Engineering Complement Factor I as a Protease Medicine: Tuning Potency And Specificity For Complement-mediated Disorders

5th Complement-Based Drug Development Summit 2021

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Chief Scientific Officer

CATALYST BIOSCIENCES

Forward looking statements

Certain information contained in this presentation and statements made orally during this presentation include forward-looking statements that involve substantial risks and uncertainties. All statements included in this presentation, other than statements of historical facts, are forward looking statements. Forward-looking statements include, without limitation, statements about the product candidates of Catalyst Biosciences, Inc. (the “Company”) and the benefits of its protease engineering platform; the potential markets for and advantages of the Company's complement product candidates, including C3b and C4b degraders; the ability of the ProTUNE™ platform to generate these or other product candidates; and the potential for C3b and C4b degraders to treat human disease including IgA nephropathy (“IgAN”). Actual results or events could differ materially from the plans, intentions, expectations and projections disclosed in the forward-looking statements. Various important factors could cause actual results or events to differ materially, including, but not limited to, the risk that pre-clinical studies may be delayed as a result of COVID-19 and other factors, that C3b and C4b degraders are not yet in human clinical trials and will require additional manufacturing validation and pre-clinical testing before entering human clinical trials, the risk that human clinical trial will not replicate the results of studies in mice or other animals, competition and other risks described in the “Risk Factors” section of the Company’s Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC") on March 4, 2021, on Form 10-Q filed with the SEC on August 5, 2021, and in other filings with the SEC. The forward-looking statements in this presentation represent the Company's view as of the date of this presentation and the Company does not assume any obligation to update any forward-looking statements, except as required by law.

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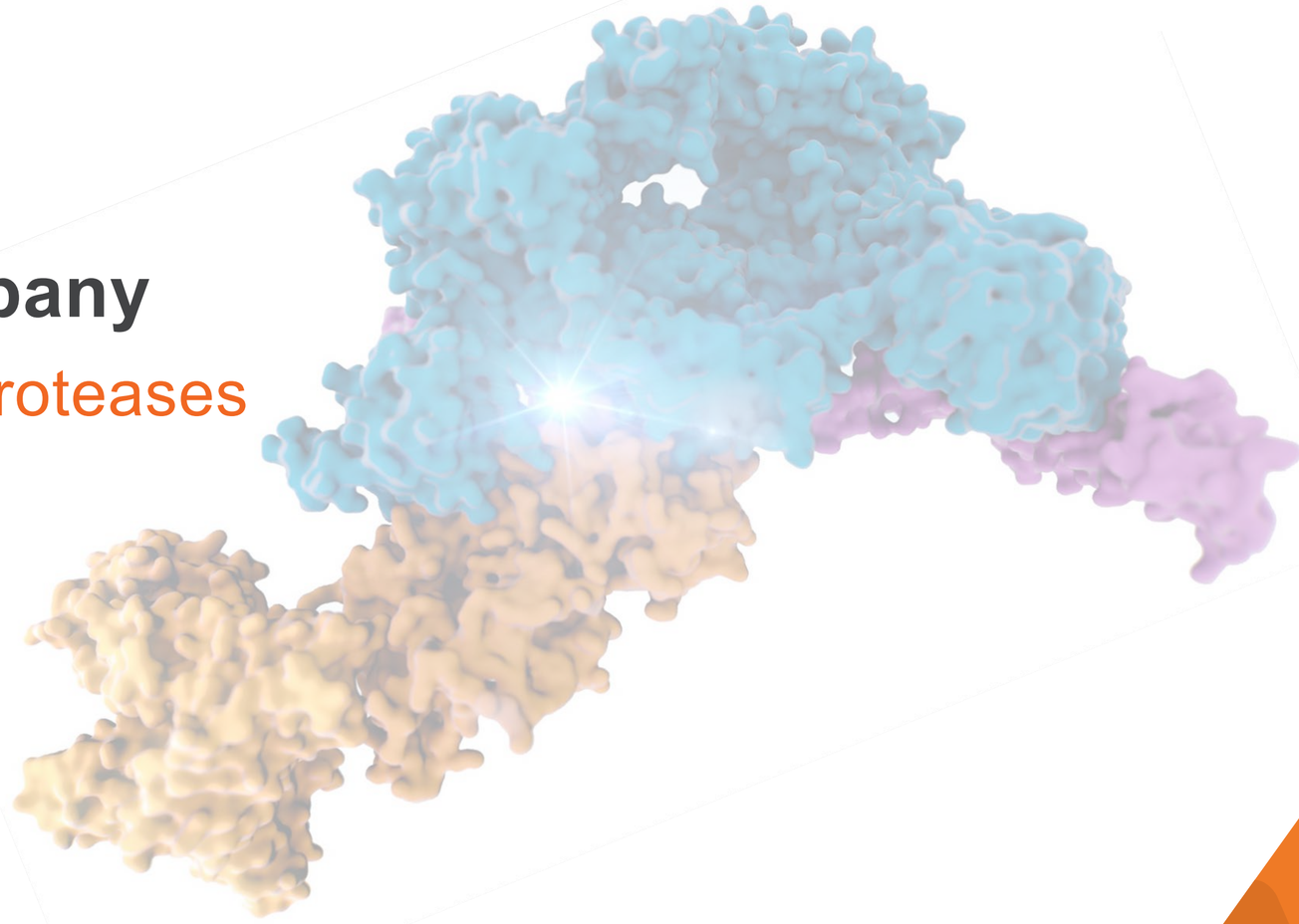
The Protease Medicines Company

Harnessing the catalytic power of proteases



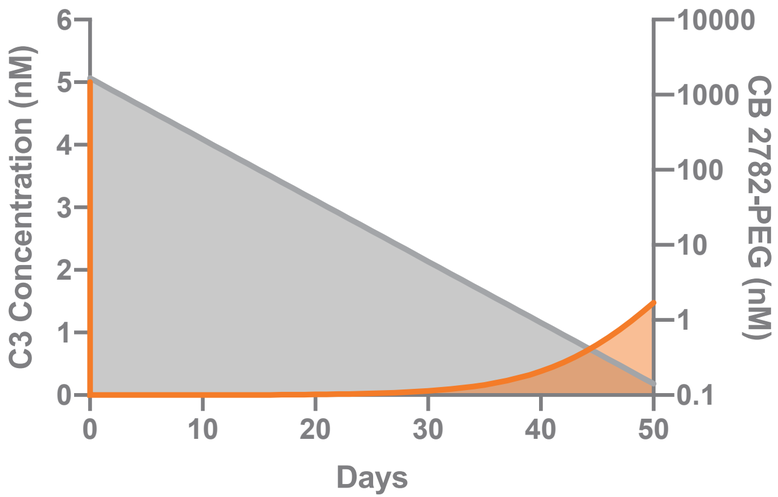
- Novel differentiated medicines
- Robust complement portfolio
- Clinical-stage assets
- Unique expertise in protease engineering

Catalyst protease platform

Validated across three programs

CB 2782-PEG Biogen

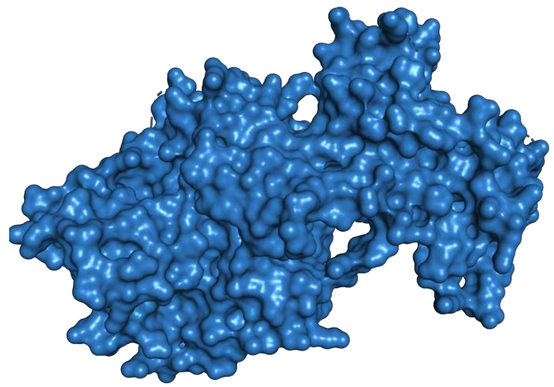
Best-in-class profile for dry AMD
Extended pharmacodynamics



Novel C3-degrader partnered to Bio for dry AMD

CB 4332 Enhanced CFI

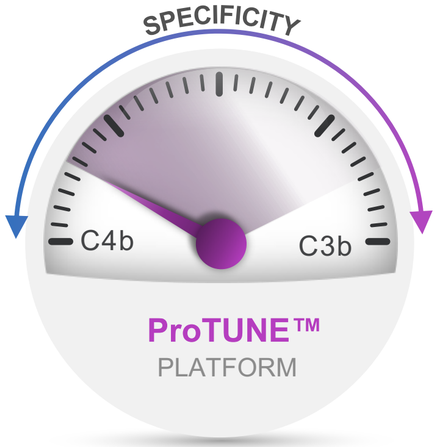
Restoring balance to complement in patients with dysregulated CFI



Engineered CFI entering the clinic in 2022

Engineered proteases

Protease platforms tailored to restore function in specific indications



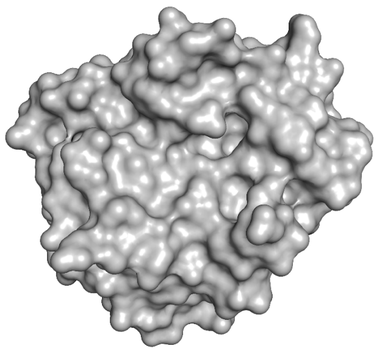
C3b/C4b degrader platform delivering candidates 2022

