Introduction to COMPLEMENTsym

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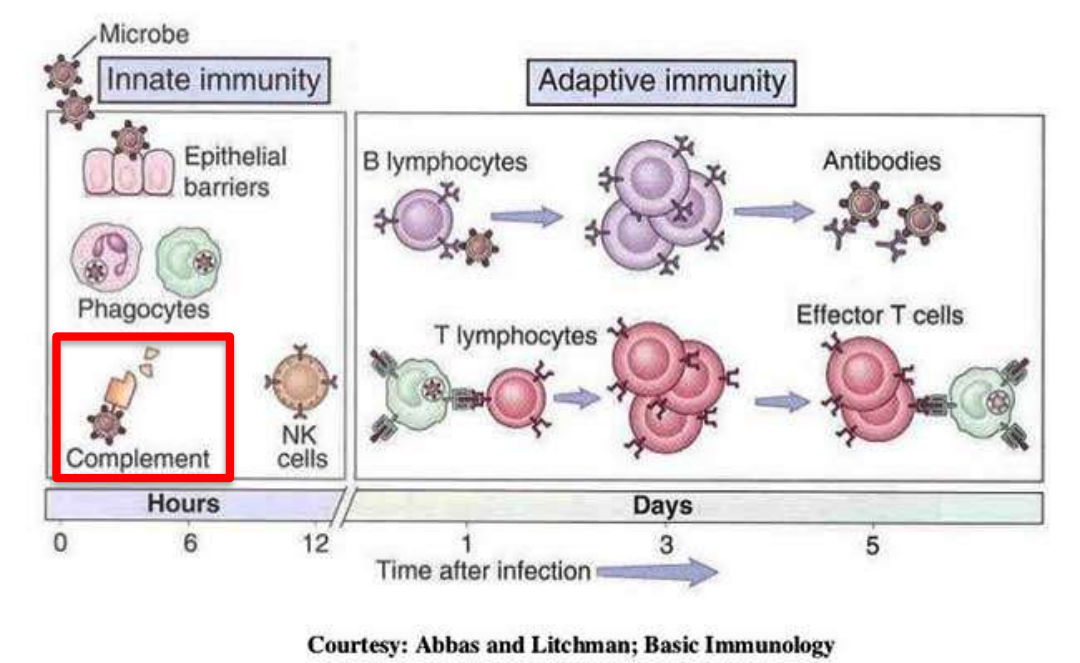
Simulations Plus is developing a QSP model of complement, with potential application to many disease indications

(including diseases where complement dysfunction is the primary lesion and diseases where complement is a key contributor to disease pathophysiology)

The base model leverages an extensive body of publicly available literature in healthy volunteers and can be customized to specific diseases

What is Complement?

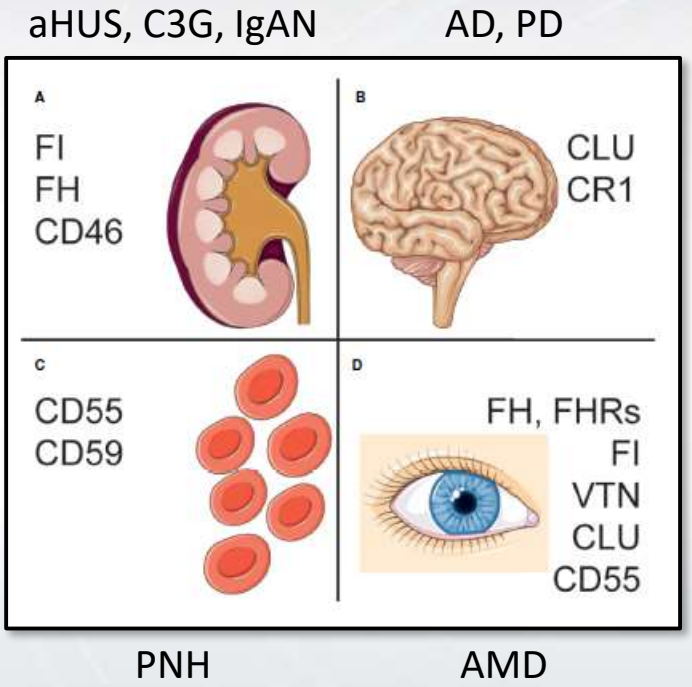
- Traditionally considered part of the innate immune response, participating in rapid initial response to microbial infection
- Complement deficiencies often associated with recurrent infections



Courtesy: Abbas and Litchman; Basic Immunology

Complement Dysfunction Implicated as a Key Contributor in Several Diseases

- Several (mostly rare) diseases have been associated with abnormalities in complement regulation
- Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by increased risk of complement-mediated hemolysis due to deficiencies in regulatory proteins, CD55 and CD59

