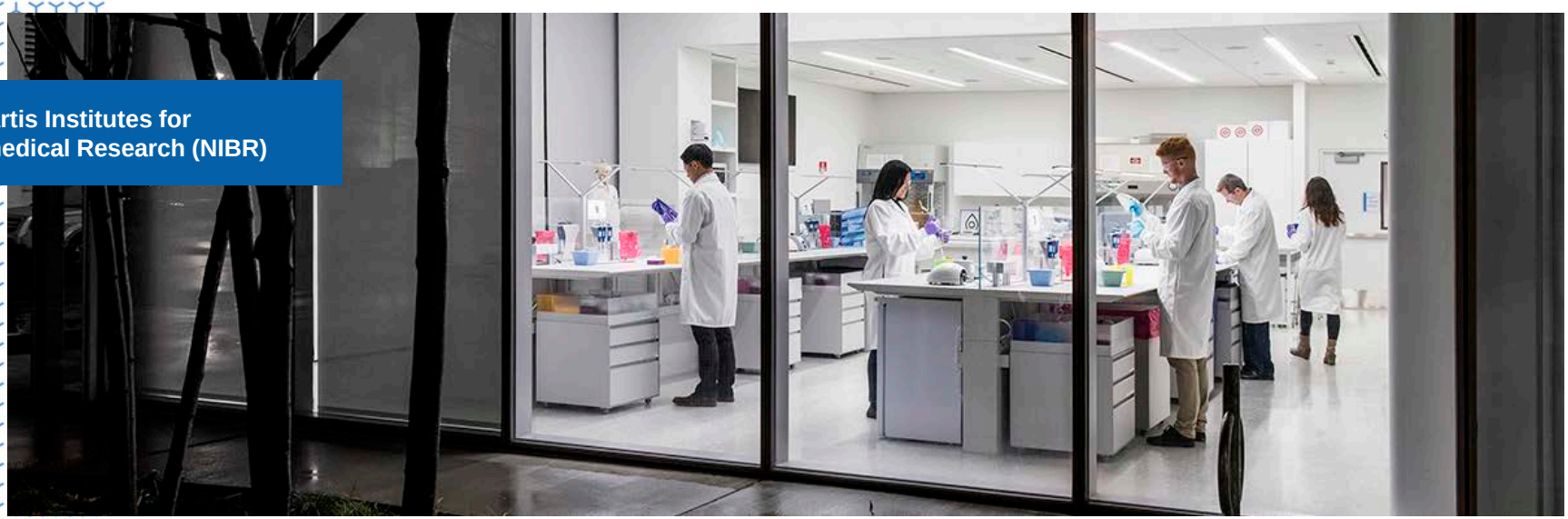
Novartis Institutes for Biomedical Research (NIBR)



A Diverse Pipeline of Targets and Modalities:

Novartis' Approach to Modulating the Alternative Complement Pathway

Christopher M. Adams and Thomas M. Smith

November 14, 2019

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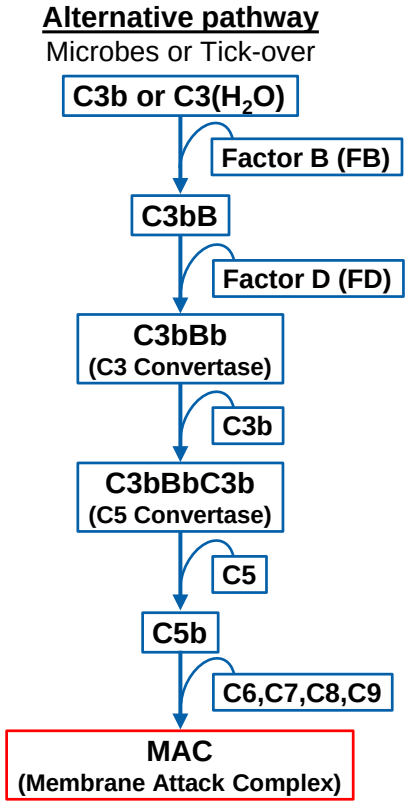
The Alternative Complement Pathway