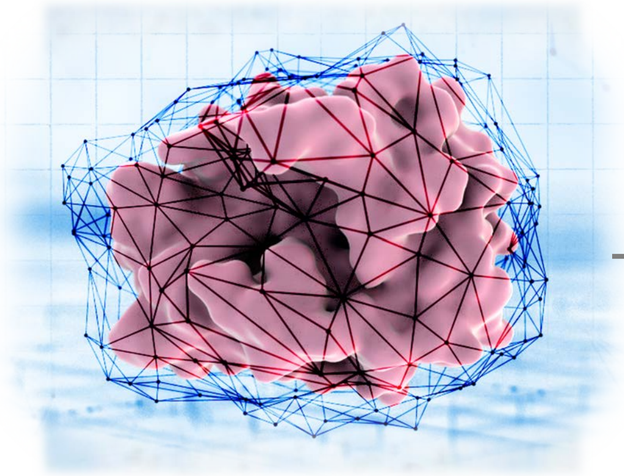
Catalyst protease platform

Unique expertise enables design of optimized & differentiated protease candidates

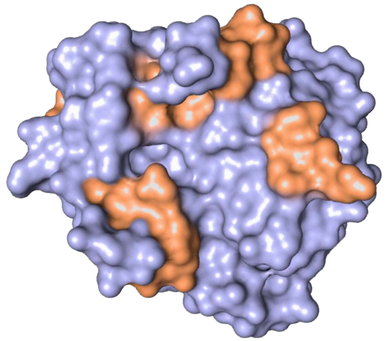
Discovery Platform

Protease Scaffold





Protease Candidate



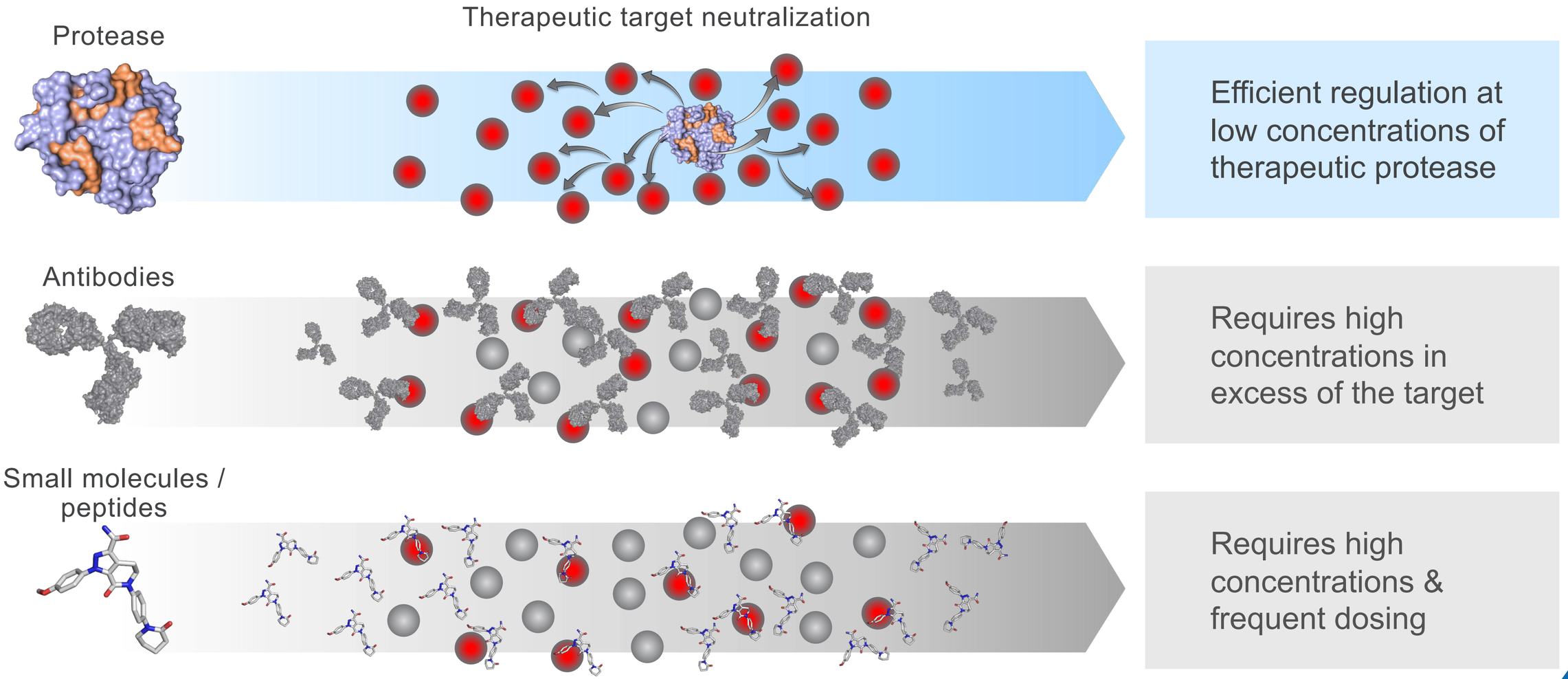
- **Structure Guided Design**
- **Molecular Evolution**
- **Engineered Regulation**
- **Pharmacokinetic Improvement**

Our Proteases

+ Functionally enhanced natural proteases in the complement & coagulation cascades
+ Engineered novel protein degraders in the complement cascade
+ Modulate or target biological activation or inactivation

Proteases are ideal for high abundancy targets & cascades

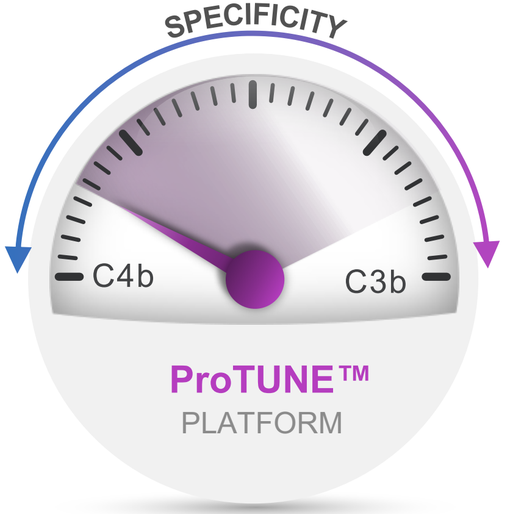
A better way to regulate biological processes compared with antibodies & small molecules

