A Challenge Model of TNF_α Turnover with LPS Provocations and Drug Intervention

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Background

Tumor necrosis factor alpha (TNF_α) is a pro-inflammatory cytokine associated with the pathogenesis of several immune-mediated diseases. Free TNF_α is almost undetectable in blood of healthy organisms. Experimentally, the effect of inflammatory mediators is studied in-vivo after intravenous administration of lipopolysaccharides (LPS), where the challenger causes a rapid but transient release of TNF_α.

Goals:

- Determine key characteristics of TNF_α-response with and without test compound dosing through exploratory data analysis.
- Create a challenge model [1] to assess the pharmacodynamic effect of test compound on TNF_α.

Experimental Setup

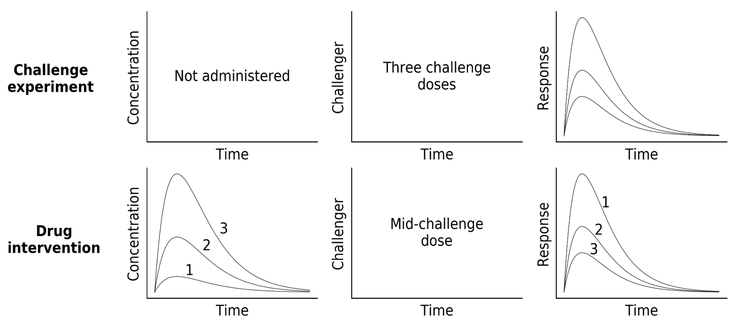

Fig 1. Data from two experiments was used for model development

Exploratory Data Analysis

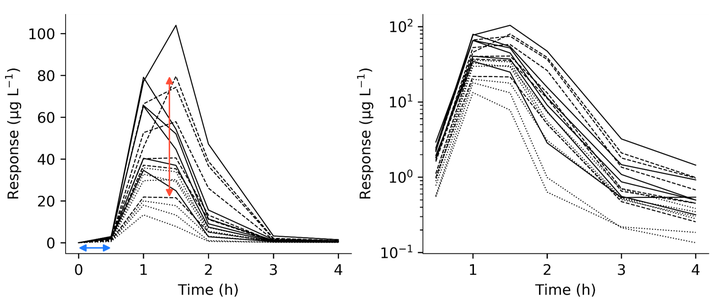

Fig 2. Experimental data showing a 30 min time lag in onset coupled with a peak-shift in TNF_α-response at increasing LPS doses

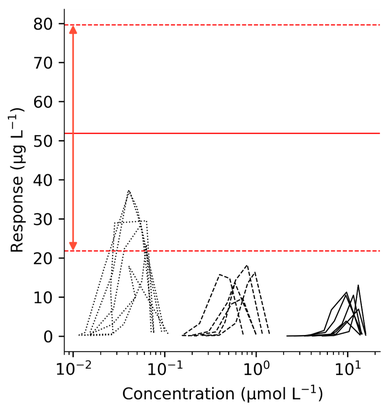

Fig 3. Hysteresis plot of TNF_α over drug concentration showing the non-linear suppression on TNF_α by the compound

