A PBPK and immunogenicity model integrated into two disease models

S. Arsène[1], C. Couty[1], I. Faddeenkov[1], T. Galland[1], N. Go[1], S. Granjeon-Noriot[1], D. Šmít[1], S. Martis B.[1], R. Kahoul[1], J-P Boissel[1], A. Chevalier[2], L. Lehr[2], C. Pasquali[2], A. Kulesza[1]

Affiliation: [1]Novadiscovery, Lyon, France, [2]OM Pharma, Meyrin, Switzerland
alexander.kulesza@novadiscovery.com

INTRODUCTION

Physiologically based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP) are physiological mechanistic approaches. A platform character (serial rather than single applicability of the model) [2] is more appropriate for the integration of this king of approaches with model informed drug discovery and development (MID3) as well as for increase their regulatory acceptance [1].

When a model combines aspects of PBPK and QSP by including administration, distribution, metabolism and excretion processes as well as a multitude of potential targets and biological mechanisms with downstream effects up to clinical outcomes, it is then possible to systematic evaluate choices and variations of regimen for alternative drugs and drug-candidates in a specific disease. However, considerable time and resources needed to build models with such a complexity impedes screening of the efficacy of one treatment candidate in different indications.

A promising approach to address this bottleneck is to build a library of complex disease models, each interfaced with a common treatment model (Figure 1). Here we demonstrate the feasibility of assessing an immunomodulating bacterial lysate (OM-85) in two different indications, respiratory tract infection (RTI) prophylaxis and atopic dermatitis (AD) improvement, in frame of a PBPK/PD-QSP framework.

ORAL ADMINISTRATION PBPK-PD MODEL OF OM-85

A PBPK/PD model of oral administration of OM-85, systemic and local uptake into the gut Peyer's Patches, specific and non-specific activation of the gut immune system, and dissemination of immune effectors into different tissues has been set up with inter- and intraspecies allometric scaling (Figure 2).

The PBPK model has been calibrated against the available bacterial lysate rodent (mouse, rat) radiolabelling PK data.

We then integrated immune effector dissemination into target tissue (T-reg and innate memory-like cells) in the PBPK model and interfaced it with two disease models (atopic dermatitis, AD; respiratory tract infection, RTI) with incorporating additionally of between-patient variability.

With this model, one can quantify dosing regimen dependent pro-type I immunomodulation through activation of immune effectors and their effect in the respiratory tract and skin, respectively [3]. We conducted controlled in silico clinical trials using a simulation setup that mimicked trial protocols relevant to these two disease areas.

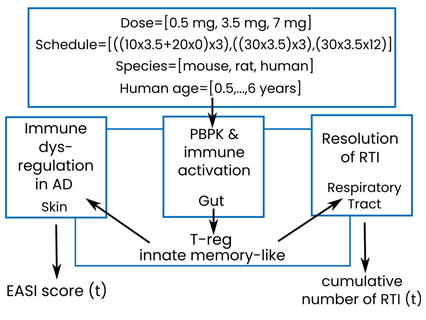

Figure 1: Approach for combining two disease models with a common treatment model.