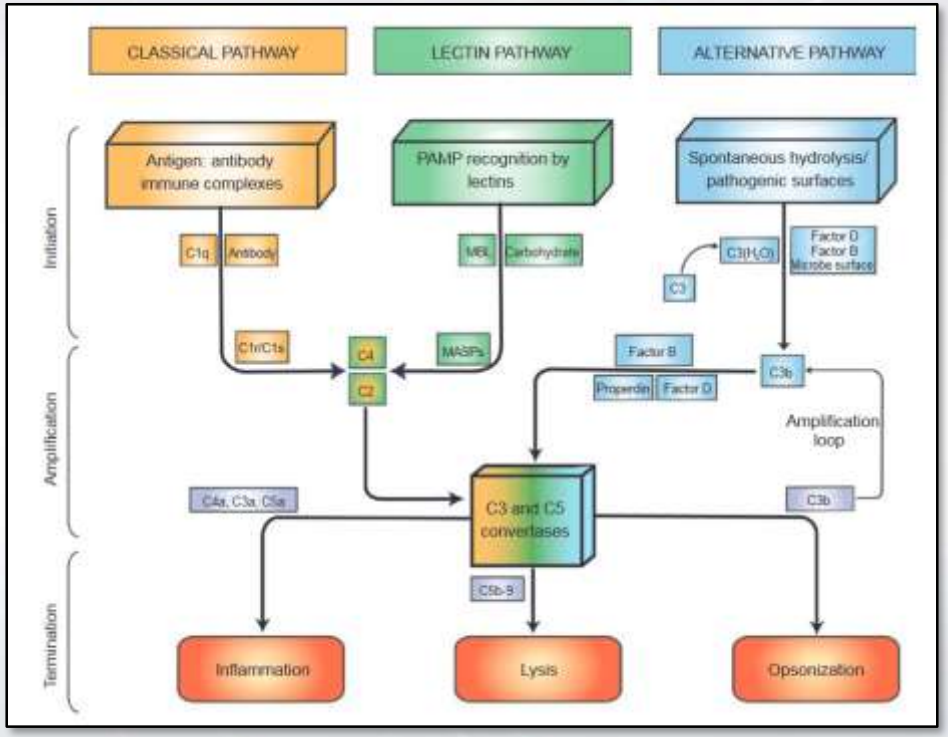


atypical hemolytic uremic syndrome (aHUS), C3 glomerulopathy (C3G), IgA nephropathy (IgAN), Alzheimer's disease (AD), Parkinsons's disease (PD), paroxysmal nocturnal hemoglobinuria (PNH), age-related macular degeneration (AMD)

De Boer 2020

Three Mechanisms Initiate Complement Activation Resulting in Complement-Mediated Activity

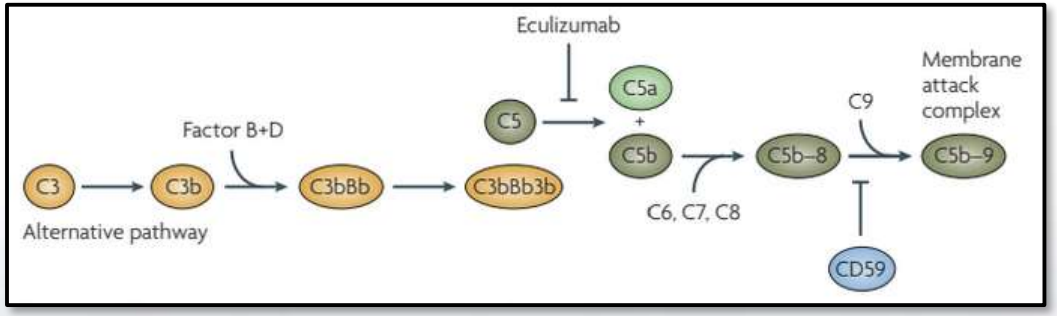
- Complement is activated by three different pathways: classical, lectin, and alternative
  - Differ in recognition, i.e., initiation
  - Converge on convertase formation
  - Drive inflammation, cell lysis or opsonization
- Alternative pathway characterized by “tick-over” and amplification loop
  - Tick-over generates a continuous state of readiness to respond
  - Amplification loop allows for initial signaling to generate a robust response
  - Alternative pathway estimated to account for ~80% of complement pathway activity, even when initiated by classical recognition



Dunkelberger 2009

Approval of Treatments Targeting C5 and C3 Demonstrates Therapeutic Value

- Eculizumab (Soliris™) targeting C5, approved by FDA for PNH in 2007
  - Subsequently approved for multiple other indications (e.g., aHUS, gMG, NMOSD)
- Ravulizumab (Ultomiris™) targeting C5, approved by FDA for PNH in 2018
  - Subsequently approved for multiple other indications (e.g., aHUS, gMG)
- Pegcetacoplan (Empaveli™) targeting C3 and C3b, approved by FDA for PNH in 2021