A seemingly simple cascade



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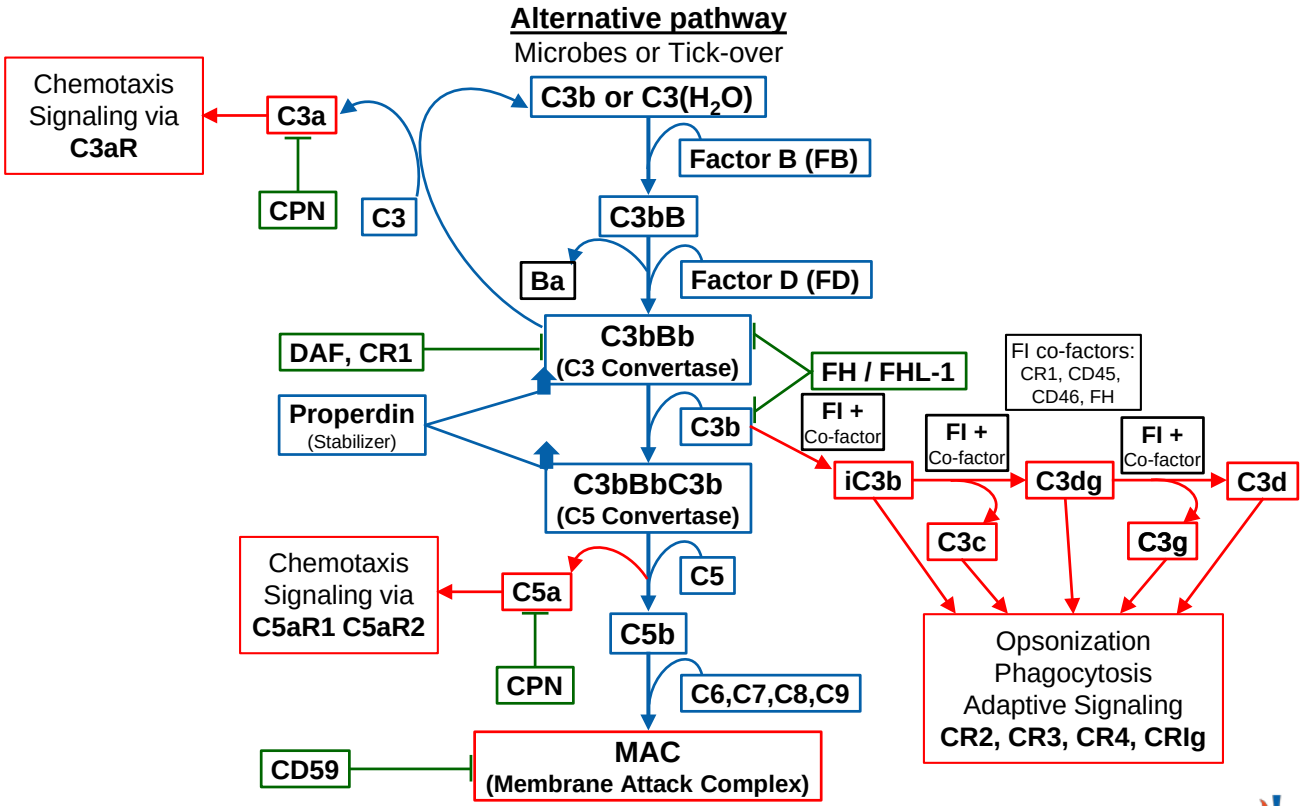
The Alternative Complement Pathway

A seemingly simple cascade is in reality a highly complex system

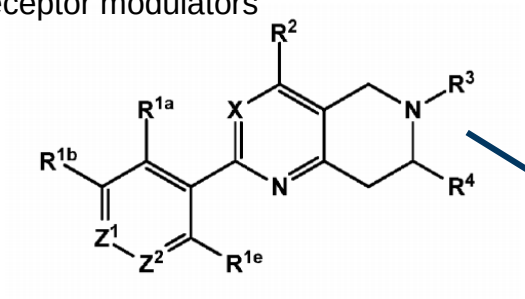


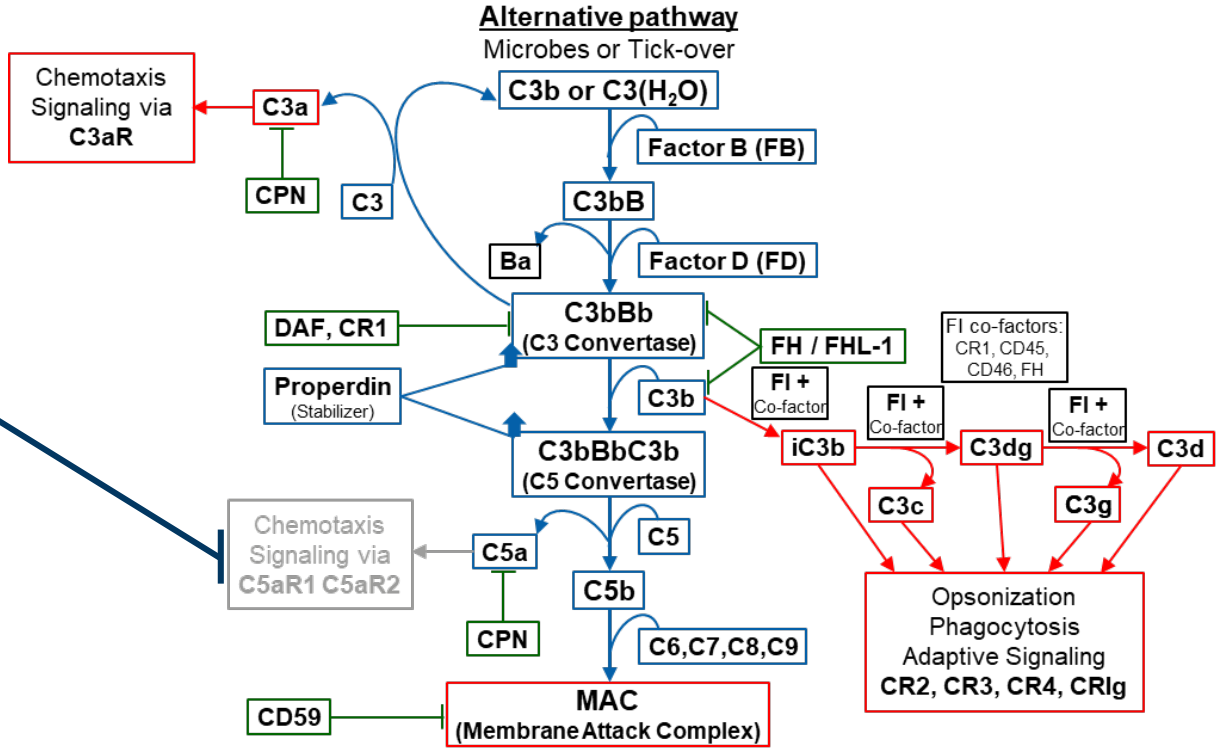
The value in targeting specific nodes

C5aR antagonists attenuate inflammation while maintaining MAC formation

WO 2013/016197

Tetrahydropyrido-pyridine and tetrahydropyrido-pyrimidine compounds and uses as C5a receptor modulators





