Systems pharmacology modelling of the alternative pathway to study target suitability

Suruchi Bakshi[1], Marta Biedzka-Sarek[2], Eva-Maria Nichols[2], Fraser Cunningham[2], Stefano Zamuner[3], Piet H. van der Graaf[1,4]

[1] Certara QSP Canterbury CT2 7FG, UK and Breda 4818 SJ, The Netherlands; [2] Cytokine, Chemokine & Complement DPU, Immunoinflammation TA unit, GSK; [3] Clinical Pharmacology, Modelling and Simulation, GSK; [4] Cluster Systems Biomedicine and Pharmacology, LACDR, University of Leiden, Netherlands.

Abstract

Complement system (CS) is integral to innate immunity and can be activated via three different pathways. Of these, the alternative pathway (AP) is central to routing and amplifying signals from all three pathways[1] (Fig 1). A few potential AP targets are highly abundant or show high turnover. However, such information is not available for the remaining targets. We use QSP approach to rank targets for their suitability against small and large molecule drugs.

Background

Dysregulation of AP is implicated in several autoimmune as well as inflammatory diseases. The central role of AP in CS activation makes it an attractive therapeutic target[2].

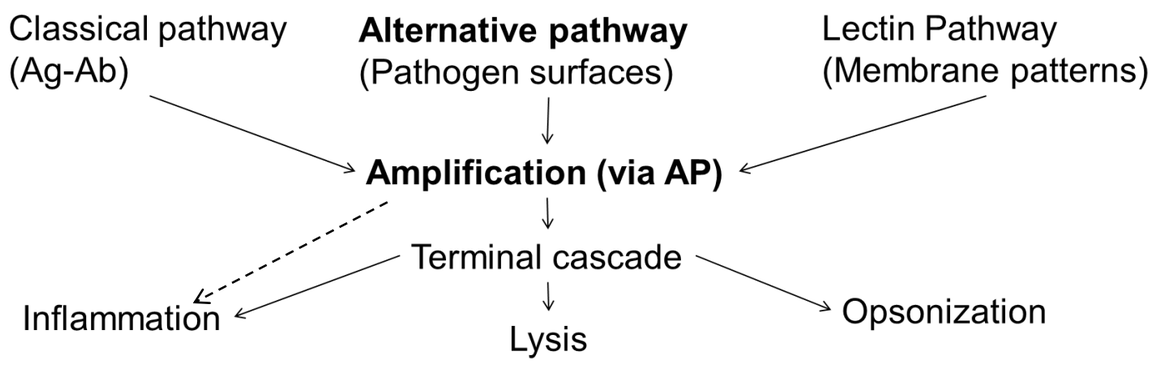

Figure 1: Schematic representation of CS showing the central role of AP.

Methods

We used previously validated models of AP activation (minimal model) and steady state (steady state model) (Figure 2)[3].

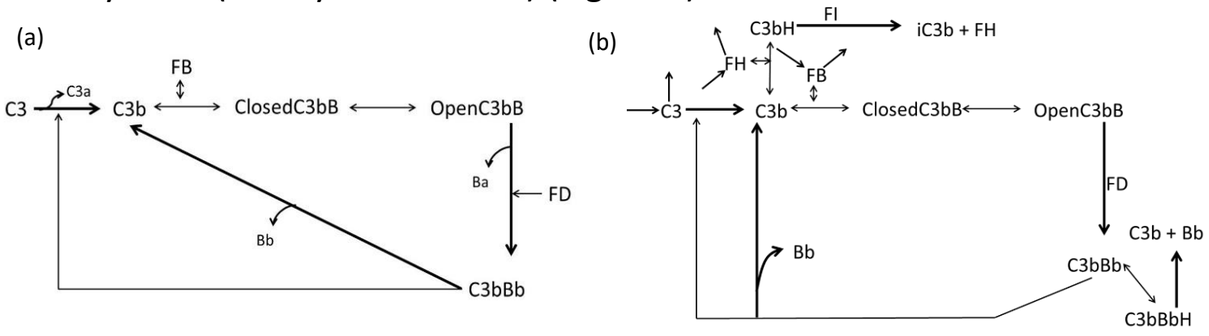

Figure 2: Schematics of the minimal model of AP activation (a) and steady state model (b).