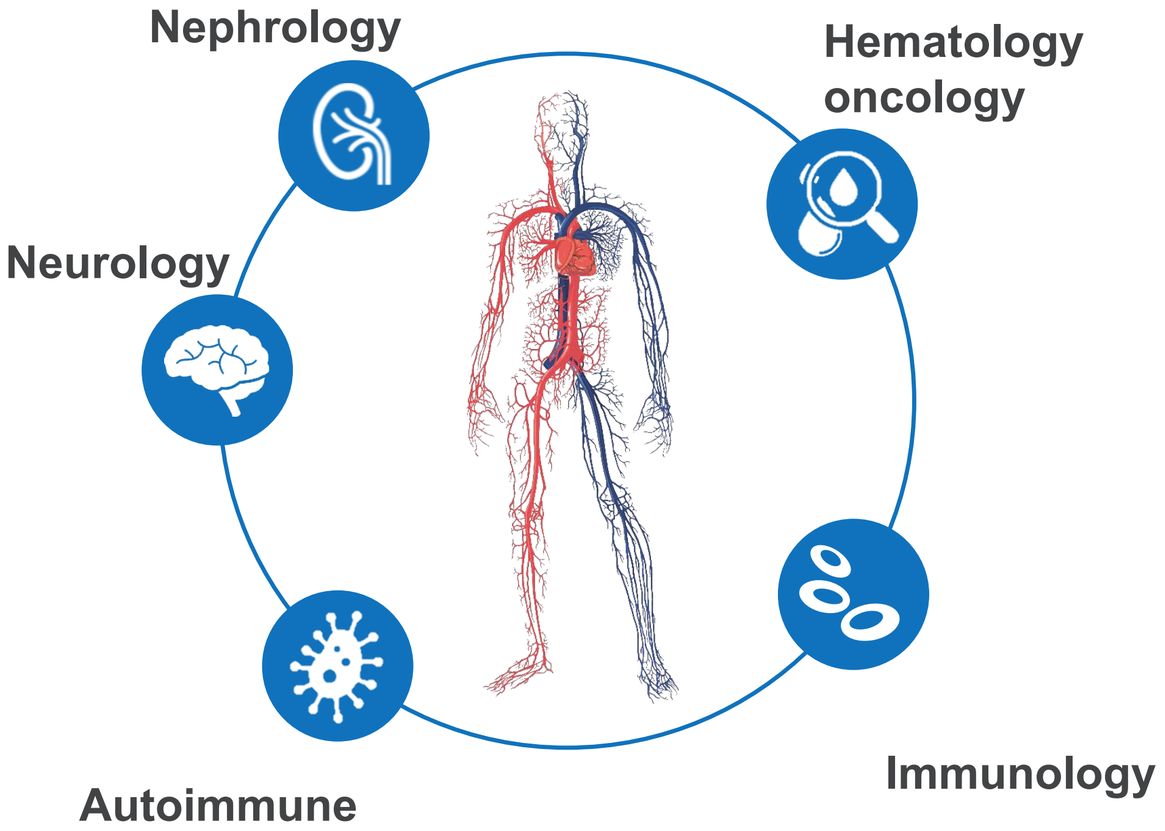


Our protease platforms are tailored to specific indications

Tuning functionality to restore complement homeostasis & immunoregulation

ProTUNE™ C3b/C4b

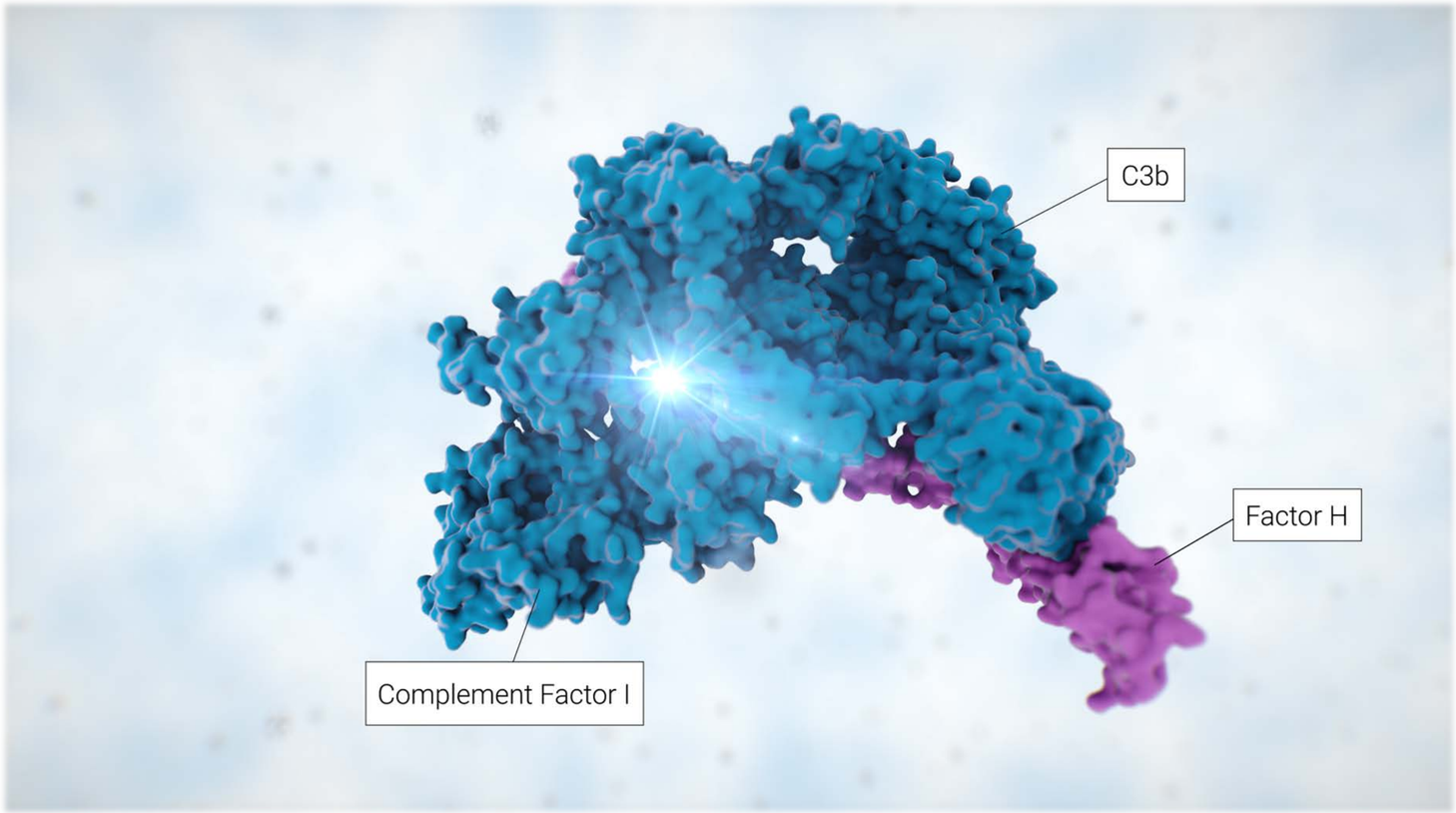




ImmunoTUNE™ C3a/C5a

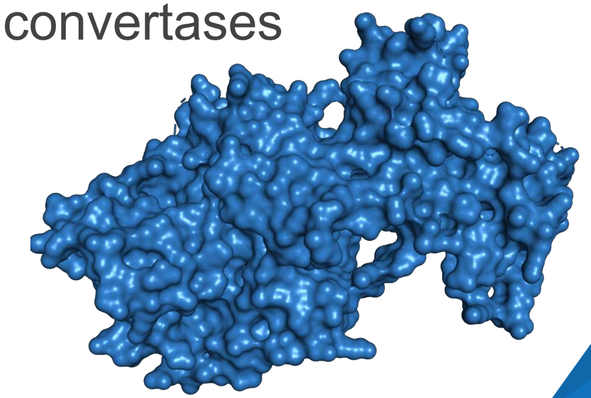
Specific inhibition of complement components at different sites of the complement cascade allows a personalized approach to treating complement disorders

Complement Factor I (CFI) – The negative regulator of complement



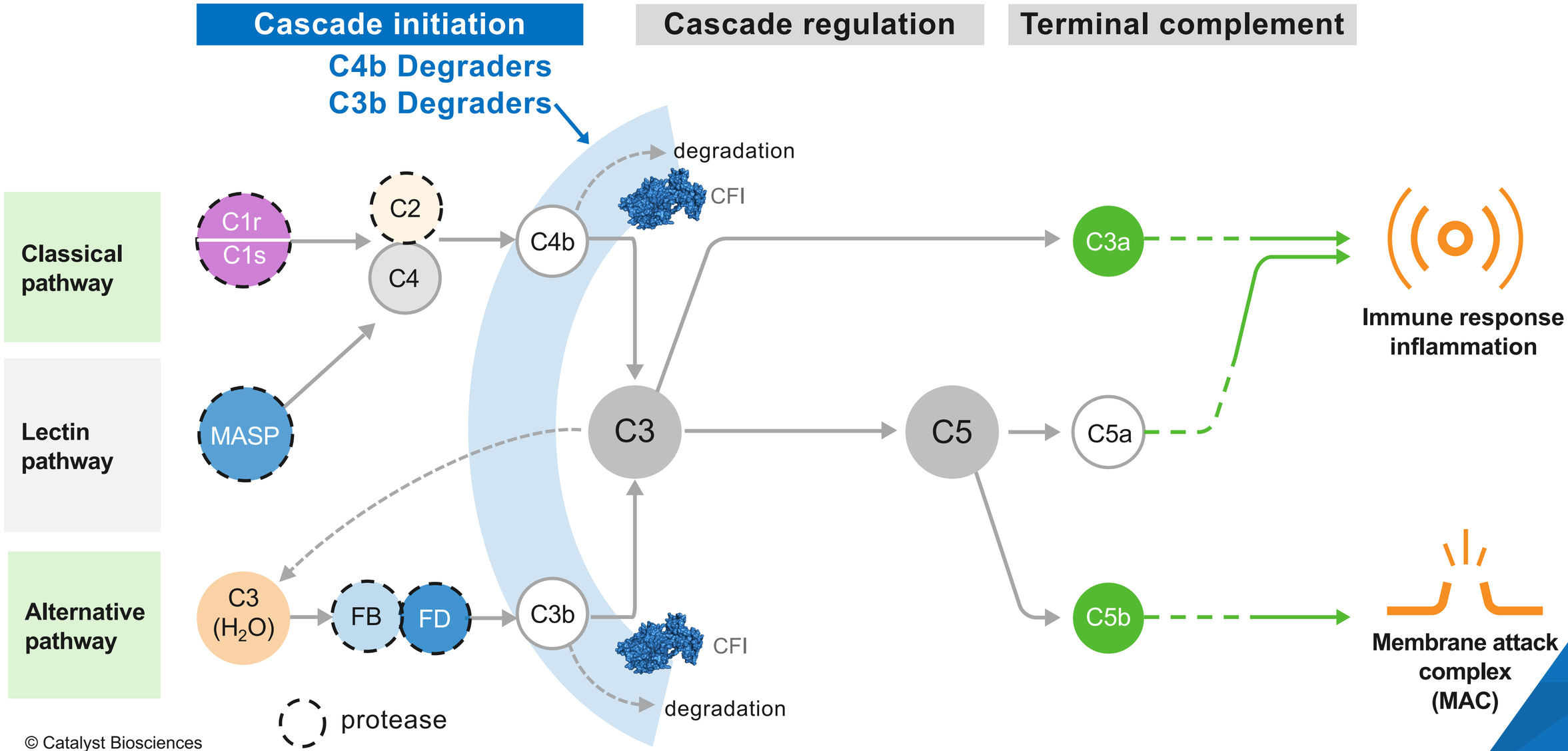
Complement Factor I

+ Negative regulator of complement at the C3 axis
+ Maintains balance in the complement cascade
  - Dysregulated CFI has clinical implications and unchecked complement activation
+ Dual specificity to regulate both the C4b2b3b & C3bBb convertases