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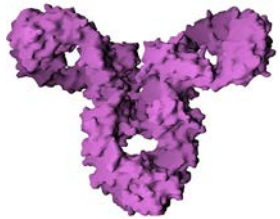
The value in targeting specific nodes

*Multiple modalities targeting **C5** inhibit terminal phase activation*

Intravitreal LFG316 in Patients With Age-related Macular Degeneration (AMD)

clinicaltrials.gov/ct2/show/NCT01527500



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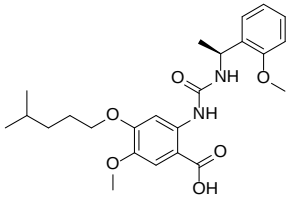
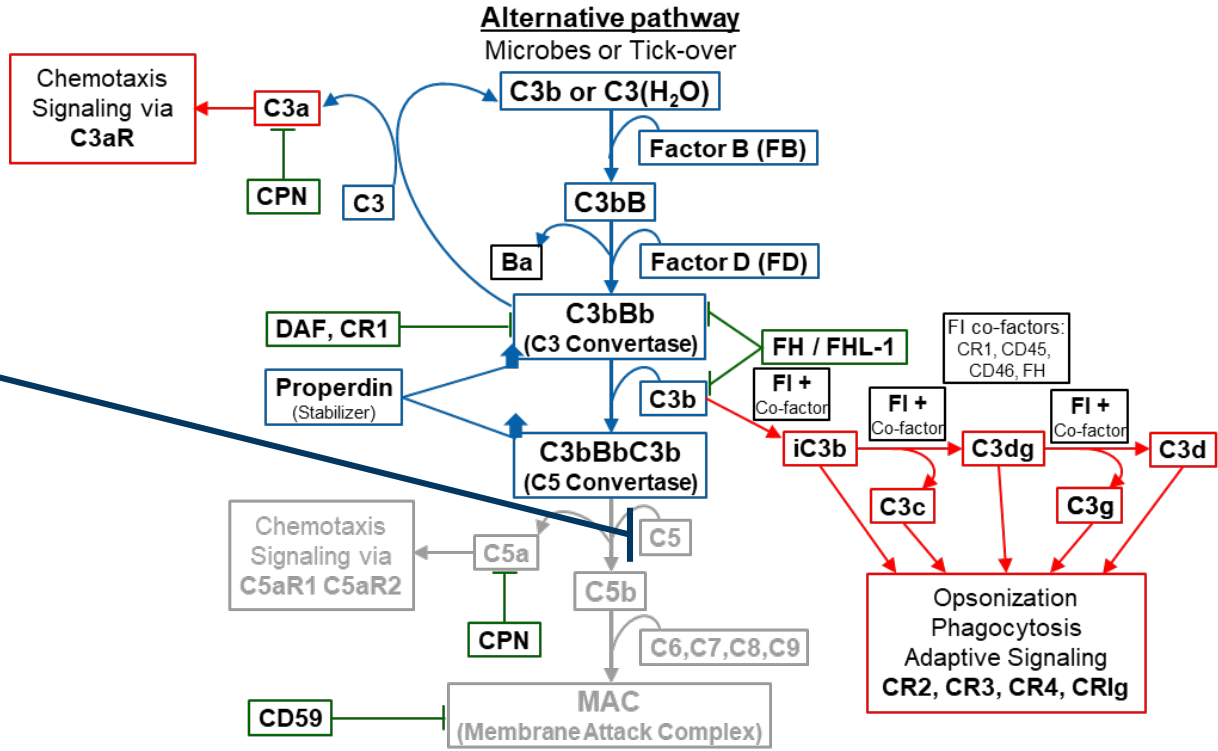
A small-molecule inhibitor of C5 complement protein

Nat Chem Biol. 2019; 15(7):666-668.





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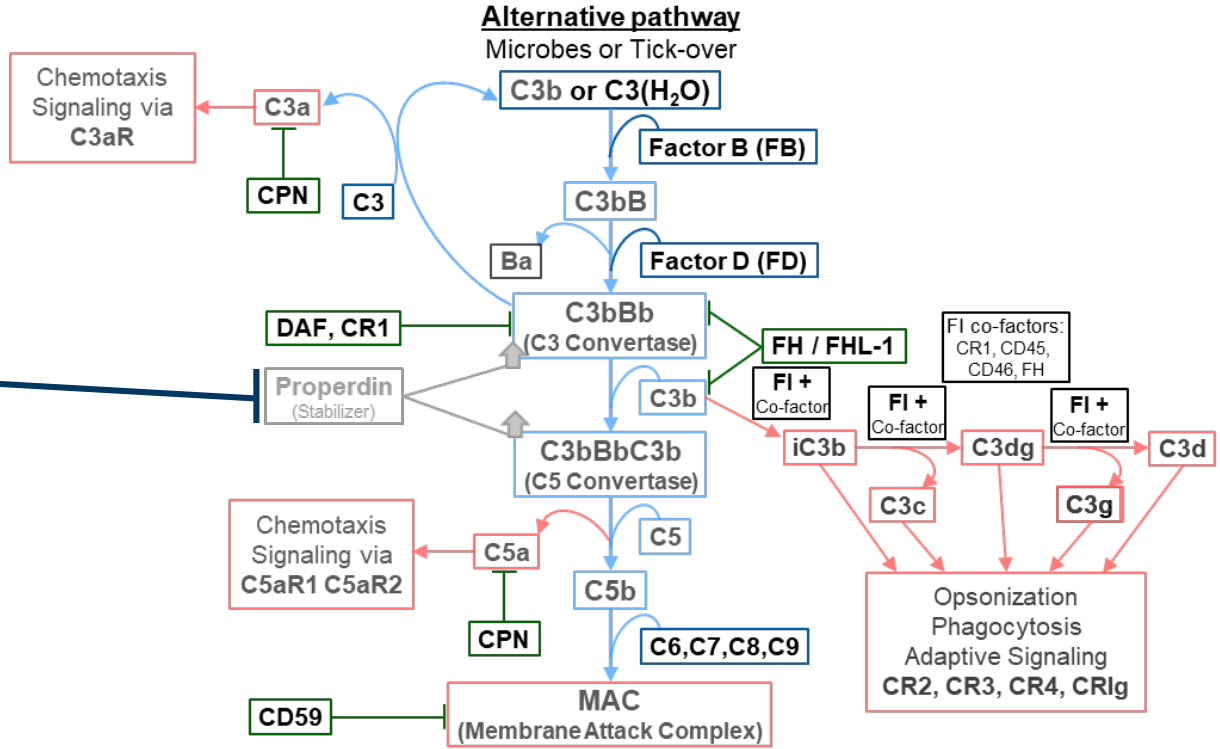
The value in targeting specific nodes