Testing target suitability:

Minimal model: For a given target, include reactions: D + T ←→ DT

Delay in C3bBb activation response is the PD marker.

Determine affinity needed to produce a desired activation delay.

Steady state model: Include the reactions:

$$\begin{array}{ccc} \downarrow & & \downarrow \\ D + T & \leftrightarrow & DT \\ \downarrow k_{el} & & \downarrow k_{el} \end{array}$$

Attenuation of C3bBb output is the PD marker.

Typical PK for a small molecule and an affinity of 1nM.

Typical PK for a large molecule and an affinity of 0.01nM.

Sensitivity analysis (SA): Run simulations with physiological initial conditions (*IC(1)*) and *IC*s changed by 1%. Calculate sensitivity index ***S*** as

$$S(t) = \left(\frac{|C3bBb(t, IC(1)) - C3bBb(t, IC(2))|}{IC(1) - IC(2)}\right)\left(\frac{IC(1)}{C3bBb(t, IC(1))}\right),$$

$$SI = \sum_{t=0}^{\infty} S(t),$$

where *C3bBb(t,IC(1))* and *C3bBb(t,IC(2))* denote the time-profiles of C3bBb at two different *IC*s. *S(t)* is normalized with original IC (IC(1)) and original output and then summed over all time to obtain fully normalized *SI.*

Results

Minimal model:

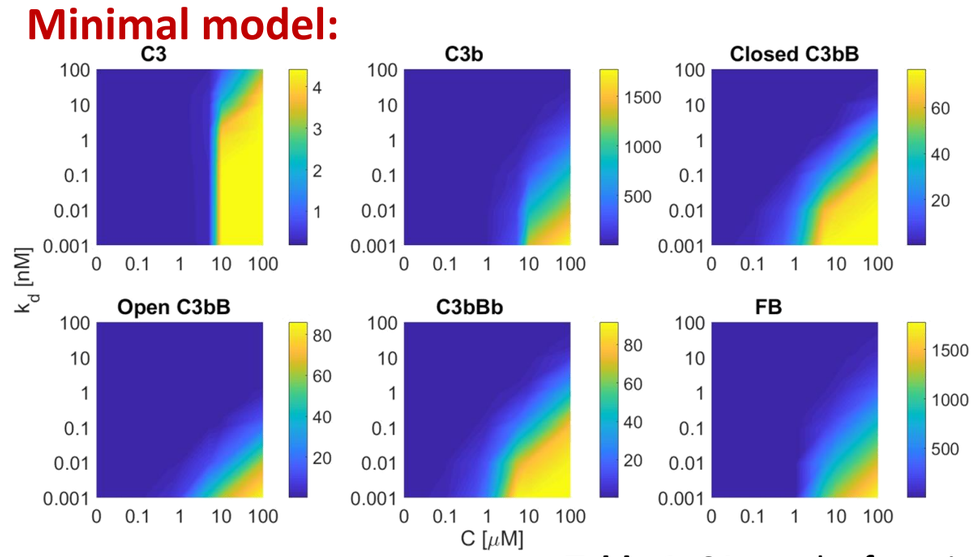

Figure 3: Challenging minimal model with a hypothetical drug at different affinities and concentrations. Colorbar: activation delay in hours.

- FB and C3b show maximum impact
- C3 and FB respond only at high C
- Results are applicable in *in vitro* settings

Table 1: SA results for minimal and steady state models show that C3 & FB are most sensitive.

Targets	*SI* (minimal)	*SI* (steady state)
C3	164	9872
C3b	2.3	183
Closed C3bB	6.1	200
Open C3bB	46.9	191
C3bBb	53.3	196
FB	404	9955

Steady state model:

More realistic model → results are physiologically relevant.