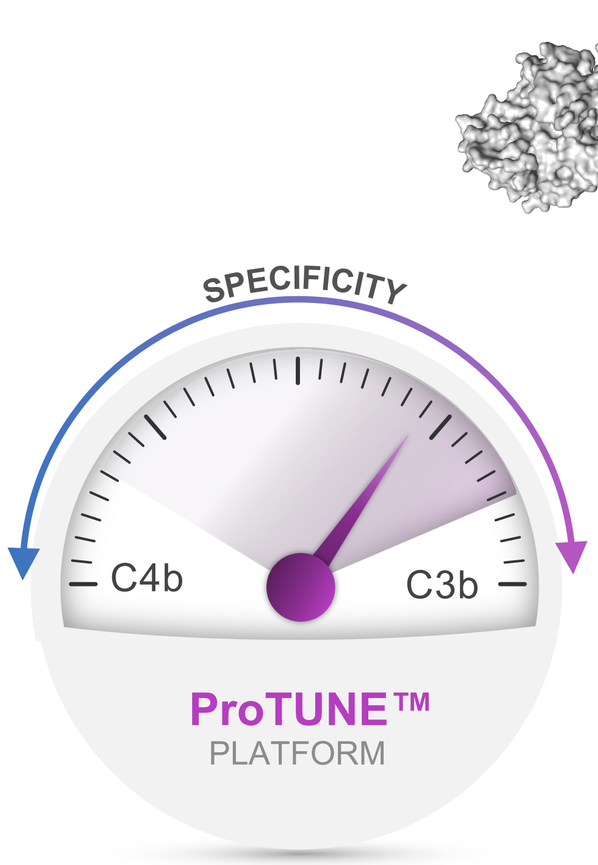
C3b/C4b degraders – unique approach to complement regulation

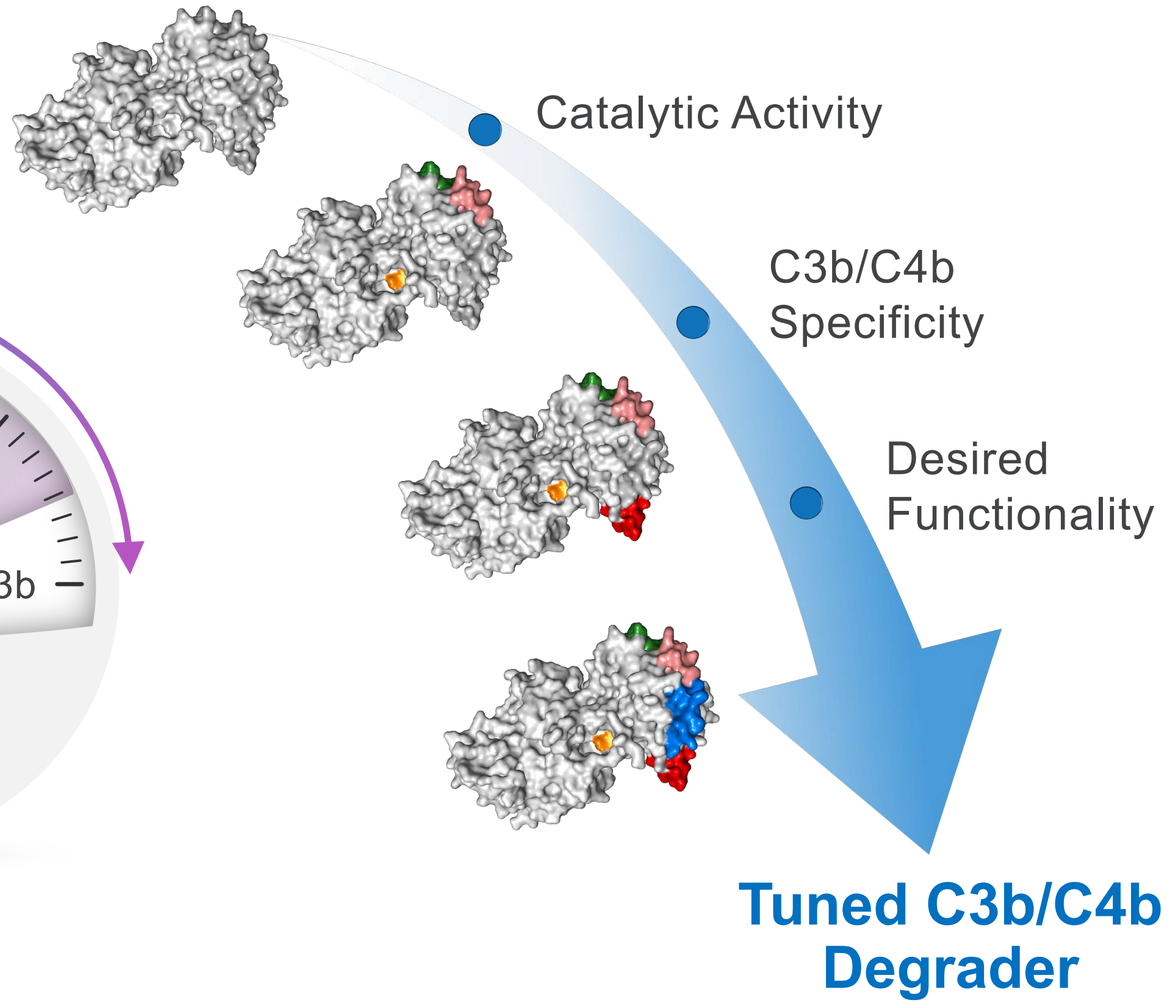
Diseases of classical, lectin and/or alternative pathway driven pathogenesis



Dialing catalytic power & specificity into CFI

Using ProTUNE™ engineering platform to tune C3b & C4b degraders



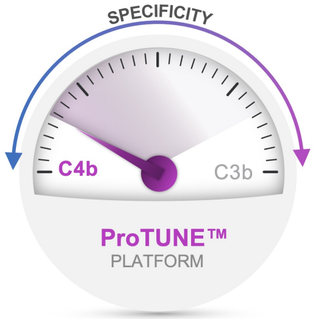


Precision CFI Therapeutics

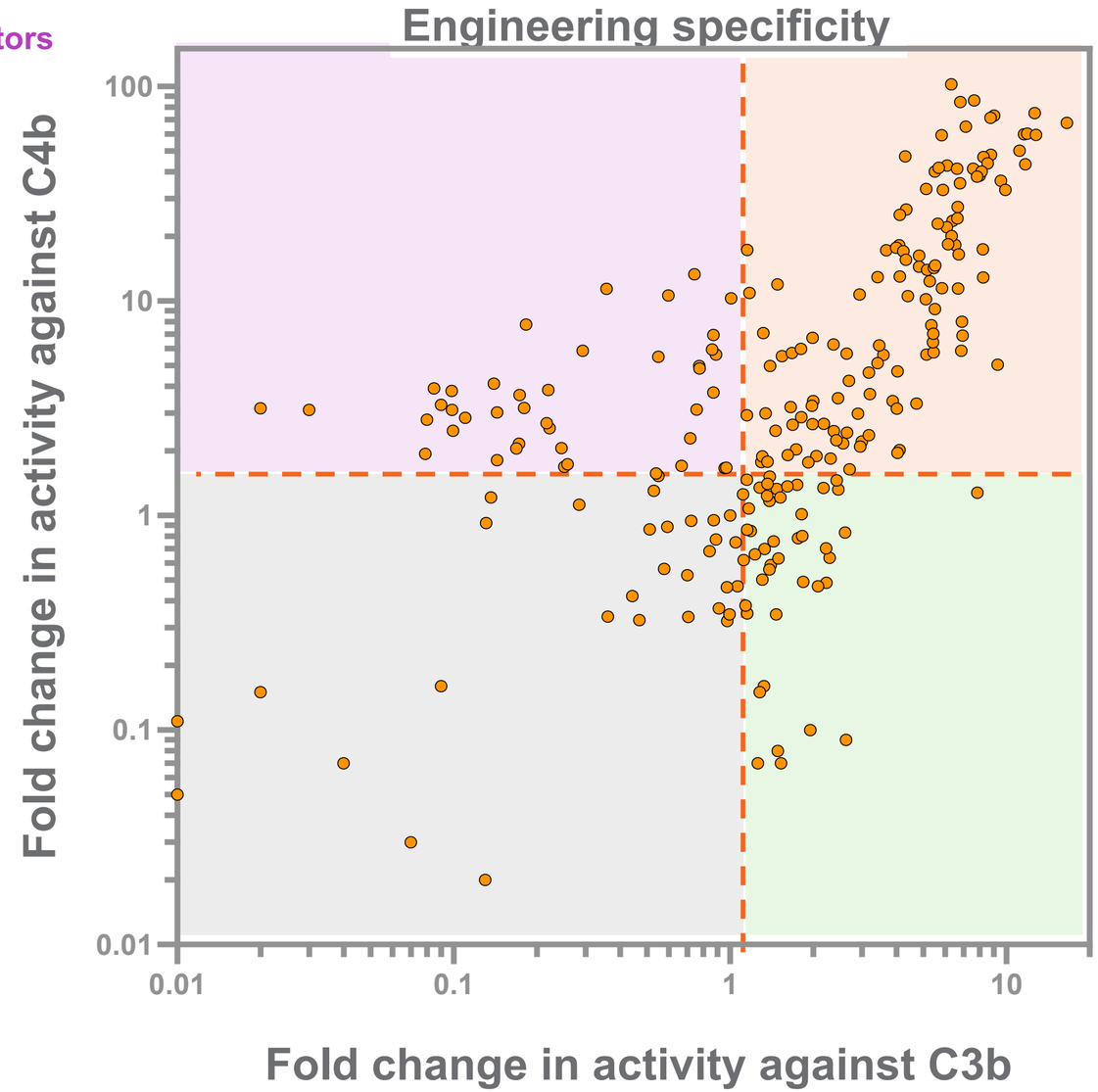
- Tunable **potency** to control dysregulated complement
- Tunable **specificity** toward C3b & C4b to restore the **right** balance to complement