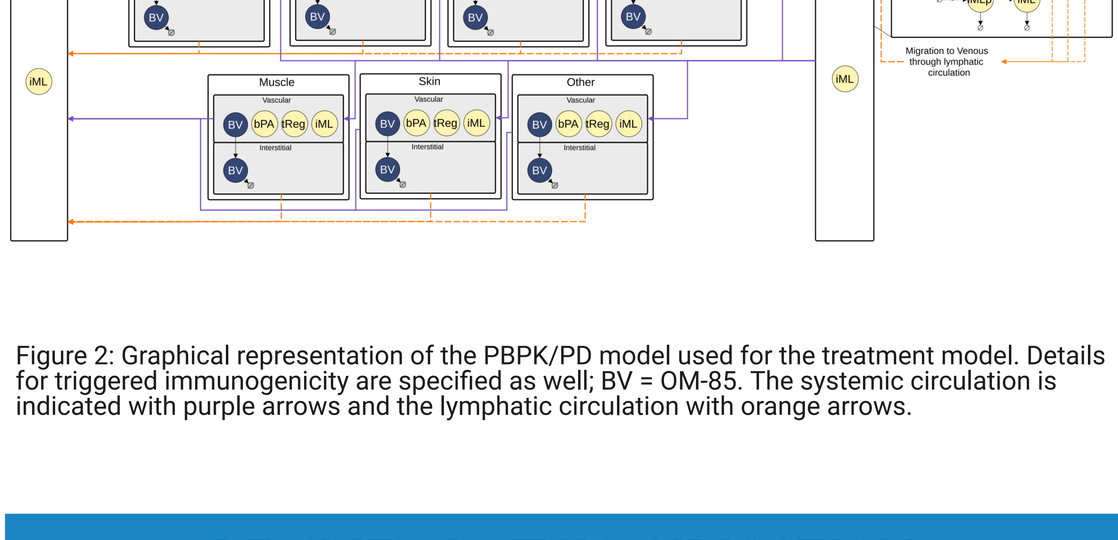

Figure 2: Graphical representation of the PBPK/PD model used for the treatment model. Details for triggered immunogenicity are specified as well; BV = OM-85. The systemic circulation is indicated with purple arrows and the lymphatic circulation with orange arrows.

IMMUNOLOGICAL QSP DISEASE MODELS

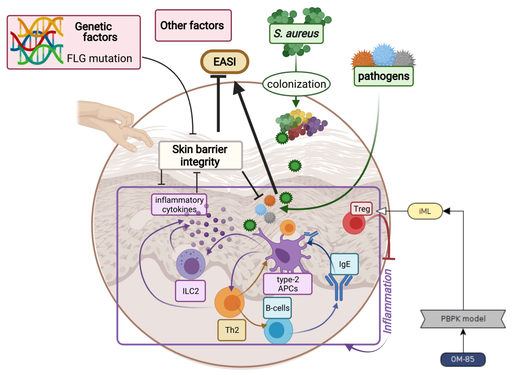

Figure 3: Atopic dermatitis (AD) model.

The AD model (Figure 3) describes levels of immune cells and secretory factors (cytokines, chemokines) and their mutual regulation as a function of AD severity (EASI, SCORAD). On top of targets for biologics and corticosteroids, immunomodulation (i.e. T-regs) through ingress from the circulation is also detailed.

A virtual population decribes the interpatient variability in immune endotypes and disease severity.

The AD model and virtual population were calibrated against skin proteomics data and EASI/SCORAD distributions and correlations. In silico trials resembling the Bodemer et al study [4] served to calibrate the efficacy profiles of OM-85 vs topical corticosteroids on top of emollients after an induction period.

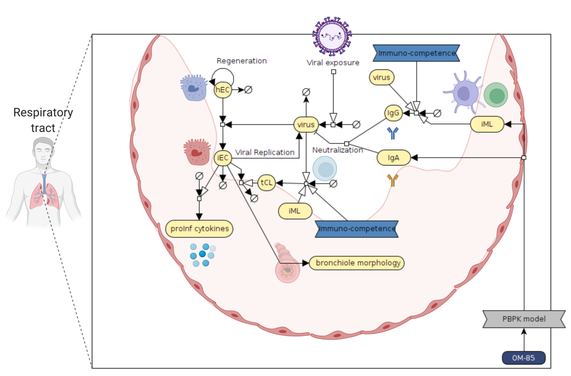

Figure 4: Respiratory Tract Infection (RTI) model.

The RTI model (Figure 4) describes lytic and nonlytic immune effectors involved in the resolution of individual infection events.

Several viral exposures are linked to the instantaneous hazard from RTI seasonality and give rise to the cumulative count (or annual rate) of RTI obtained from the viraemia/inflammation profile. Variability of an age-dependent master regulator of immuno-competence introduces between-patient variability.

The model has been calibrated against human PD marker data. Additionally, the overall virtual population has been calibrated against distribution of RTIs in cohorts of patient populations, whereas in silico trials were calibrated against the meta-analyzed clinical data of OM-85 in children [5].

REGIMEN IN TWO INDICATIONS

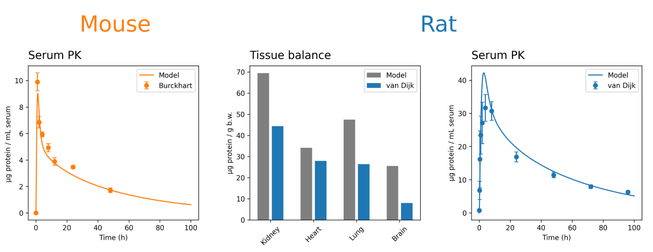

Figure 5: PBPK model calibration with rodent PK data.