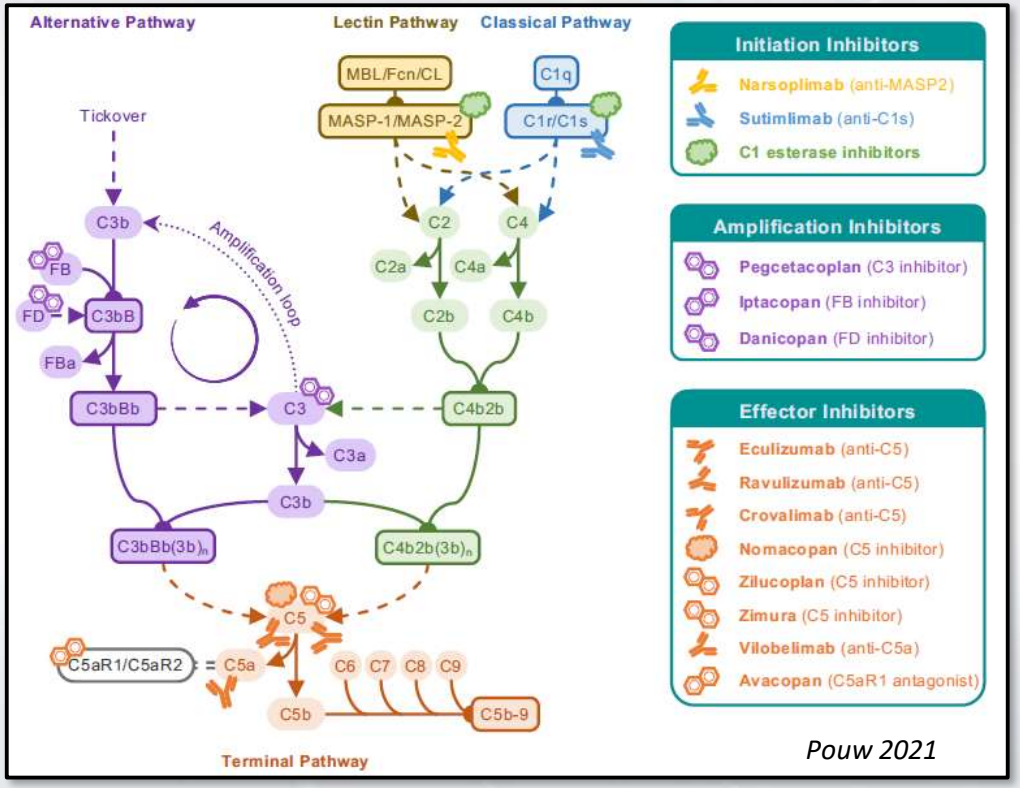


Parker 2007

atypical hemolytic uremic syndrome (aHUS), C3 glomerulopathy (C3G), generalized myasthenia gravis (gMG), neuromyelitis optica spectrum disorders (NMOSD)

Efforts Underway to Establish Other Complement-Targeted Therapeutics

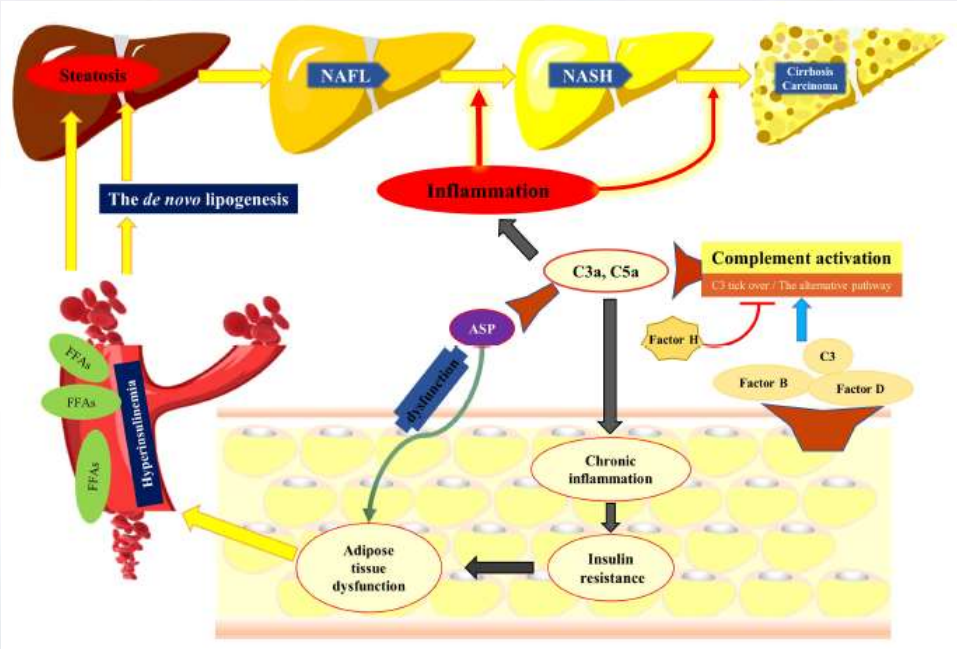
- Multiple other targets in the complement pathways (initiation, amplification, and terminal) in development
- Challenges include
  - Relative abundance of some proteins in circulation
  - Rapid turnover of some proteins
  - Accounting for feedback and regulatory mechanisms
  - Balancing efficacy with increased infection risk