Using ProTUNE™ engineering platform to tune C3b & C4b degraders

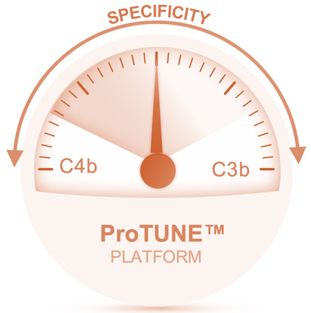
Classical-Lectin pathway specific regulators



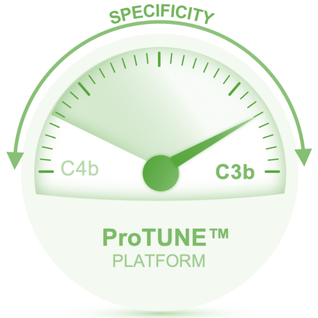
ProTUNE™ Platform allows precision medicine



Dual regulators



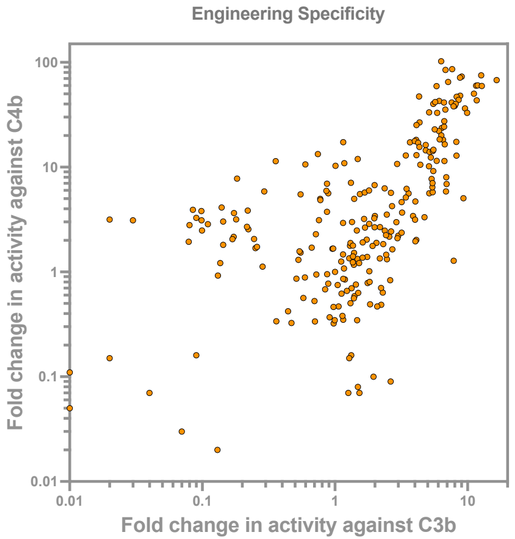
Alternative pathway specific regulators



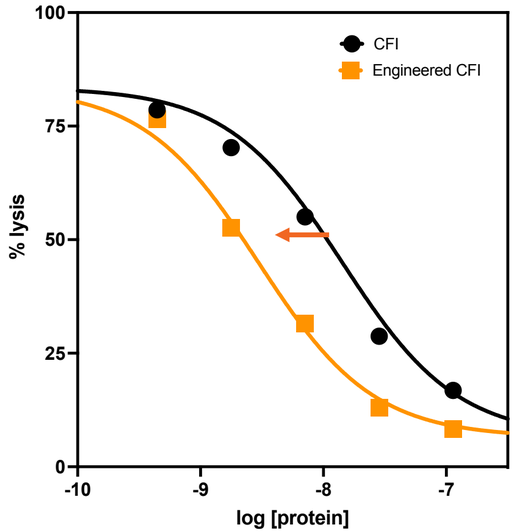
Screening strategy for complement therapeutics

In vitro assays and *in vivo* models are used to evaluate C3b & C4b degraders

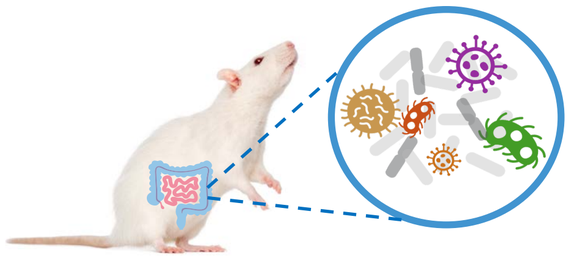
~1200 variants	~30 variants	~10 variants	ongoing
+ In vitro cleavage of C3b & C4b fragments by ELISA	+ Hemolysis inhibition	+ In vivo activity in **acute** rodent models	+ In vivo activity in **chronic** rodent models

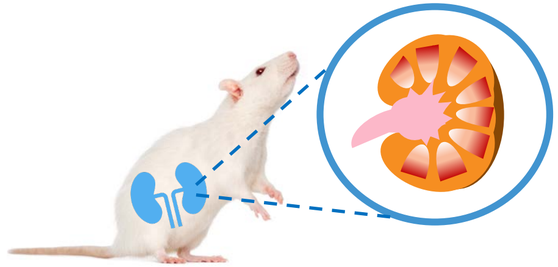


Measure cleavage fragments of C3b (iC3b) and C4b (C4c)

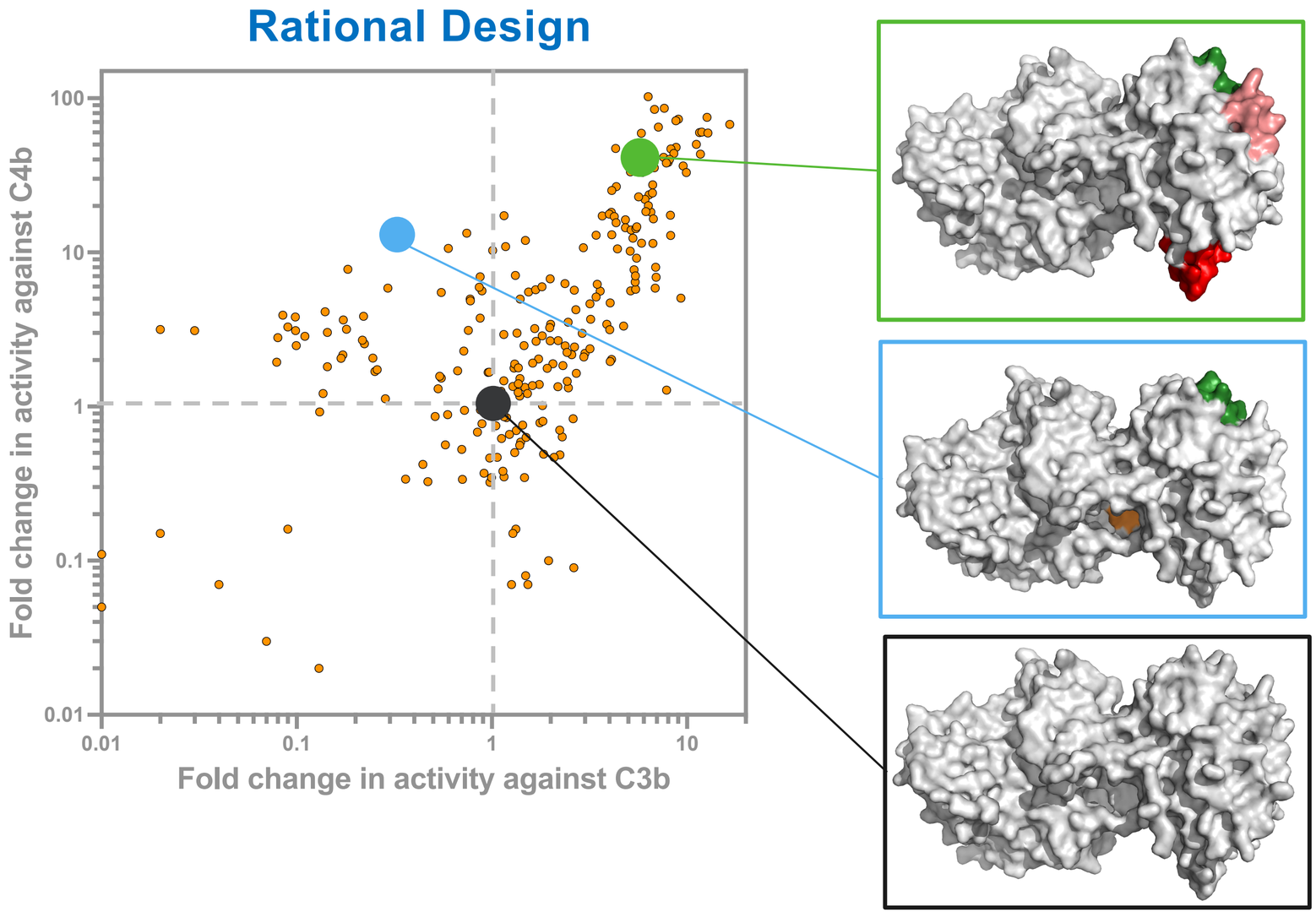


Measure inhibition of red blood cell lysis





Using ProTUNE™ Platform to tune C3b & C4b cleaving capabilities



Dual degrader:

High cleavage activity of C3b

High cleavage activity of C4b

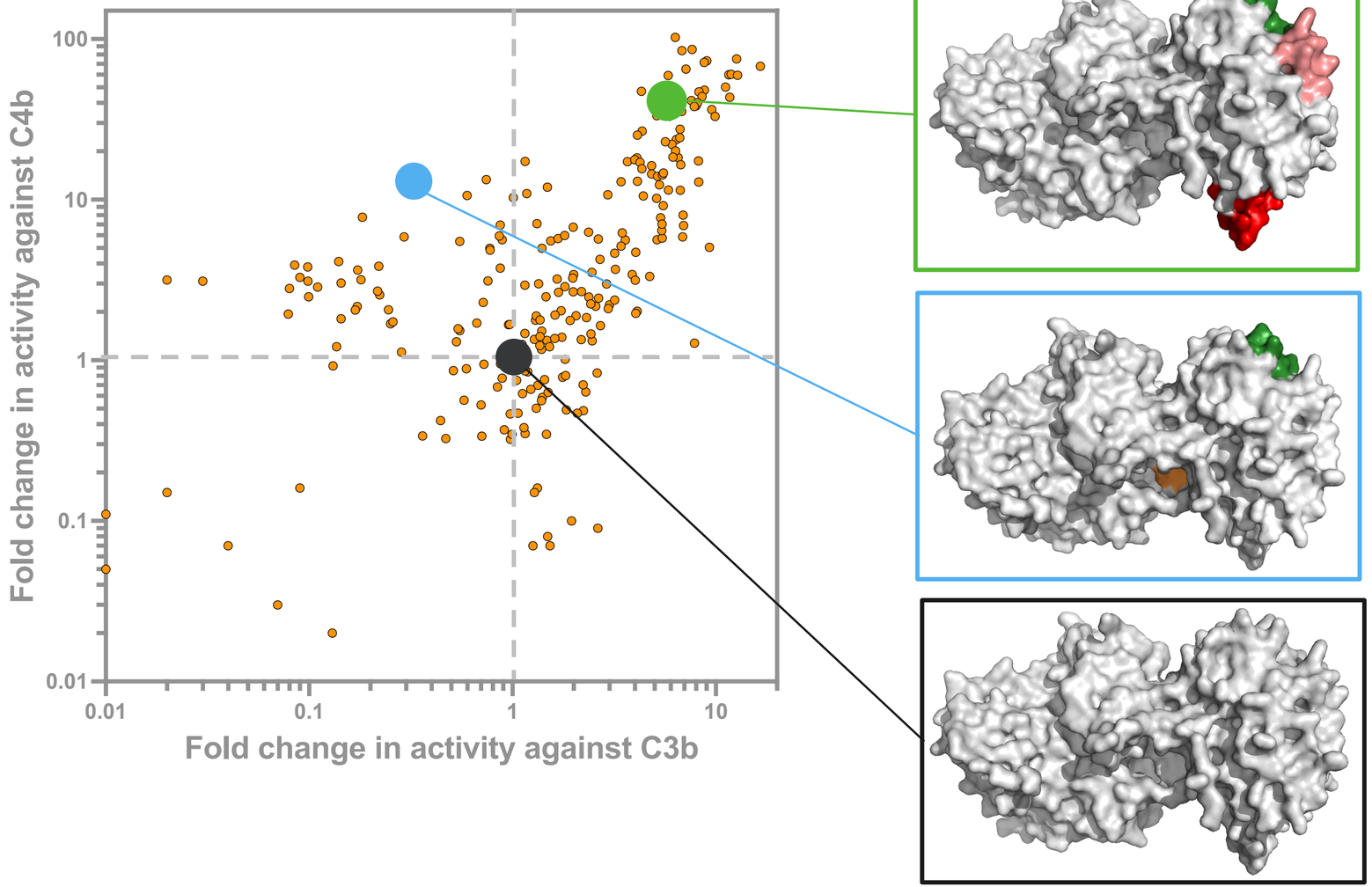
Exclusive degrader:

High cleavage activity of C4b

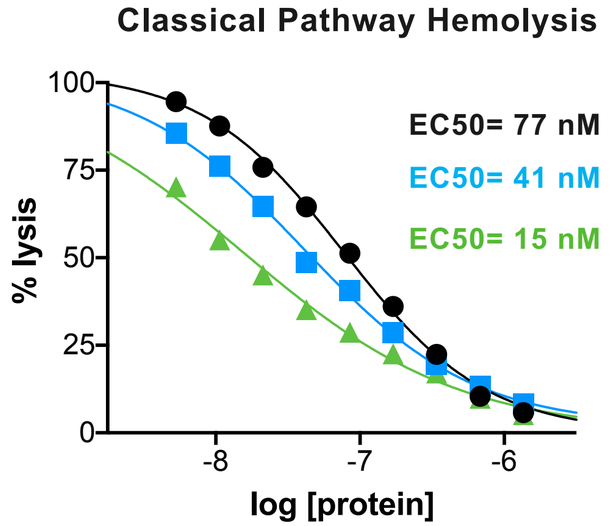
CFI base scaffold

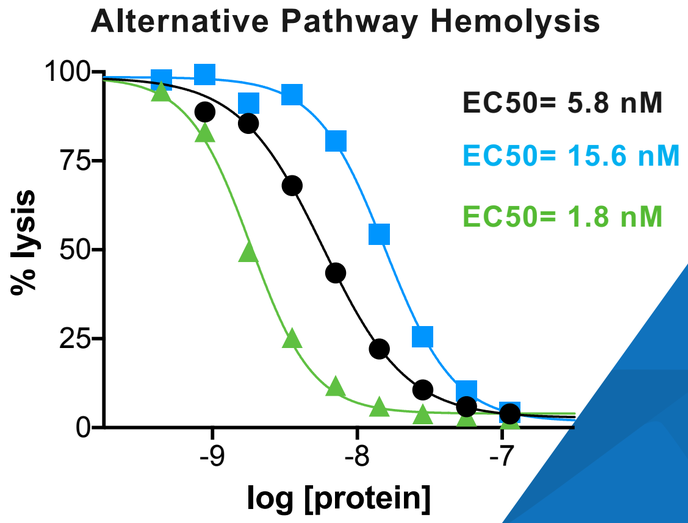
Using ProTUNE™ Platform to tune C3b & C4b cleaving capabilities

Rational Design



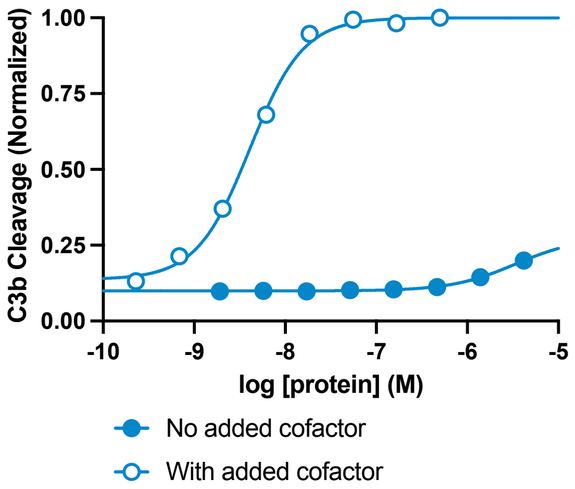
Reduction of Hemolysis

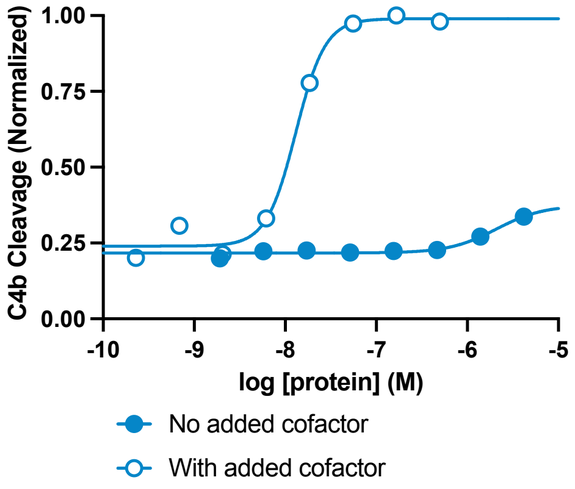




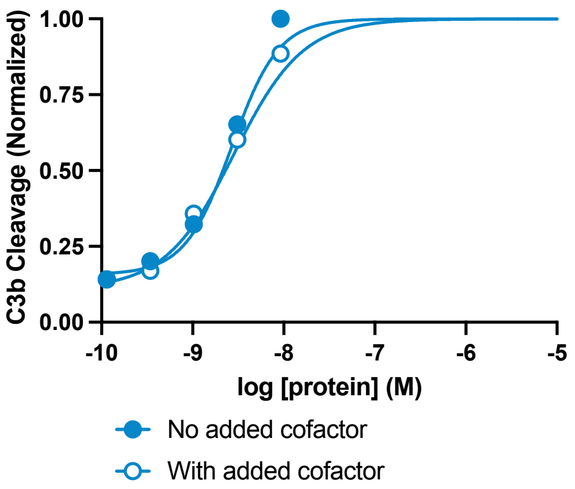
Engineered C3b & C4b cofactor independence