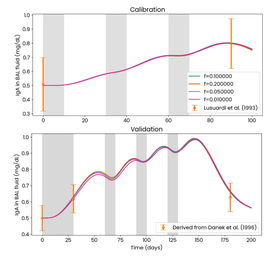

Figure 6: Pharmacodynamics (PD) in humans.

The allometrically scaled model links rodent PK data (Figure 5) and human PD response (Figure 6) in the respiratory tract. There is a timescale separation between the PK that drives the access of immunocompetent tissue to the product and the downstream immunogenic effect on respiratory tract pharmacodynamics markers. This timescale separation needs to be taken into account when designing regimen schedule changes. For skin, no PD markers are available. The currently accepted hypothesis is that, while in respiratory tract mucosal homing is imprinted to effector cells, skin will be populated by OM-85-experienced cells through the general systemic circulation, thereby aggravating the timescale separation between PK and PD. These factors lead to similar sensitivity to daily administered dose (mainly related to PK, not shown) but to different sensitivity to dosing schedule in RTI and AD as indications (presumablydue to assumedly different PD timescale), respectively (Figure 7).

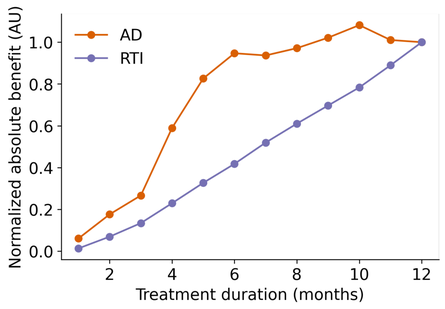

Figure 7: Absolute benefit as a function of treatment duration. Values were normalized with respect to 12 months of treatment.

Here we compare the sensitivity of OM-85 efficacy from in silico clinical trials based on the PBPK-PD model and the RTI and AD disease models. To match reference trials, the RTI in silico trials are conducted for 1-5 year old children with recurrent RTI (OM-85 against placebo) while AD in silico trials are conducted for 1-2 year old children with baseline EASI of 10 (induction period of topical corticosteroids then emollient + OM-85 or emollient). The absolute benefit is defined as the number of RTI in control minus the one in the OM-85 setting while for AD, it is the difference in mean EASI score at the end of follow up between the treatment and the control group.

CONCLUSION AND OUTLOOK

Complex disease model libraries interfaced with PBPK/PD treatment models could be a promising avenue towards screening indications by integrated computational strategies in the frame of model informed drug development.
In this contribution, we have demonstrated a modular PBPK/PD-QSP approach in the context of an in silico trial framework which couples one treatment model into two disease models. We have applied this concept to highlight differential regimen-schedule design in trials of OM-85 for RTI prophylaxis and AD severity reduction. The approach presented herein can also be applied to assess aspects of risk-benefit evaluation for other immunomodulating agents, especially those that reduce type 2 inflammation but may also reduce the anti-infectious immune effector function.

REFERENCES

[1] Bai, J., Earp, J. C., Florian, J., Madabushi, R., Strauss, D. G., Wang, Y., & Zhu, H. (2021). Quantitative systems pharmacology: Landscape analysis of regulatory submissions to the US Food and Drug Administration. CPT: pharmacometrics & systems pharmacology, 10(12), 1479–1484.
[2] Sové, R. J., Jafarnejad, M., Zhao, C., Wang, H., Ma, H., & Popel, A. S. (2020). QSP-IO: A Quantitative Systems Pharmacology Toolbox for Mechanistic Multiscale Modeling for Immuno-Oncology Applications. CPT: pharmacometrics & systems pharmacology, 9(9), 484–497.
[3] Arsène, S., Couty, C., Faddeenkov, I. et al. Modeling the disruption of respiratory disease clinical trials by non-pharmaceutical COVID-19 interventions. Nat Commun 13, 1980 (2022).
[4] Bodemer C, Guillet G, Cambazard F, et al. Adjuvant treatment with the bacterial lysate (OM-85) improves management of atopic dermatitis: A randomized study. PLoS One. 2017;12(3):e0161555.
[5] Yin J. et al. (2018) "Broncho-Vaxom in pediatric recurrent respiratory tract infections: A systematic re- view and meta-analysis", Int Immunopharmacol. 54:198-209.