
Tissue PD EC_{90} = circ. conc. of 0.3 ug/ml

PHN Rat (SC)
Potent Effects on Tissue PD and Efficacy



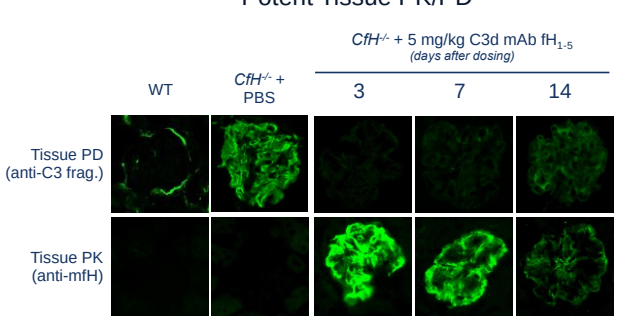
Tissue PD EC_{90} = circ. conc. of 0.3 ug/ml
Urine protein EC_{70} = circ. conc. of 0.3 ug/ml

PHN Rat (SC)
Potent Podocyte Protection



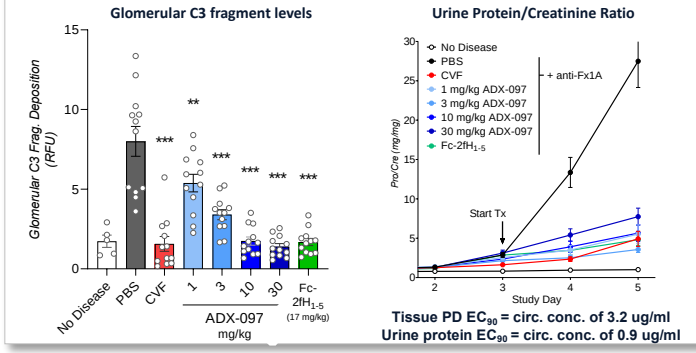
3 mg/kg SC = circ. conc of 0.3 ug/ml

fH KO mice
Potent Tissue PK/PD



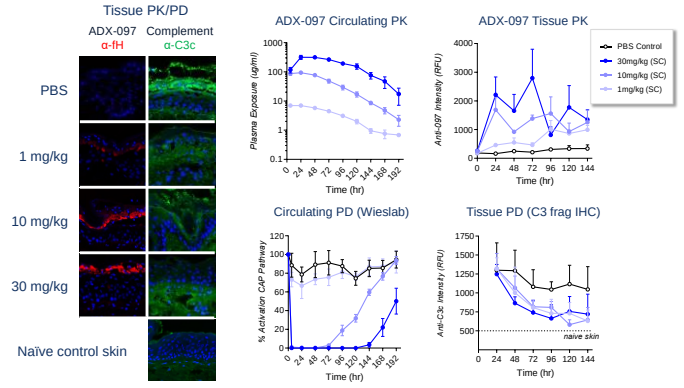
Tissue PD EC_{90} = circ. conc. of 0.3 ug/ml

PHN Rat (IV)
Potent Effects on Tissue PD and Efficacy



Tissue PD EC_{90} = circ. conc. of 3.2 ug/ml
Urine protein EC_{90} = circ. conc. of 0.9 ug/ml