Pouw 2021

Increasing Appreciation for Complement Contribution in Other Diseases

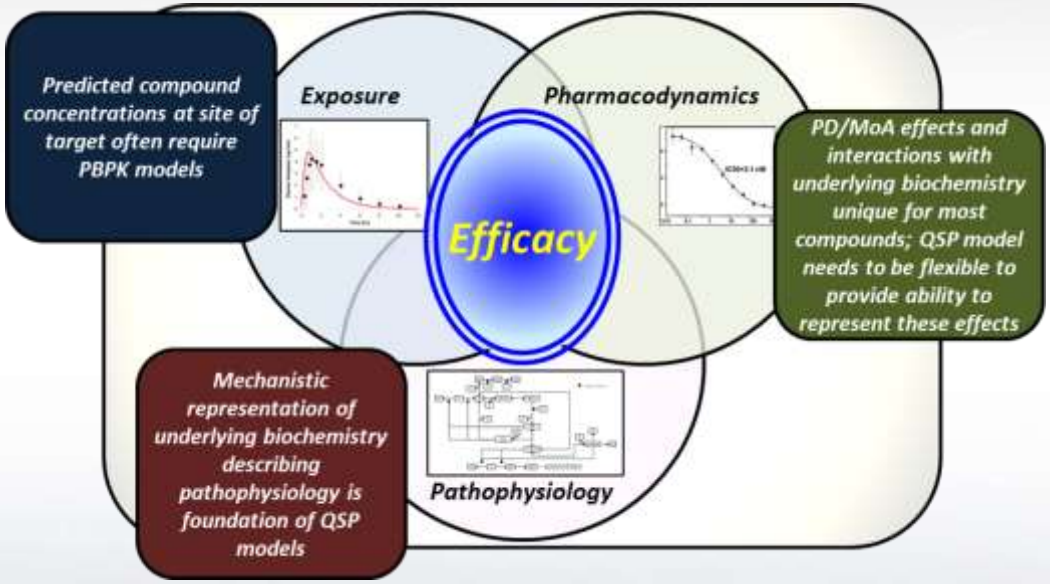
- Complement contributions to non-alcoholic fatty liver disease (NAFLD), cancer, and autoimmune diseases under increased scrutiny
- Several studies linking increased complement levels with NAFLD
- Histological evidence of liver complement deposition and potential contribution to liver inflammation
- Adipose tissue as a source for complement proteins and as main source of Factor D
- Complement activation products, e.g., C3a-desArg, associated with insulin resistance



Guo 2022

Leveraging QSP Modeling to Benefit Complement-Focused Drug Development

- QSP modeling includes a mechanistic representation of patient (patho-) physiology and drug exposure to predict clinical efficacy
- Advantages
  - Mechanistic representation of amplification and regulation, i.e., mathematical tracking of feedback loops
  - Mechanistic interactions and predictions with multiple targets
  - Quantitative accounting of complement and regulatory protein levels
  - Leverages existing datasets and identifies data gaps (potential to guide further experimentation)



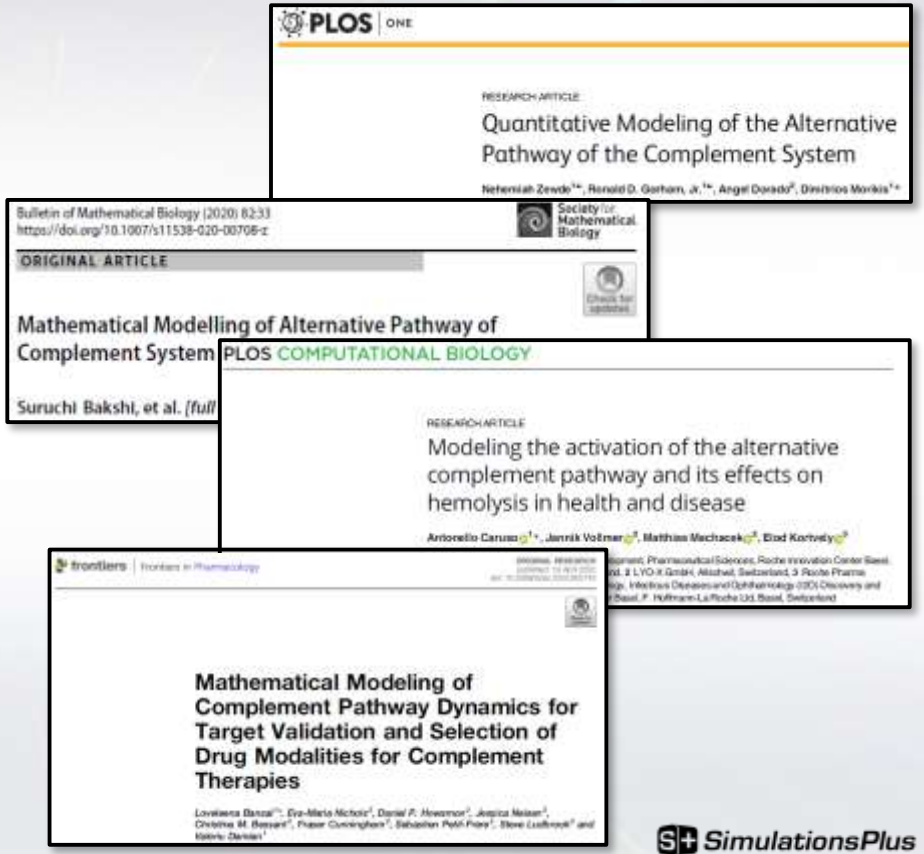
Complement QSP Modeling Leverages Detailed Pathway Measurements and Previous Modeling

Table 10.2 Metabolism of C3 in normal stubjects

Number	Fractional catabolic rate (FCR) (% plasma pool/h)[a]	Synthesis rate (SR) (mg kg^{-1} h^{-1})[a]	Extravascular/intravascular pool ratio[a]	Reference
10	2.35 ± 1.05	1.38 ± 0.51	0.90 ± 0.41	15
12	2.12 ± 0.56	1.16 ± 0.26	0.52 ± 0.39	16
11[b]	1.45 ± 0.55[b]	1.50 ± 1.67[b]	0.80 ± 1.27[b]	18
9	2.5 ± 1.0	1.5 ± 0.6	–	21
10	1.83 ± 0.72	0.83 ± 0.47	–	22
11	1.66 (± ~0.30)	0.81 (± ~0.16)	0.35 (± ~0.18)	23
20[c]	2.31 ± 1.14	0.69 ± 0.32	–	24

[a] The mean ± 2 SD.
[b] Includes two normal subjects, eight stable allograft recipients and one anephric patient.
[c] Some subjects are included among normals in the studies of Carpenter *et al.*[18] and of Hunsicker *et al.*[22]. Fractional catabolic rates are uncorrected, although the authors advocate correcting them (see text).