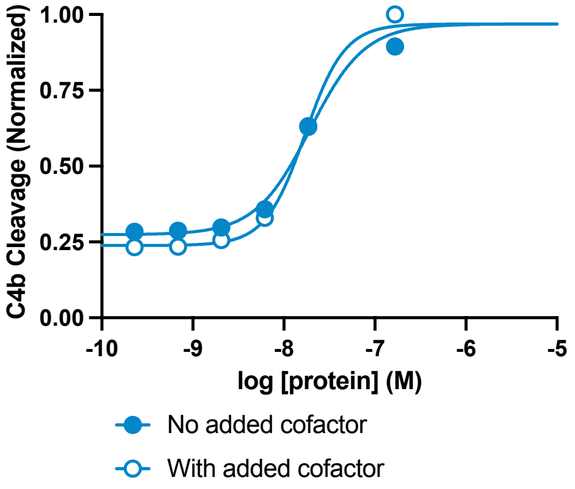
Cofactor Dependent



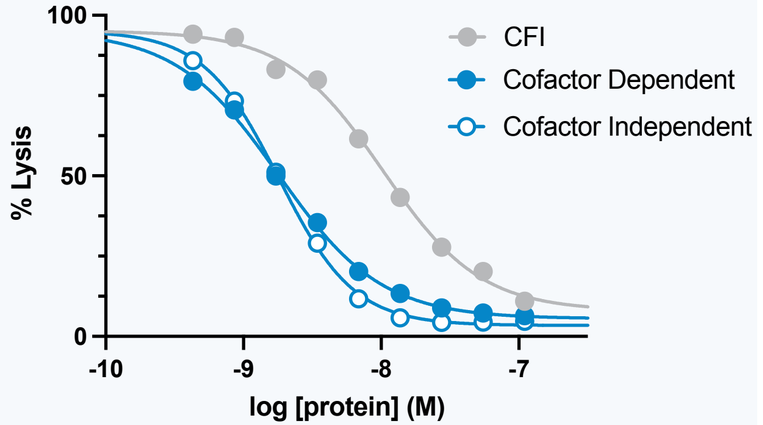


Cofactor Independent

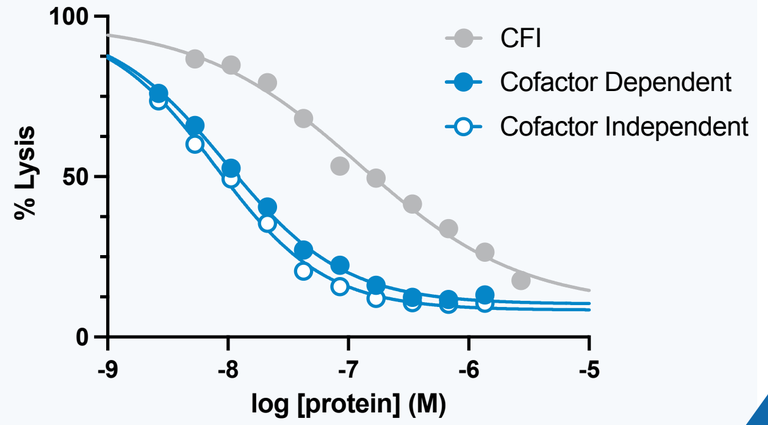




Alternative Pathway Hemolysis



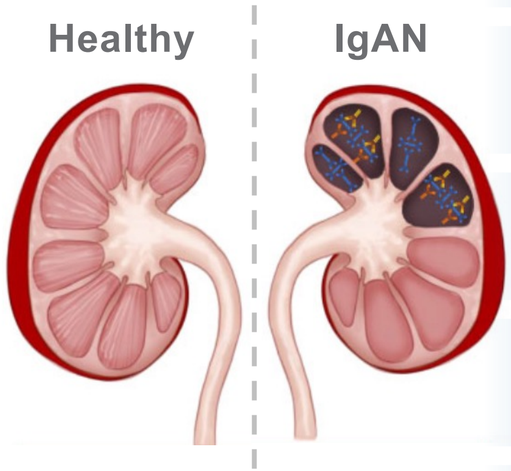
Classical Pathway Hemolysis



C3b/C4b degraders for IgA nephropathy patients

Disease in which both lectin & alternative pathways drive pathogenesis

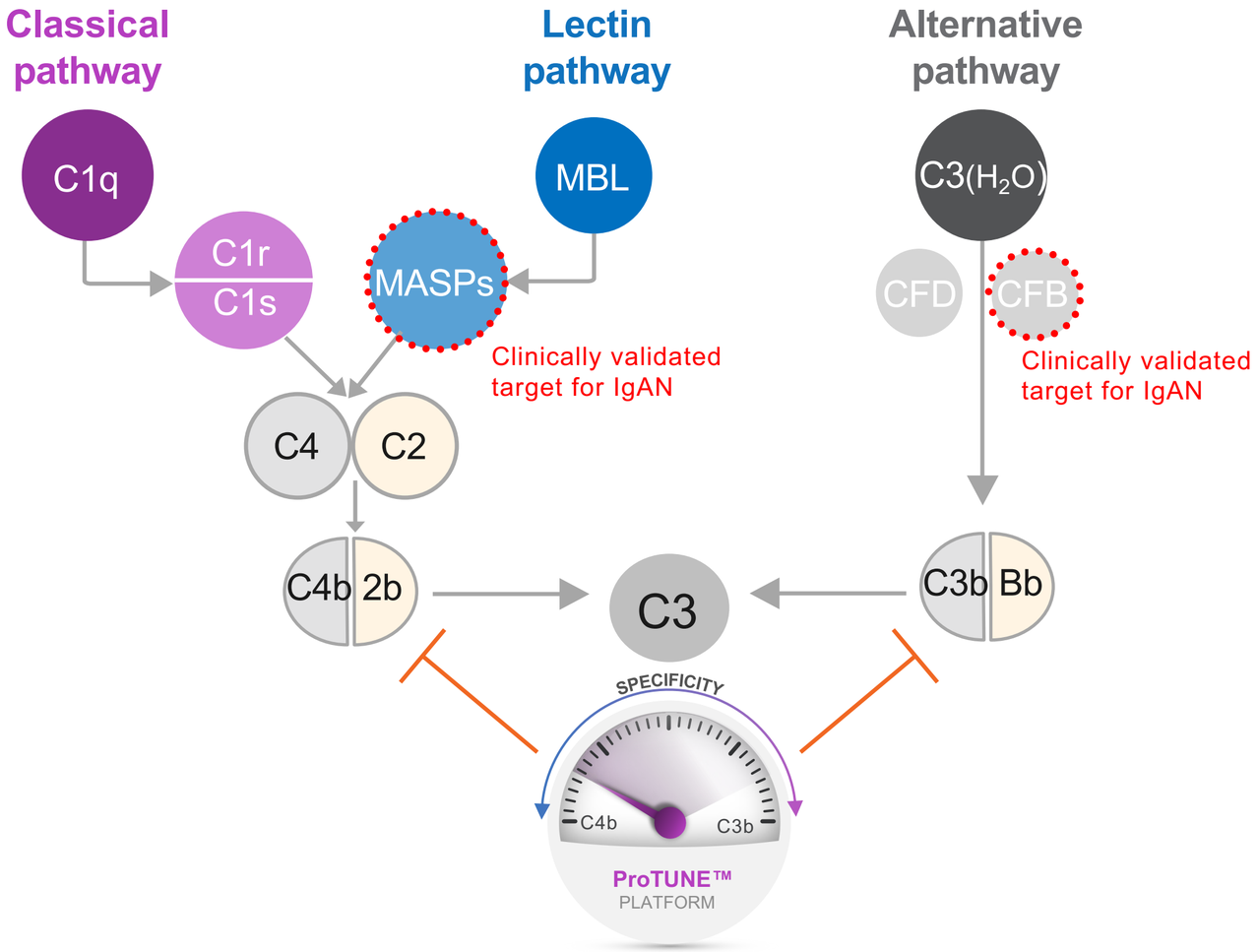
High unmet need – current treatments only addressing symptoms



+ Most common form of glomerulopathies worldwide
+ Accumulation & deposition of IgA immune complexes leading to deterioration of renal function
+ **10%** patients with rapidly progressive glomerulonephritis
+ **40%** of IgAN patients develop end stage renal disease over 20 years & need dialysis/renal transplant in order to survive
+ Significant burden on healthcare resources with an estimated cost of **$49.2 billion** in 2020 in the US

C3b/C4b degraders for IgA nephropathy patients

Dual targeting of alternate & lectin pathways



Differentiation

+ Dual targeting mode of action: lectin **&** alternative pathways

Rationale for IgA nephropathy

+ Both lectin **&** alternative pathways are involved in IgA nephropathy & correlate with severe clinical manifestation [1, 2, 3]

Clinically validated targets

+ Inhibition of only MASP2 or Factor B may be insufficient to reduce proteinuria in IgA nephropathy patients

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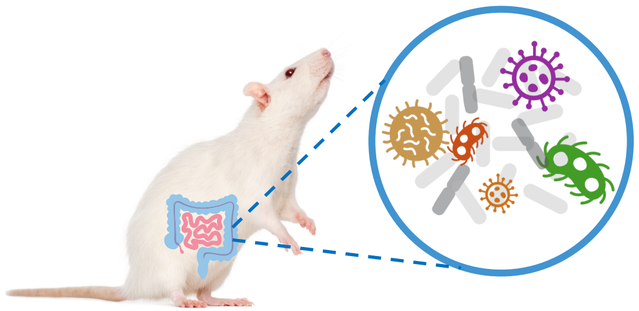
1. Medjeral-Thomas *et al*. Kidney International Reports (2018); 2. Bi *et al*. BMC Nephrology (2019); 3. Roos *et al*. J Am Soc Nephrol (2006)