NHP UVB Skin Challenge
Relationship of Blood to Tissue PK/PD



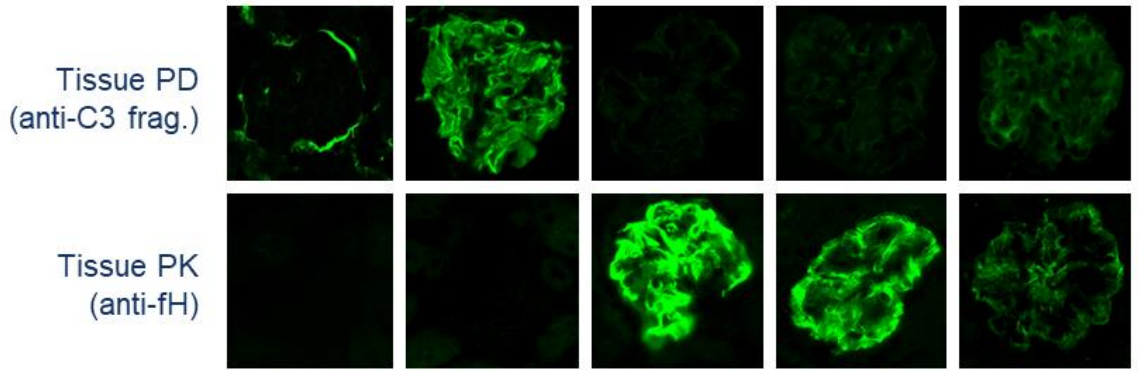
Tissue PD EC_{85} = 3.1 ug/ml

Several Disease Models (Mouse, Rat and NHP) Establish Drug Levels Anticipated for Maximal Tissue PD & Activity

Potent Tissue PK/PD

fH KO mice

CfH$^{-/-}$ + 5 mg/kg IV C3d mAb fH$_{1-5}$ *(days after dosing)*



Tissue PD EC$_{90}$ = circ. conc. of 0.3 ug/ml

- ✓ **Long term, durable kidney PK/PD**
- ✓ **Supports dosing every 1 – 2 weeks**

Preclinical Dis… … d PoM/PoC

fH KO mice
Relationship of Circulating to Tissue PK/PD

PHN Rat (SC)
Potent Podocyte Protection

Vehicle
ADX-097

Drug level at 3 mpk = 0.3 ug/ml

PHN Rat (IV)
Potent Effects on Tissue PD and …

Glomerular C3 fragment levels

Urine Pro…

Drug ≥ EC$_{90}$, tissue PD = 3.21 ug/ml
Drug ≥ EC$_{90}$, urine protein = 0.93 ug/ml

Skin Challenge
Blood to Tissue PK/PD

ADX-097 Circulating PK

ADX-097 Tissue PK

Circulating PD (Wieslab)

Tissue PD (C3 frag IHC)

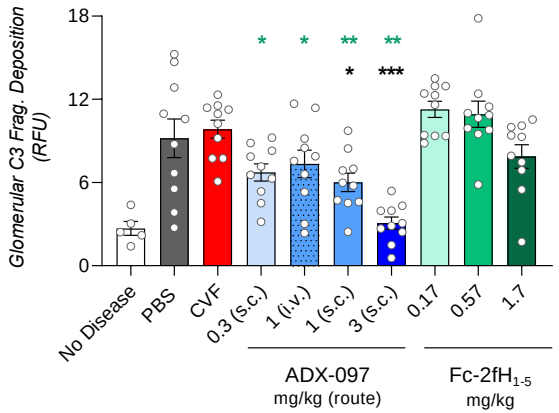
Drug at maximal tissue PD = 3.1 ug/ml

Several Disease Models (Mouse, Rat and NHP) Establish Drug Levels Anticipated for Maximal Tissue PD & Activity

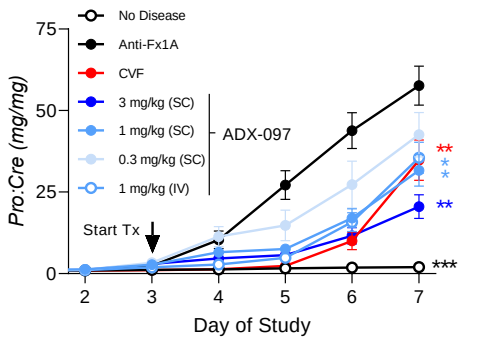
Potent Tissue PD and Activity

PHN Rat (SC)