Small molecule drug:

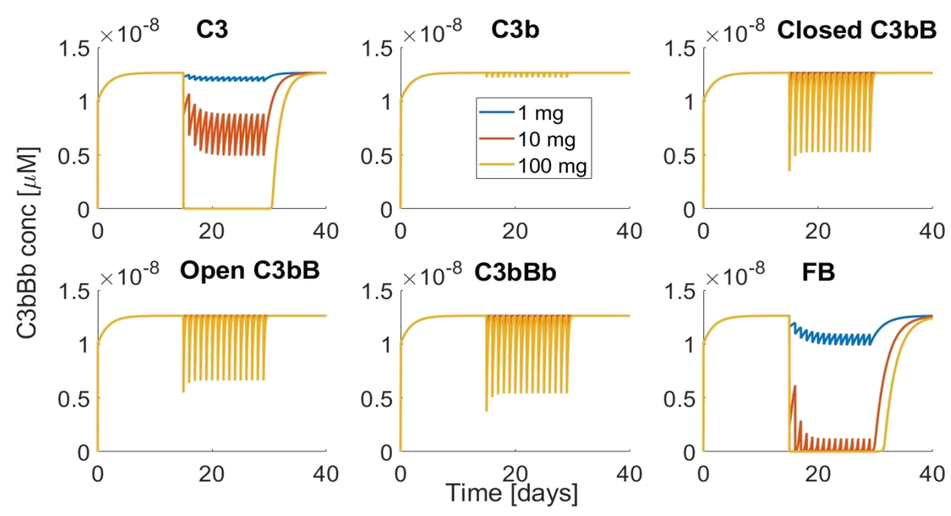

Figure 4: Challenging steady state model with small molecule drug shows C3 and FB as most responsive targets.

Large molecule drug:

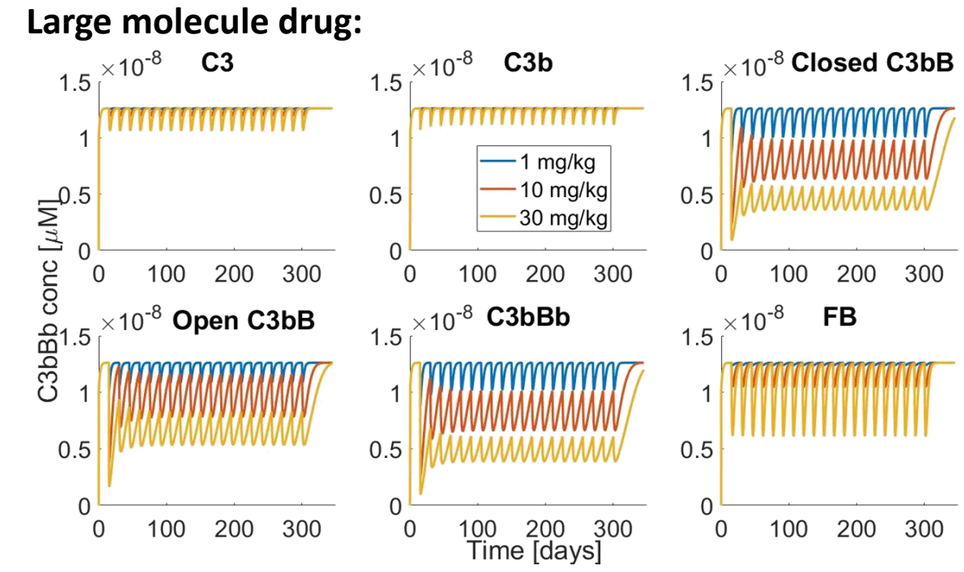

Figure 5: Challenging steady state model with large molecule drug shows closed, open C3bB and C3bBb as most responsive targets.

Conclusions

- C3 and FB are most suitable small molecule targets
- C3bB (closed, open) and C3bBb are most suitable large molecule targets
- SA shows that C3 and FB are most sensitive targets
- Full systems pharmacology modelling is necessary to understand target suitability.

[1] Thurman JM, Holers VM. The Journal of Immunology. 2006;176(3):1305-1310.

[2] Morgan BP, Harris CL. Nature Reviews Drug Discovery. 2015;14(12):857-877.

[3] Bakshi S, Biedzka-Sarek M, Nichols EM, Cunningham F, Petit-Frere S, et al. Submitted.