*Inhibiting **properdin** attenuates but does not stop AP activation*

A first in human study of Intravitreal (IVT) CLG561 in Subjects with Advanced Age-Related Macular Degeneration (AMD). IOVS 2016, Vol 57, 2672

Commons.Wikimedia.org



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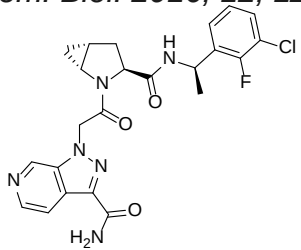
The value in targeting specific nodes

*Inhibiting **Factor D** can completely inhibit AP activation*

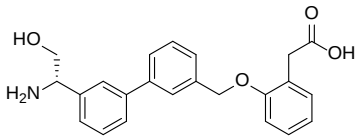
Small-molecule factor D inhibitors targeting the alternative complement pathway

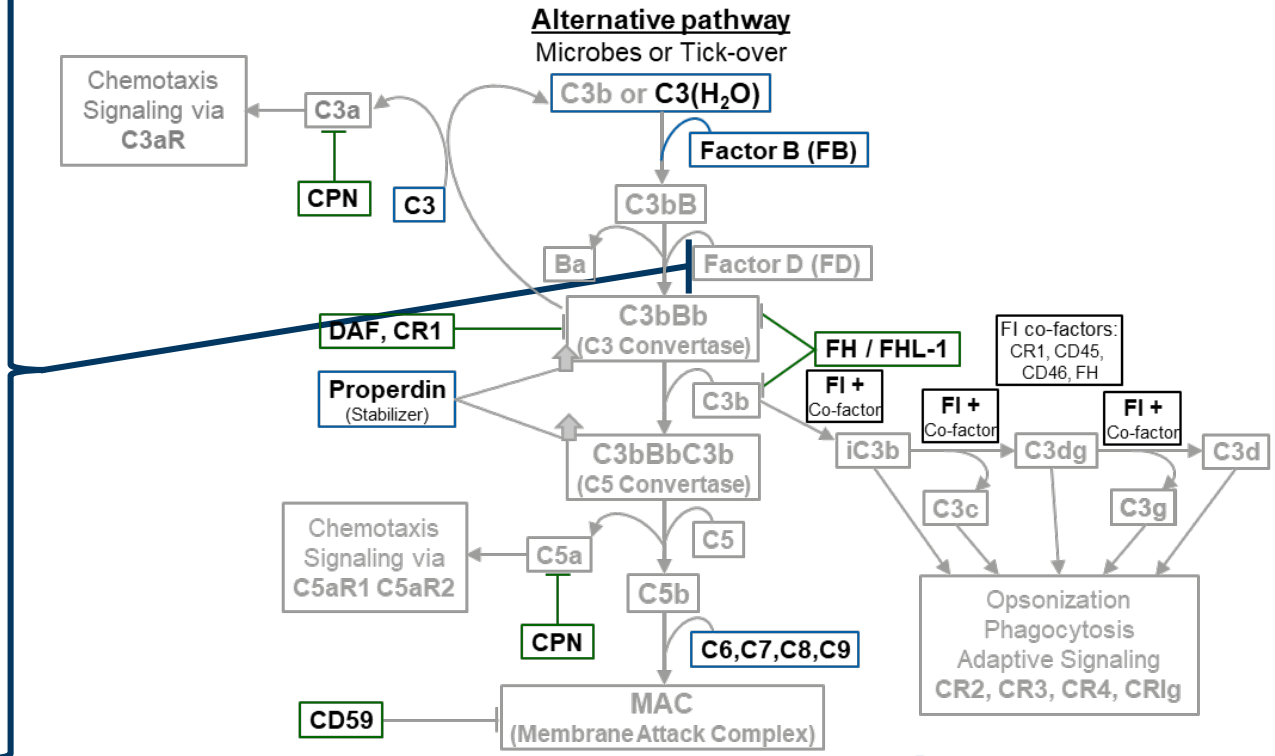
Nat. Chem. Biol. 2016, 12, 1105



Design, Synthesis, and Preclinical Characterization of Selective Factor D Inhibitors Targeting the Alternative Complement Pathway