Glomerular C3 fragment levels



Urine Protein/Creatinine Ratio

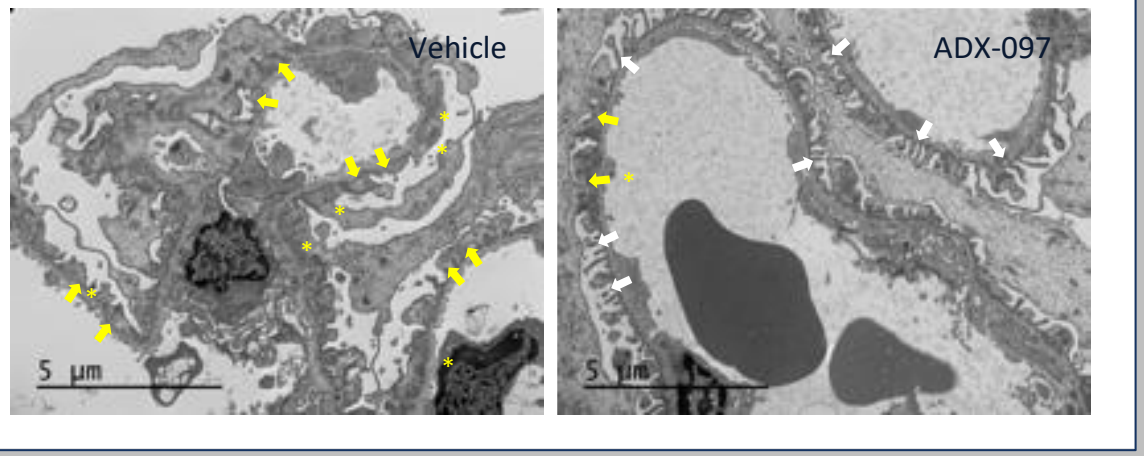


Tissue PD EC_{90} = circ. conc. of 0.3 ug/ml
Urine protein EC_{70} = circ. conc. of 0.3 ug/ml

✓ **Reduction in urinary protein with low, SC doses that do not inhibit systemic complement**

Several Disease Models (Mouse, Rat and NHP) Establish Drug Levels Anticipated for Maximal Tissue PD & Activity

Podocyte Protection



- ✓ **Key to preventing protein leakage**
- ✓ **Common across indications**

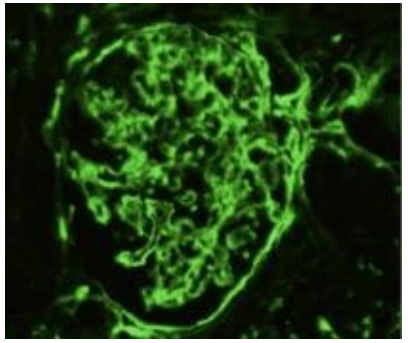
ADX-097 target expression (C3d) has been validated in numerous complement-associated human kidney diseases