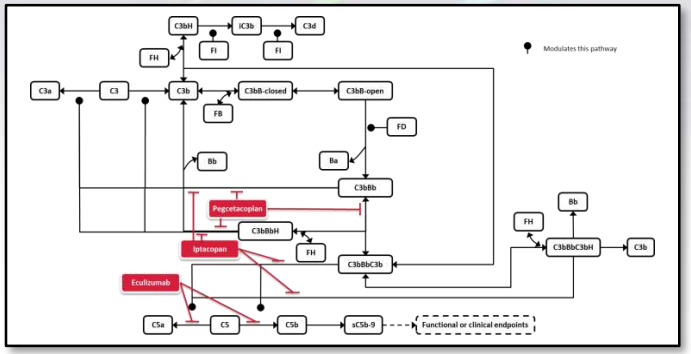
Alper 1984



Our Vision for Complement QSP Modeling

- **Base model**: Represent the complement alternative pathway (AP) and terminal pathway (TP) in the circulating compartment
  - Develop SimPops with inter-patient variability
    - Normal healthy volunteers (NHVs)
    - Disease-driven complement activity in the circulating compartment
  - Represent exemplar compounds (eculizumab, pegcetacoplan, iptacopan)

- **Customized disease models**: Develop representation of disease pathophysiology within target tissue (e.g., blood, renal, ocular)
  - Potential to leverage proprietary data
  - May require developing local complement production, interactions at cell surfaces, and interactions with circulating pool
  - Would mechanistically model pathophysiology and clinical outputs
  - Include aspects of lectin and classical pathways as needed for disease activity or to evaluate infection risk (safety)