The Model

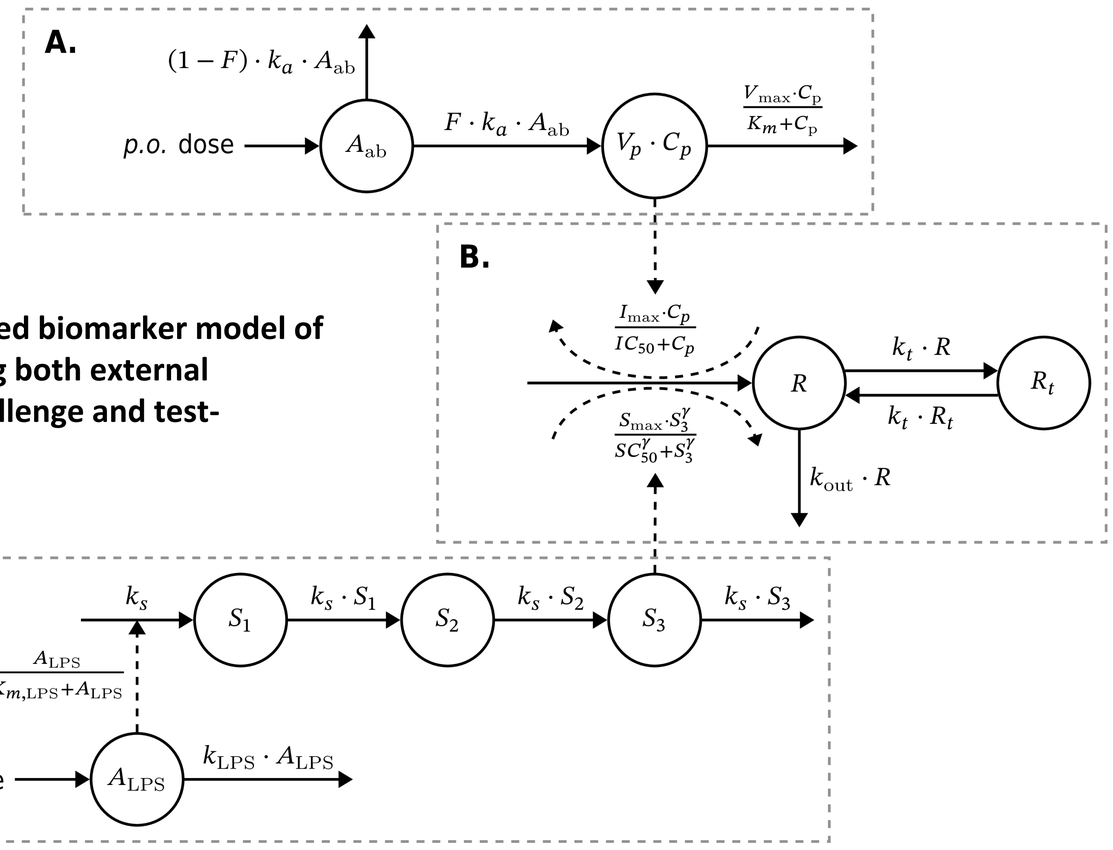

Fig 4. A mechanism-based biomarker model of TNF_α-response including both external provocations of LPS challenge and test-compound intervention