Immunohistochemistry of C3d

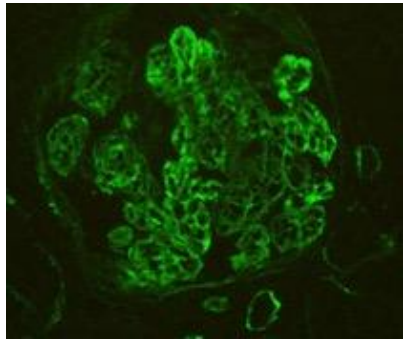
Negative controls

Acute Tubular Necrosis

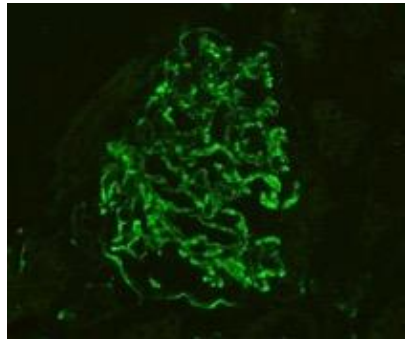
Disease



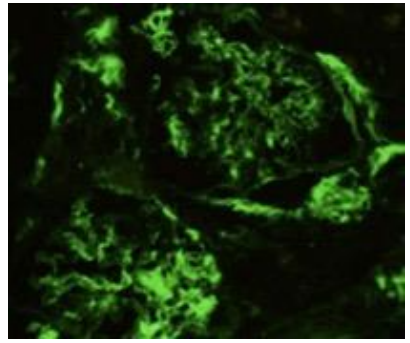
IgA Nephropathy



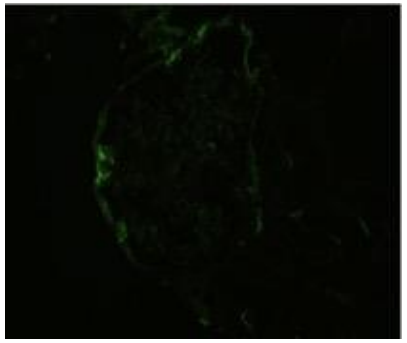
Lupus Class IV



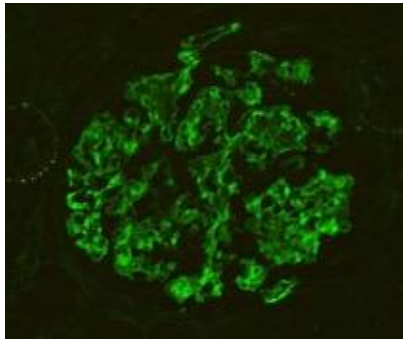
Lupus Class V



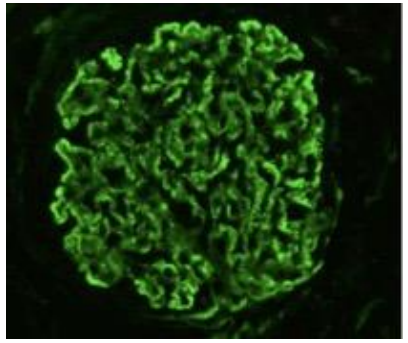
Minimal Change Disease



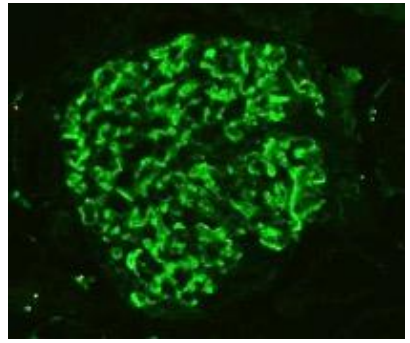
Thin Glomerular BM



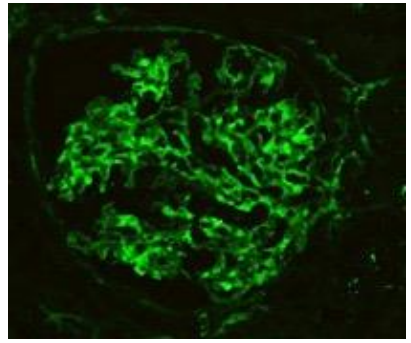
MPGN



Membranous (PLAR2+)



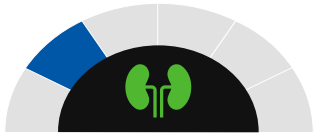
C3 Glomerulopathy



Diabetic Nephropathy

LN, IgAN, C3G:
Need for alternatives to broad acting immunosuppressives

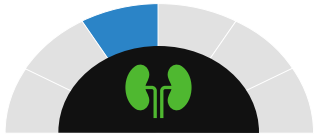
LN, IgAN, C3G Unmet Need



Lupus Nephritis
100K (US) [18,19]

6-fold mortality risk increase vs general population[1,2]

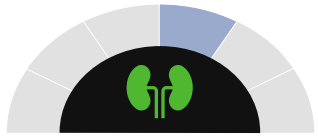
Up to 30% develop **kidney failure** requiring dialysis or kidney transplant **within 15 years of diagnosis**[3,4]



IgA Nephropathy
185K (US) [20, 21]

Up to 40% develop ESRD w/in 20 years of diagnosis[5,6], and patients have **10 years** reduced life expectancy[7,8]

~70% not adequately controlled w/supportive care[5,9]



C3 Glomerulopathy
3K (US) [22]

Up to 50% of adult, 70% of pediatric patients progress to **kidney failure** within 10 years[10-13]

>70% experience **recurring disease**; ~50% experience allograft loss w/in 10 years of kidney transplant[10,14-17]