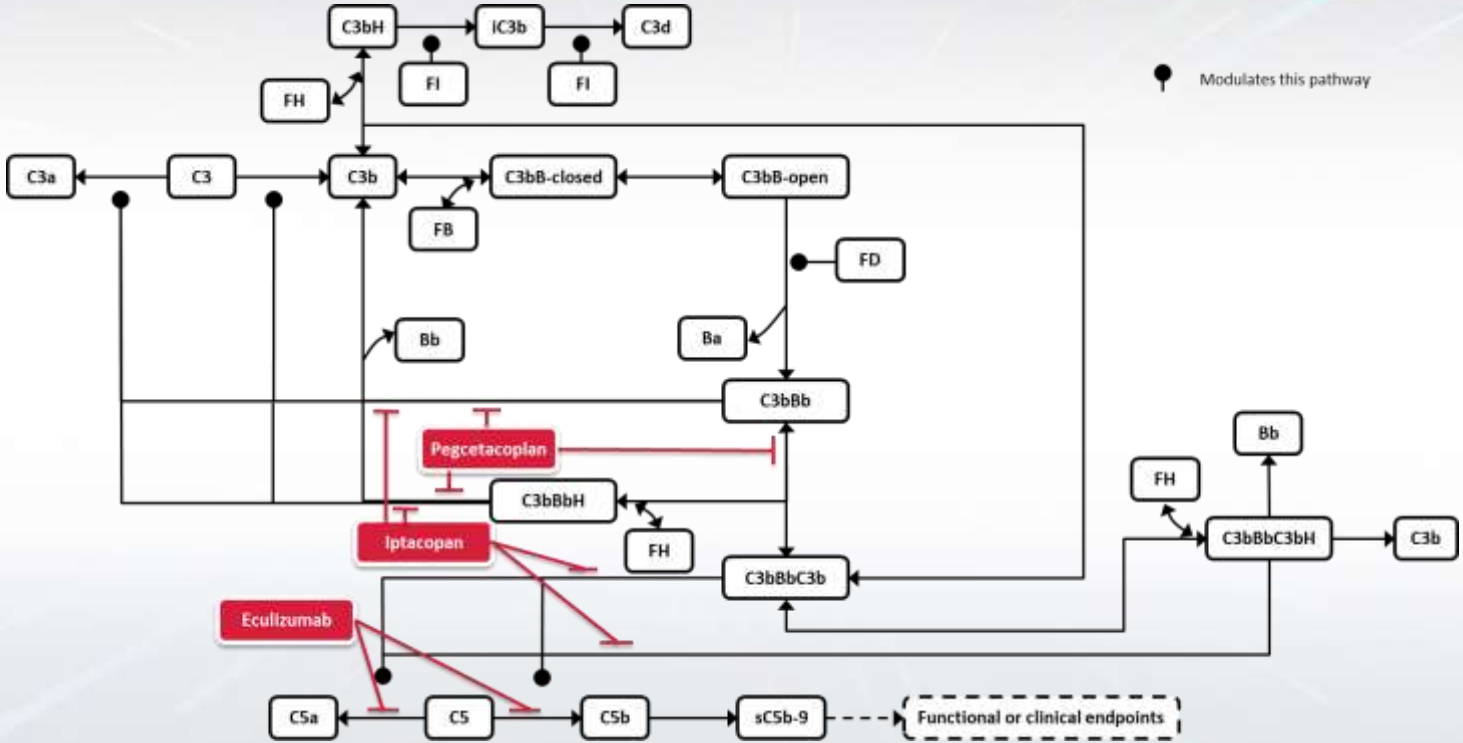
Blood

Renal

Ocular

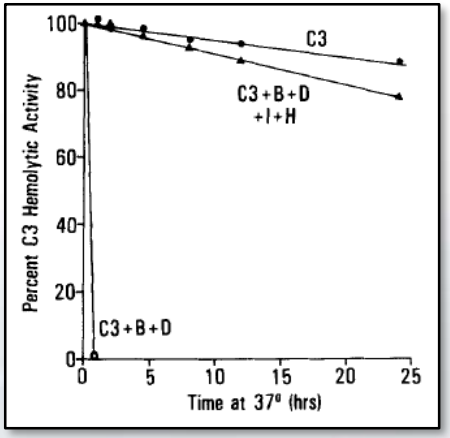
Safety

Initial Complement QSP Model is Focused on the Alternative and Terminal Pathways

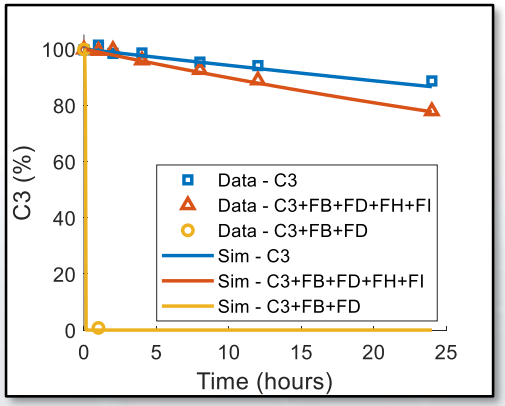


Complement QSP Model Reproduces Reported In Vitro Experimental Behaviors

- Model incorporates in vitro data and tests sub-system behaviors
- In vitro assay conducted to assess spontaneous decay of C3 hemolytic activity in the absence or presence of regulators (i.e., FB, FD, FI, FH)
- Simulations reproduce rapid decay in the presence of positive regulators and a more controlled rate of decay in the presence of negative regulators (FI, FH)