Results

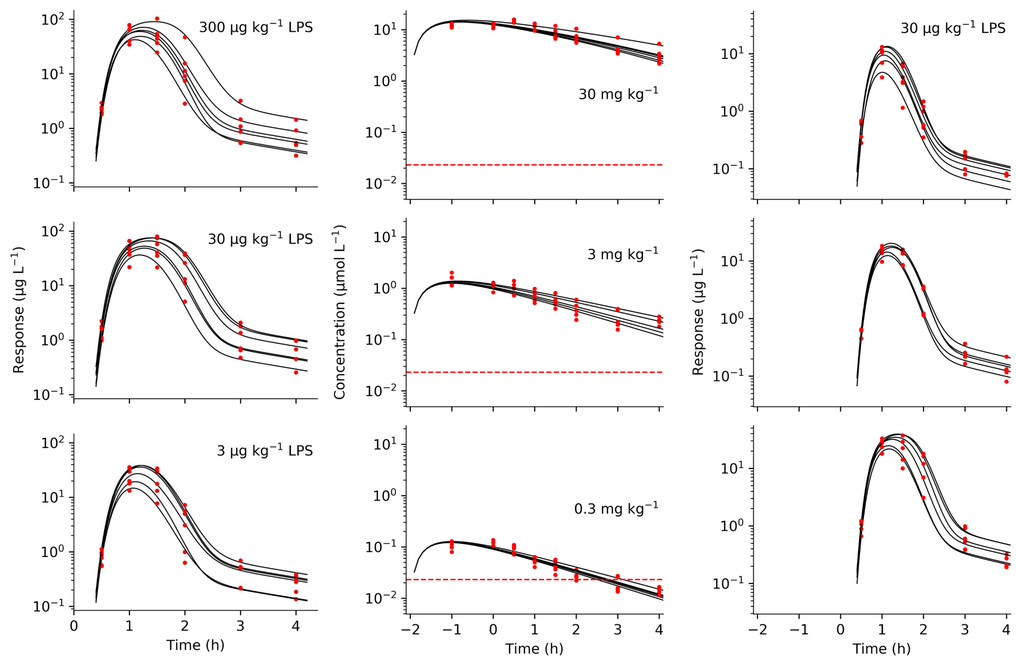

Fig 5. Predicted time courses of TNF_α without test compound administration (left), test compound concentration (middle) and TNF_α after test compound administration (right)

Table 1. Final parameter estimates, CV% and half-life estimated by Monolix [2]

Parameter	Estimate	CV%	Half-life
k_{LPS} (h^{-1})	8.36	29	5 min
K_s (h^{-1})	3.28	8.1	13 min
$K_{m,\,LPS}$ ($\mu g \cdot kg^{-1}$)	0.0789	19	
S_{max} ($ng \cdot L^{-1} \cdot h^{-1}$)	$6 \cdot 10^5$	12	
SC_{50}	0.469	14	
γ	3.79	2.5	
K_{out} (h^{-1})	5.65	30	7 min
K_t (h^{-1})	0.419	37	100 min
I_{max}	0.675	5	
IC_{50} ($nmol \cdot L^{-1}$)	23.1	26	

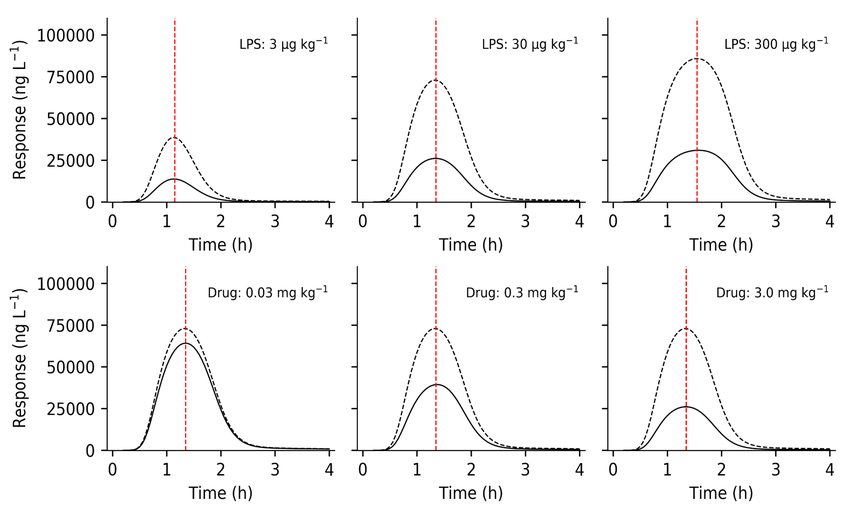

Fig 6. Model simulations of TNF_α-response with a fixed test-compound dose (3 $mg \cdot kg^{-1}$) and increasing LPS challenges (upper) as well as a fixed LPS challenge (30 $\mu g \cdot kg^{-1}$) and increasing test-compound doses (lower)

Summary and Conclusions

- A model of TNF_α-response capturing
  - LPS dose independent delay of onset
  - Peak shift for increasing LPS doses
  - Saturation of TNF_α-response wrt LPS doses
- Selection of future drug candidates could be based on estimation on potency and efficacy using the developed model
- The model may serve as a general basis for the collection and analysis of pharmacological challenge data of future studies, see [3]

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References

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[2] Monolix version 2018R1 (2018) Lixoft SAS, Antony, France.

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