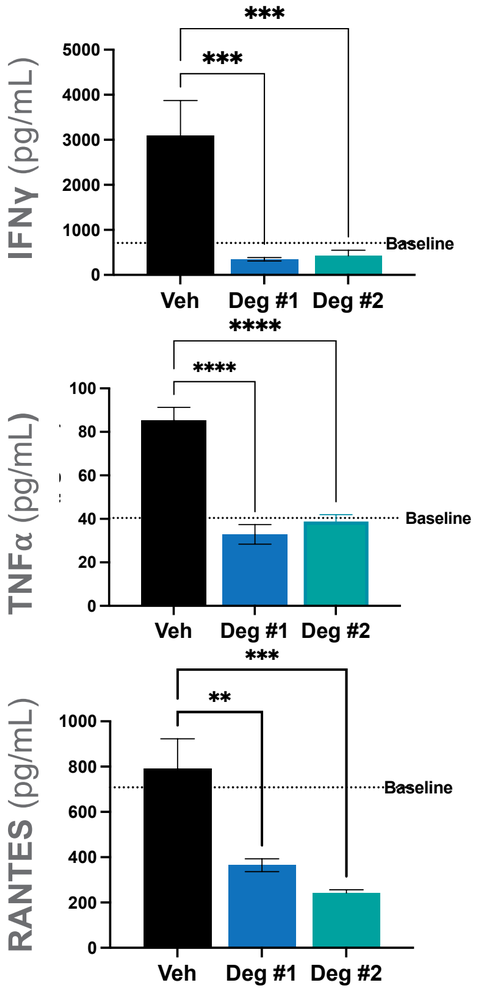
C3b/C4b degraders significantly reduce inflammation *in vivo*

Rat model of complement activation

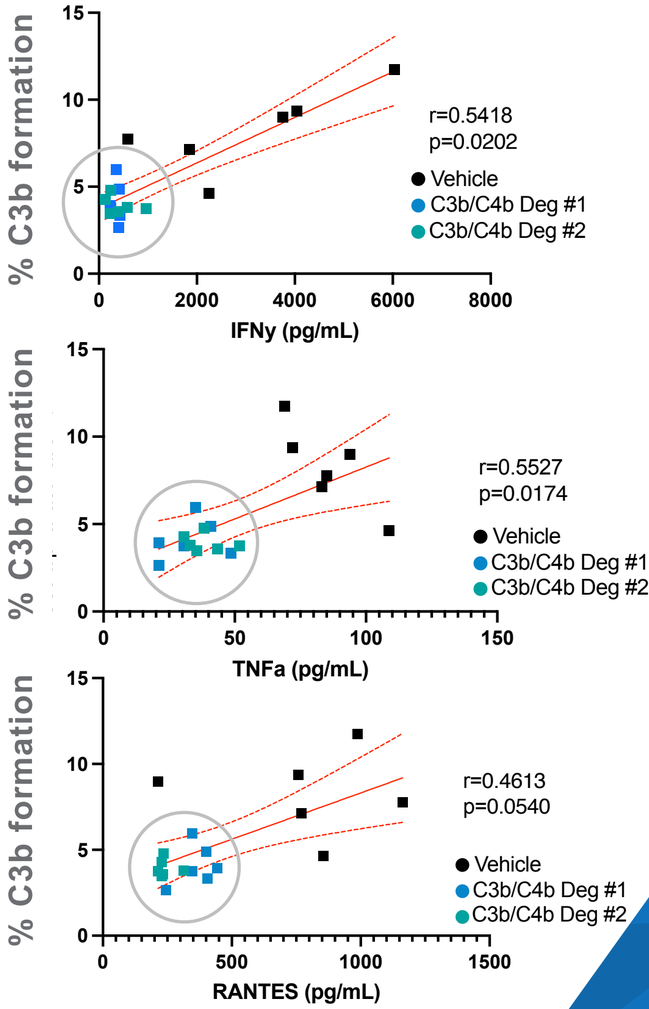


- Reduction of **IFNγ, TNFα, & RANTES** involved in kidney damage & proteinuria in IgA nephropathy patients[1, 2, 3]

Inflammatory markers in IgA nephropathy



Concomitant reduction of inflammatory markers and complement C3 cleavage

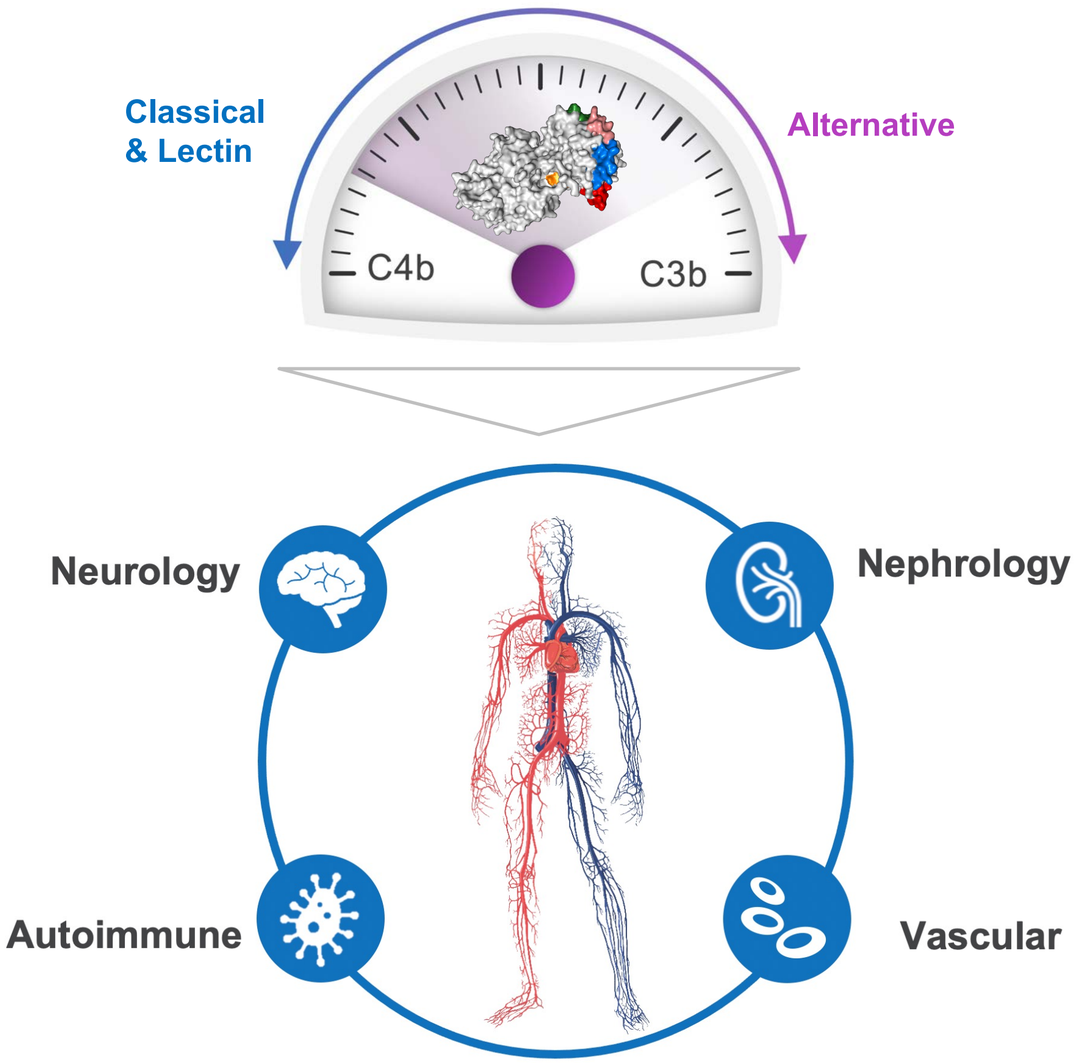


1. Yano, N. *et al.* Phenotypic Characterization of Cytokine Expression in Patients With IgA Nephropathy. *J Clin Immunol* **17**, 396–402 (1997).
2. Lim, C. S. *et al.* Th1/Th2 predominance and proinflammatory cytokines determine the clinicopathological severity of IgA nephropathy. *Nephrol Dial Transpl* **16**, 269–275 (2001).
3. Brabcová, I. *et al.* Intrarenal gene expression of proinflammatory chemokines and cytokines in chronic proteinuric glomerulopathies. *Physiol Res* 221–226 (2007)

Values are mean +/- SEM, **p<0.01 ***p<0.001 p<0.0001 using One Way or Two-way ANOVA.

C3b/C4b degraders for precision medicine

Diseases in which classical, lectin and/or alternative pathways drive pathogenesis



Specific inhibition of complement components at different sites of the complement cascade allows a personalized approach to treating complement disorders

Acknowledgements

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THANK YOU

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