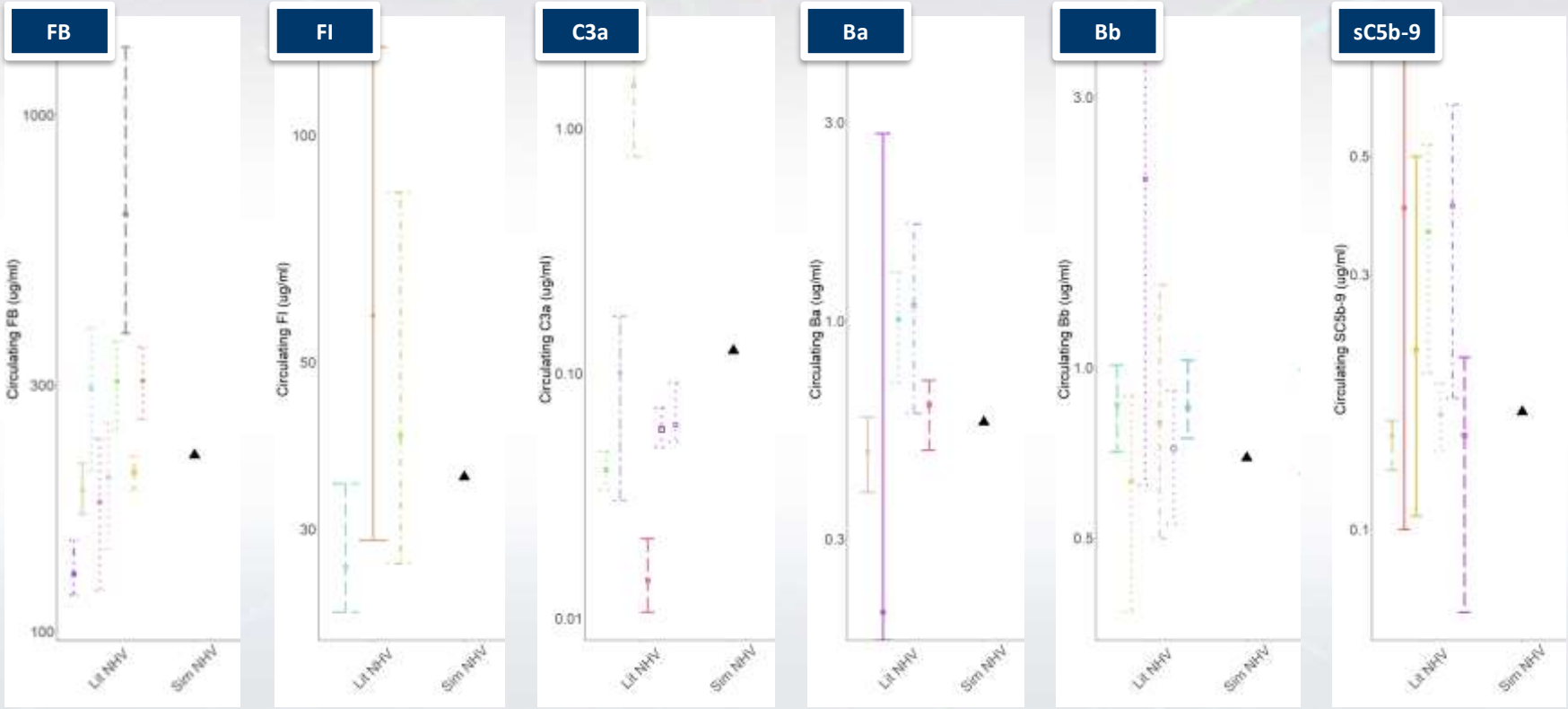


Pangburn 1981



COMPLEMENTsym

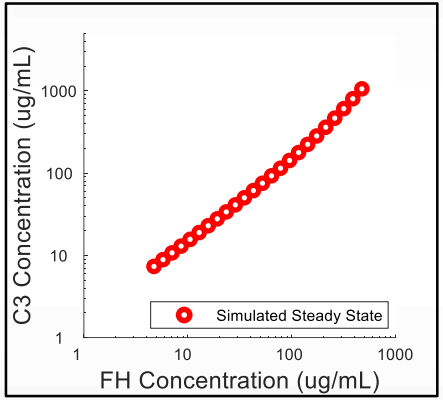
Initial Simulated Individual Aligns with Published Data on Complement Levels in NHVs

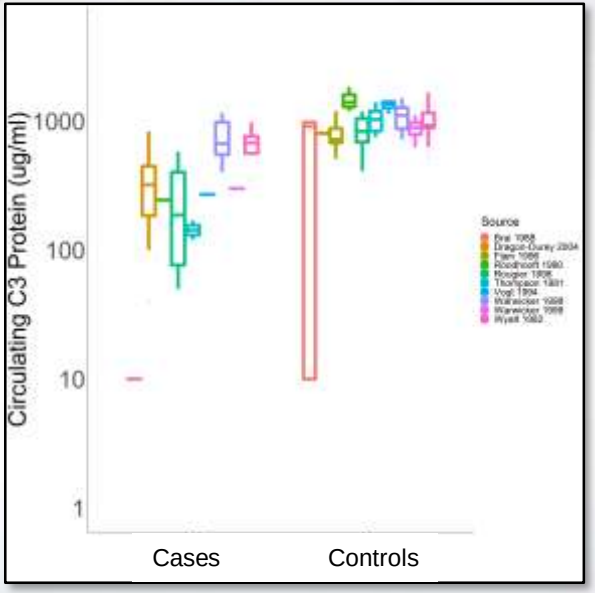


Initial Simulated NHV Evaluated Against Published Data on FH Deficiency

- Case studies on individuals with FH mutations have reported concomitant decrease in C3 levels
- FH depletion simulated in initial NHV to evaluate ability of QSP model to reproduce corresponding C3 decrease
- Initial simulated NHV demonstrates range of C3 reduction, depending on extent of FH depletion, suggesting QSP model appropriately represents relationship between FH and C3

C3

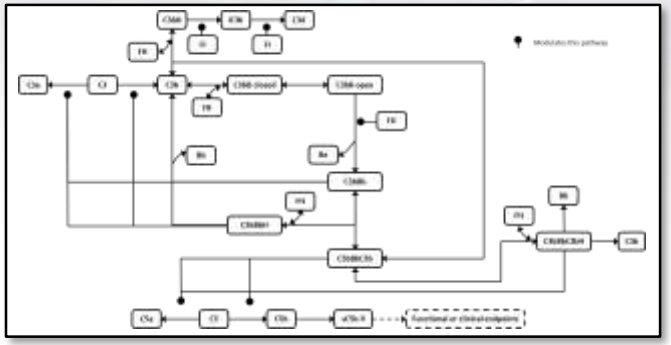




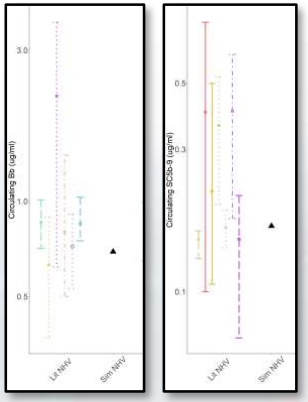
Clinical data: largely case studies compared against family members; FH levels and functional capacity vary amongst cases.

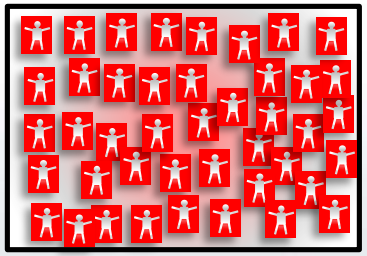
Mechanistic Variability Represented in Simulated Populations (SimPops)

- SimPops are population samples with mechanistic variability across key areas of physiology/pathophysiology
- Multiple parameters are varied to produce diverse possible simulated individuals
- Simulated individuals are qualified by comparison against a multitude of clinical data
- Response data (e.g., clinical response to exemplar compounds) used to further validate disease SimPops