J. Med. Chem. 2019, 62, 4656



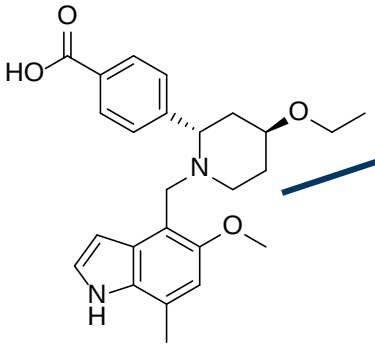


The value in targeting specific nodes

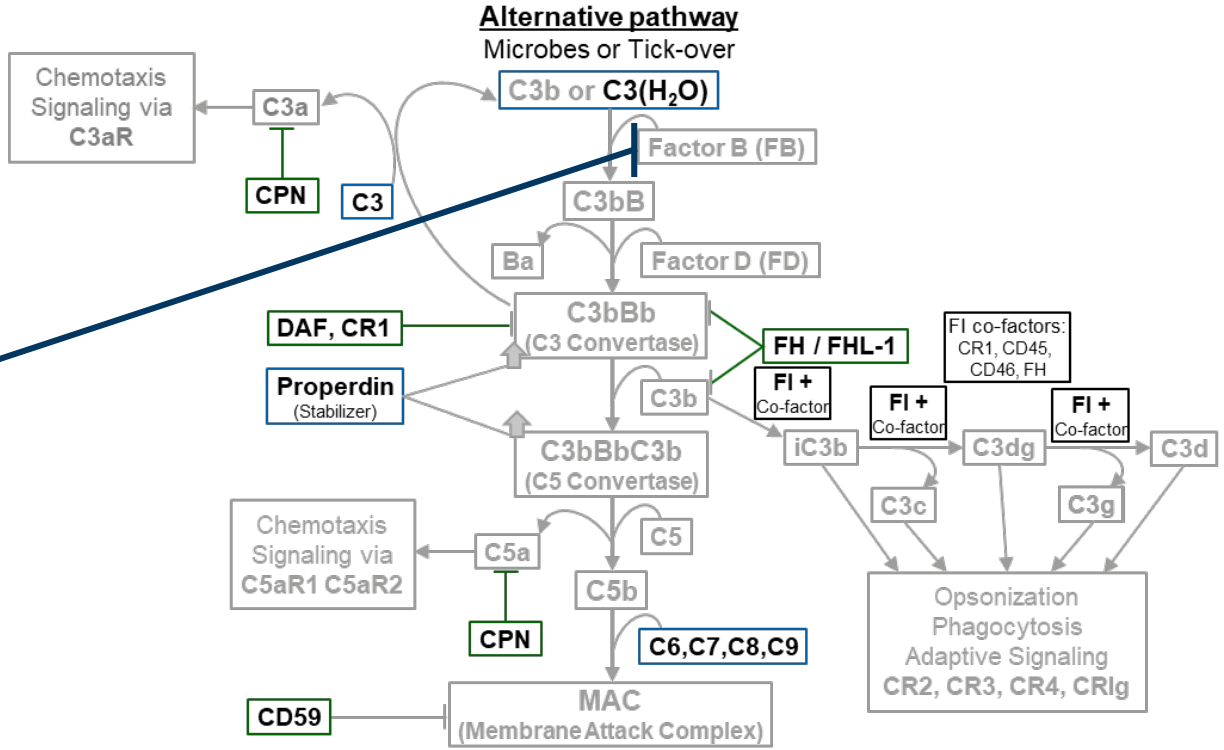
*Inhibiting **Factor B** can completely inhibit AP activation*

Small-molecule factor B inhibitor for the treatment of complement-mediated diseases

PNAS April 16, 2019 116 (16) 7926



LNP023



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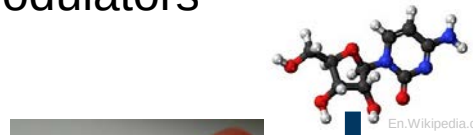
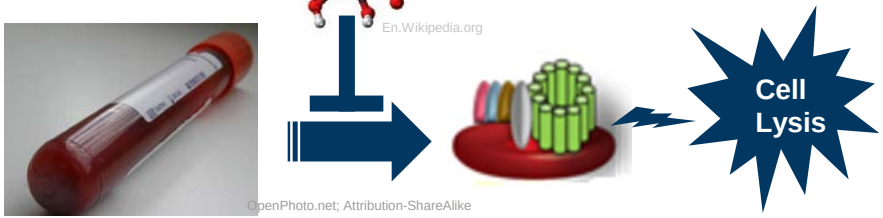
Hit finding for the alternative pathway

Broad opportunities to find inhibitors at multiple nodes

- Phenotypic screens to look for pathway modulators
  - Pros
    - Opportunity to identify new nodes in a pathway
    - Can screen against multiple targets in parallel
    - Functional readouts
  - Cons
    - Requires hit deconvolution
    - Typically lower throughput, longer campaign



En.Wikipedia.org



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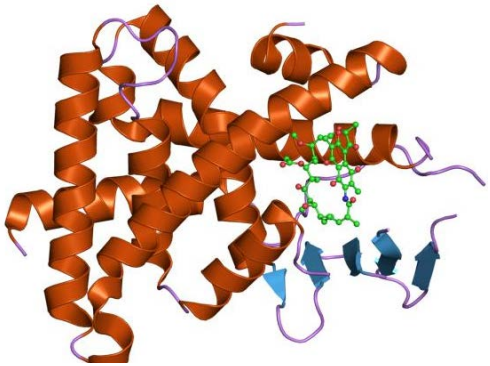
- Target-Based Screens
  - Pros
    - Can optimize screen for target of interest
    - Typically high throughput, tools for hit validation at the ready
  - Cons
    - Typically not assessing a functional readout
    - Lose opportunity for serendipity



