Title:

Development of a Quantitative Systems Pharmacology model in Crohn's Disease.

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Objectives:

Crohn's disease (CD) is a complex inflammatory bowel disease, which causes a functional impairment of the gut wall. The reported lack of effectiveness in the standard of care requires the application of techniques aiming to find new targets and therapeutic strategies. We aimed to develop a Quantitative Systems Pharmacology (QSP) model in humans characterizing the dynamics of the main immune system components involved in CD (1,2).

Methods:

We followed a workflow for robust application of Systems Pharmacology modelling proposed by Gadkar et al., in 2016 (3): (i) identify main project goals; (ii) selection of species and literature search for blood levels in healthy subjects (HS) and CD patients; (iii) representation of model topology and parametrization of the interactions using data extraction and curation. Model components kinetics were characterized by zero-or first-order synthesis and first-order degradation. Constant levels for ILs and cells at the steady state (SS) of HS and CD were assumed for synthesis rate constant derivation. To parametrize the IL interactions, different sub-models were tested using non-linear regression in Rv3.5.0. Ordinary differential equations (ODEs) were implemented in SimBiology® (MATLAB®vR2018b). Afterwards, (iv) deterministic simulations for CD were run and model evaluation was performed.

Results:

A total of 21 species representative of the innate and adaptive immune responses in CD were included as ODEs. More than 60 interactions between the interleukins

and cells were identified and modelled. Graphical representations were generated providing a big picture of model structure. Model performance was confirmed by a quantitative reproduction of CD levels and a model simulation with a therapeutic agent was able to emulate the response in patients (4).

Conclusions:

We present a QSP model for the main ILs and cells involved in CD. Not only is supported by a comprehensive repository summarizing the most relevant literature in the field, but also by a standardized methodology for QSP model building. This model proved to be promising for the *in silico* evaluation of potential therapeutic targets and the search for specific biomarkers. Finally, it can be expanded or reduced as demanded, leading to different quantitative model/s to address research gaps regarding CD.

References:

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2. Ramakrishnan et al., ACoP9. Poster T-088
3. Gadkar et al., CPT&PSP 2016:235-49
4. Fedroak et al., Gastroent 2000;119:1473-1482