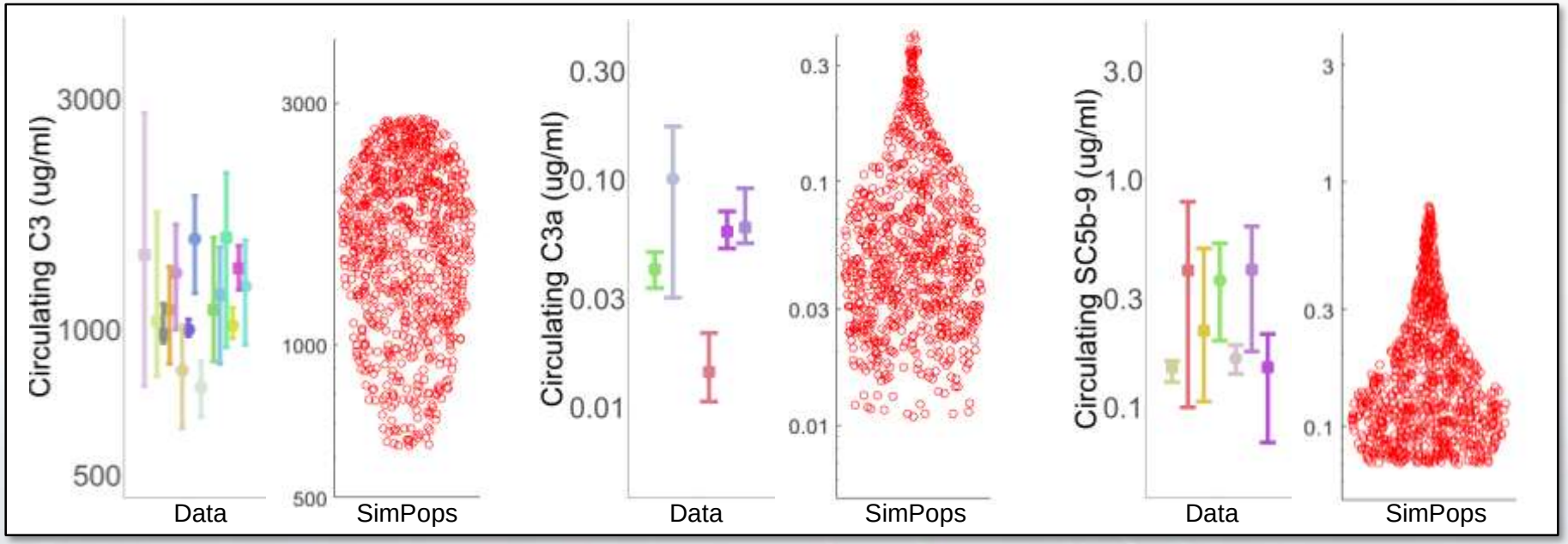
Variable Types to be Used to Construct COMPLEMENTsym v1A SimPops
Synthesis/degradation rates
Convertase catalytic activity
Properdin effect
Association/dissociation rates





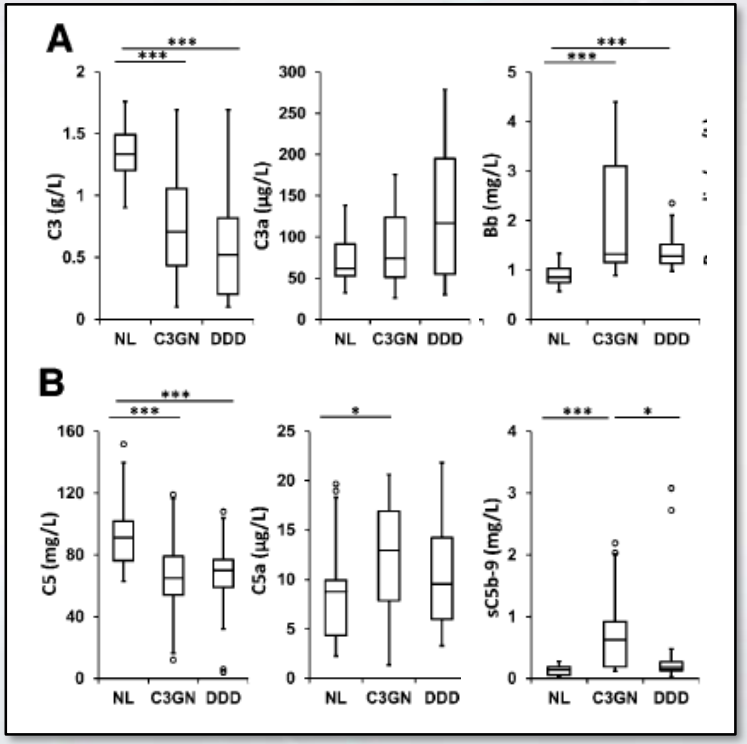
Preliminary NHV SimPops Spans Variability in Clinical Data for Complement Proteins

- Exploration of data-driven variability in input parameters, as well as plausible variability where data are lacking
- Simulated individuals are qualified by comparison with published data from NHVs



Ongoing Development of Disease SimPops Including Baseline and Treatment-Response Qualification

- Ongoing development of disease SimPops
  - Disease indication of interest identified
  - Published literature characterizing disease patients identified and curated
  - Proprietary data on disease patients being leveraged
- Simulated patients representing disease being compared with published and proprietary baseline and treatment data
- Ongoing representation of eculizumab, pegcetacoplan, and iptacopan to investigate treatment response
- Planned evaluation of known and novel targets



Zhang 2014

Acknowledgements

COMPLEMENTsym development team

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- Scott Siler

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SimulationsPlus

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Model Informed Drug Development + 2023

Q&A

Questions & Answers