1. Mahajan et al. Lupus 2020; 2. Cervera et al. Medicine 2002; 3. Maroz et al. Am J Med Sci 2013. 4. Ward et al. J Rheumatol 2009; 5. Habas et al. Medicine (Baltimore) 2022. 6. Berthoux et al. Semin Nephrol 2008; 7. Pitcher et al. Clin Jour of Amer Soc Neph 2023. 8. Hastings et al. Kidney Int Rep 2018; 9. Raun et al. N Engl J Med 2015; 10. Heiderscheit et al. Am J Med Genet C Semin Med Genet 2022. 11. Smith et al. J Am Soc Nephrol 2007; 12. Servais et al. Kidney Int 2012; 13. Rabasco et al. Kidney Int 2015; 14. Smith et al. Nat Rev Nephrol 2019. 15. Welte et al. BMC Nephrology 2018; 16. Salvadori et al. WJT 2016. 17. Regunathan-Shenk et al. AJKD 2019 18. Hoover et al. Kidney Int 2016; 19. Pryor et al. Rheum Dis Clin North Am. 2021; 20. Braun et al. Int Urol Nephrol 2011; 21. McQuarry et al. Kidney Int 2013; 22. Bomback et al. Kidney Int. 2018.

ANCA-Associated Vasculitis (AAV): Tremendous Global Unmet Need for Efficacious, Safe Chronic Therapies

AAV: 100K (US)
~10K annually newly diagnosed severe patients or patients in major relapse

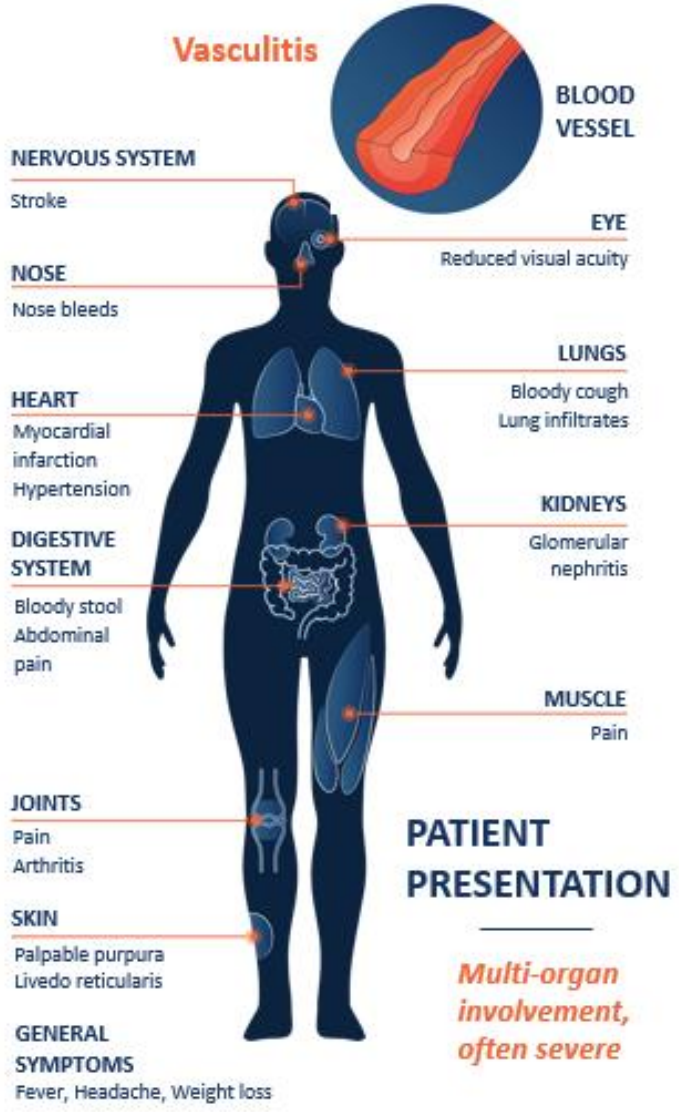
UNMET NEED

More effective induction and maintenance

- With treatment, 5-year mortality 10-30% overall
- 5-year mortality with renal disease – 20-50%
- Relapse is substantial issue: Up to 50% of patients relapse within 5 years, often 12-18 months of IST discontinuation
- Aggressive cardiovascular disease is a major late driver of death in AAV

Reduction/Elimination of Glucocorticoids (GCs)

- IST, particularly GC side effects, account for significant early treatment related morbidity and mortality, primarily due to infection



Q32 BIO

The Clinical Promise of Tissue Directed Complement Therapeutics

Thank You!