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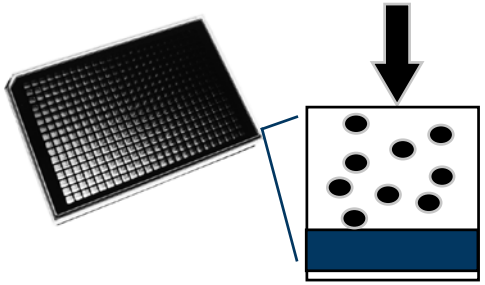
Alternative pathway phenotypic screening

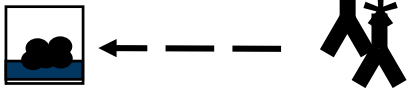
MAC ELISA

Precincubate normal human serum
(6%, complement source) ± 40uM compound



Membrane attack complex (MAC formation), 37°C

Stop reaction
by washing

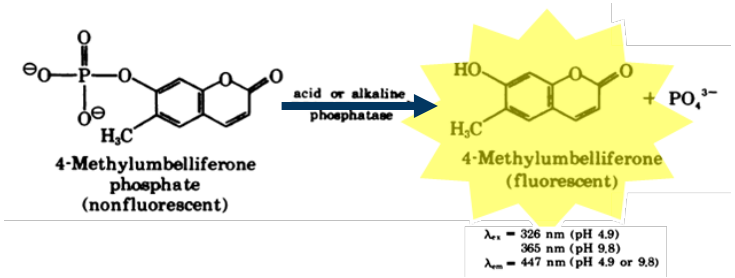


Detect bound activation products (MAC) with *alkaline phosphatase* conjugated anti-C5b-9 neoepitope antibody [MAC]

Zymosan ELISA plates

Yeast cell wall complement activator

adsorbed onto 384w ELISA plate



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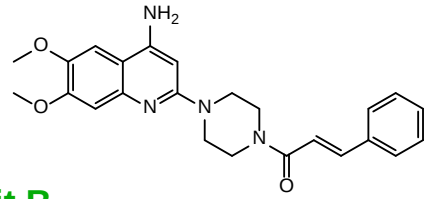
MAC ELISA validation results

Hihglights:

- Broad pathway screen, with diverse MoA inhibitors possible
- ~18 automated step colorimetric ELISA
- ~1.4 million compounds screened @ ~40uM
- 163 confirmed hits

- Follow-up *enzymatic* validation to elucidate mode-of-action
  - 130 compounds selected for FB- and FD-specific assays
  - NMR-validation on fB catalytic domain → 3 FB hits



Hit B

Human 6% serum MAC IC_{50} 0.7 μM

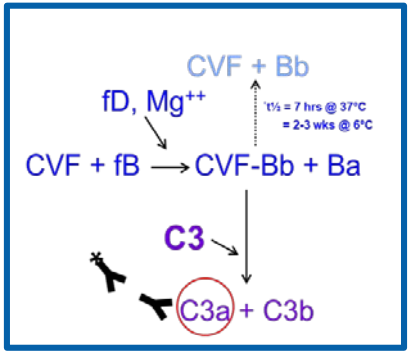
Lessons from MAC ELISA:

- 384 well format, > 1M compounds → ~ 3 months HTS
- High serum concentration → compound protein binding & reduced sensitivity
- Challenging follow-up for non-enzymatic pathway inhibitors; downstream assays prioritized enzymatic modulators

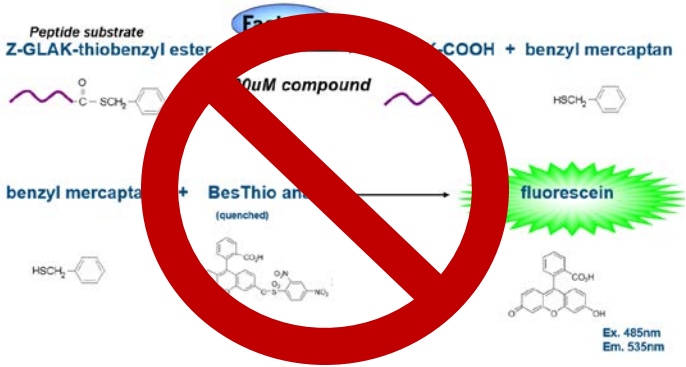
Alternative pathway target-based screening

FB specific assays

- **ELISA employing Cobra Venom Factor complex (CVF-Bb)**
  - Serum-free environment enable sensitivity to weak FB inhibitors
  - Assess functional pathway activity (detection is C3a neo-epitope)
  - Eu-secondary antibody avoids colorimetric development



- **Factor B peptide cleavage assay**
  - Biochemical assay enables sensitivity to weak FB inhibitors
  - Applicable to HTS (1 million+ compounds)



Large number of false positives

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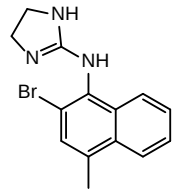
Factor B ELISA validation results

Highlights:

- Multi-step, plate-to-plate transfer → limited throughput
- ~250K compounds screened @ ~30uM
- 261 confirmed hits with IC_{50} < 100 uM

- **Validation assays:**
  - Factor B *enzymatic* assay
  - NMR binding Assay
  - Surface plasmon resonance
  - Crystallography



Hit A

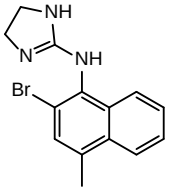
Factor B IC_{50} 6.6 μM

Lessons from Factor B ELISA:

- Challenges with C3 protein production, 384 well format and heterogeneous assay limits scale of screen
- CVF-Bb serine protease useful substitute for endogenous C3 convertase (C3bBb)
- Fluorescent readout preferable to colorimetric

Starting points from screening

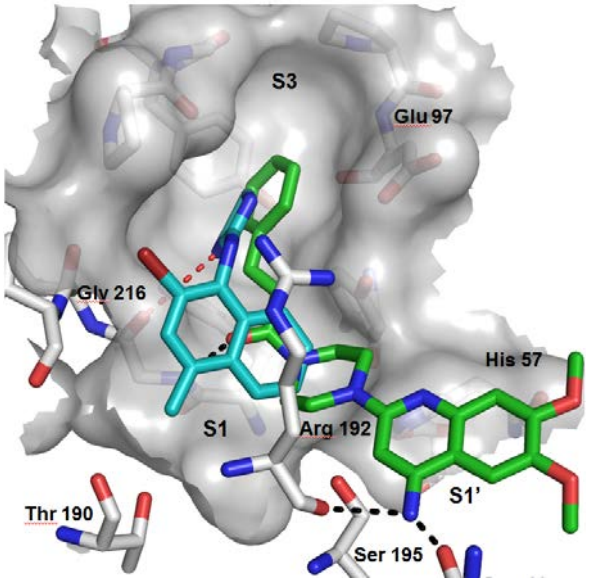
Novel scaffolds identified without activity on other S1 proteases

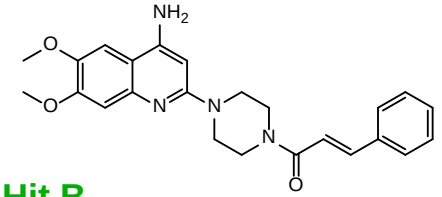


Hit A

Human Factor B IC_{50} 6.6 μM

- Fragment-like
- Binding between S1 and S3 without binding deeply in either
- H-Bond interaction with Gly216;Cation–π interaction to guanidine group of Arg192





Hit B

Human Factor B IC_{50} 1.7 μM

Human 6% serum MAC IC_{50} 0.7 μM

- Functional activity: MAC ELISA
- Binding from S3 to S1`without touching S1
- H-bond interactions with Ser195, Arg192 and Gly216

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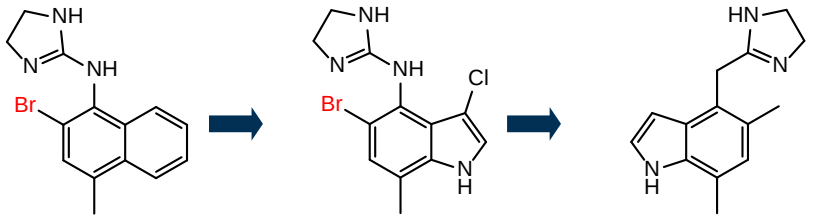
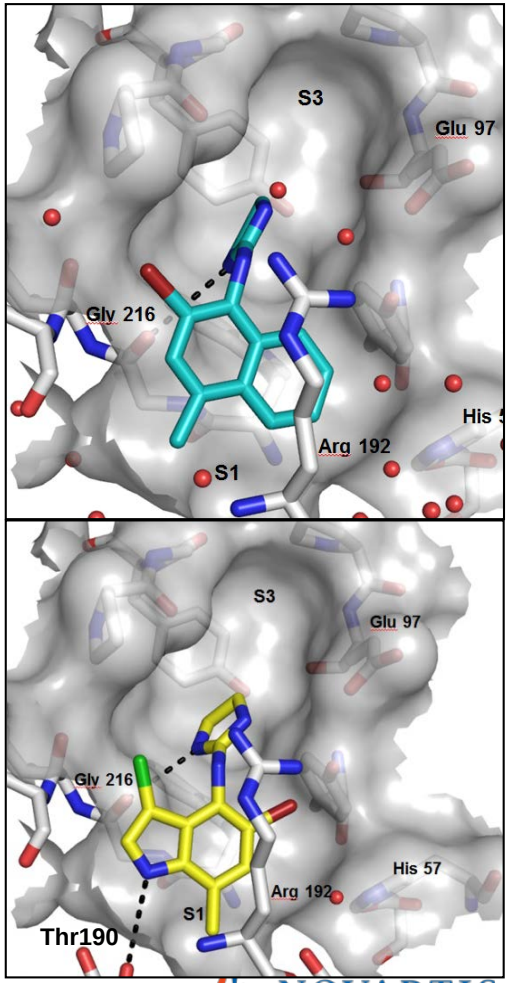
A switch to an indole core

Optimization of interactions in S1 pocket



	Hit A	1	2
Human FB IC_{50} [μM]	**6.6**	**11**	**6.3**



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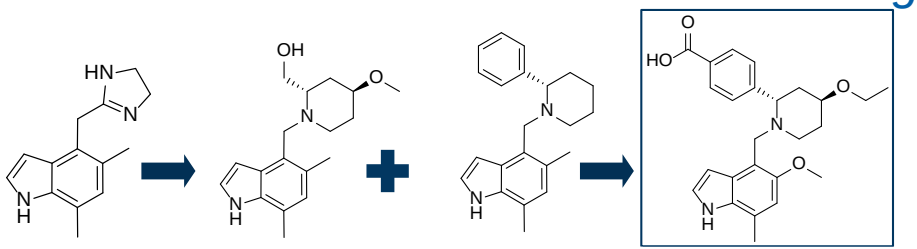
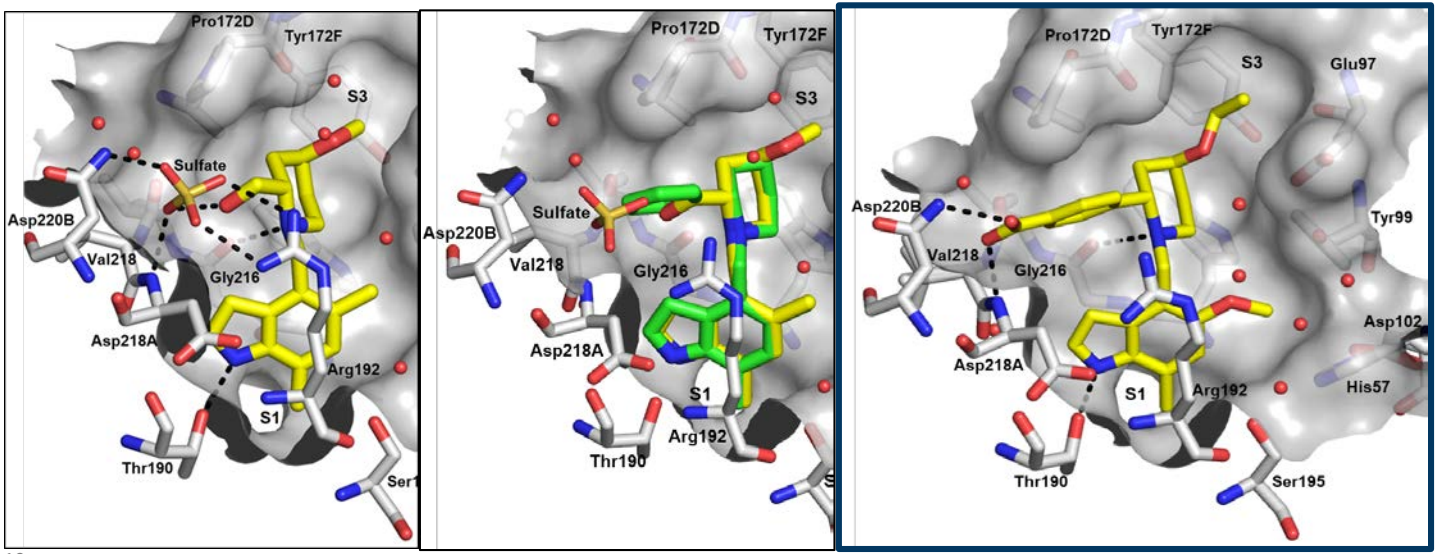
Alternative S3 moieties explored

A serendipitous discovery identifies a new interaction with FB leading to LNP023

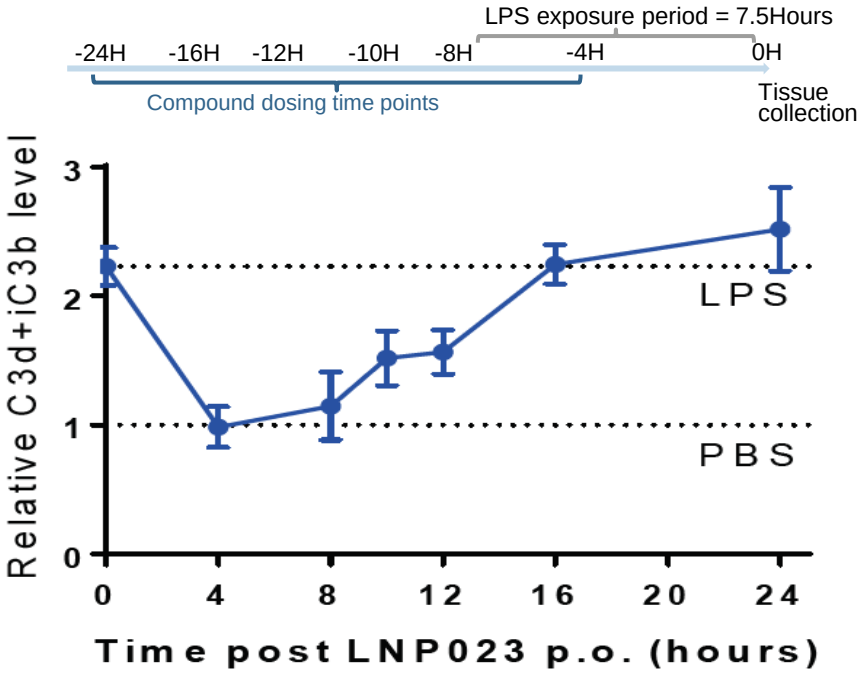


IC_{50} [μM]	2	3	4	LNP023
Human FB	6.3	3.4	5.9	**0.012**



LNP023 *in vivo* efficacy over 24 h

Time course in LPS model of AP activation in mice (30 mg/kg p.o.)



Summary

- Multiple targets of the Alternative Complement Pathway amenable to discovery efforts
  - LMW: C5aR, C5, FD, FB
  - Biologics: C5, FP
- LNP023 is a First-in-Class orally bioavailable FB inhibitor
  - Ancestor to LNP023 identified from target-based screening efforts against fB
  - High selectivity across proteases, receptors and transporters
  - Efficacy shown in LPS mouse model and on patient samples (PNH, C3G)
- LNP023 successfully completed Ph1 studies
  - Favorable safety profile in FIH: no SAE, AE-profile similar to placebo
- Currently Phase 2 studies ongoing in PNH, C3G and IgAN

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Thank you

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