PhysioPD™ Research Utilizes Mechanistic Physiological Models to Enhance Immunology Research and Drug Development

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Introduction

- Immunological processes are complex, featuring cell types and mediators with interacting and overlapping functions
- Immunological dysfunction contributes to a vast number of serious diseases, yet many mechanistic details of disease etiology and pathogenesis remain unclear
- Mechanistic modeling can help clarify the role of immunological pathways in disease processes and identify and evaluate promising treatments, thus reducing risks associated with drug development

Objectives

- Provide an overview of PhysioPD™ Platforms developed to support research in immunology indications
- Show concrete examples of impact on development decisions to support efficient compound development by:
    - Elucidating the role of different parts of the immune system in the etiology, pathogenesis, and treatment of various diseases
    - Improving the identification of promising candidate therapies and reducing risks associated with drug development

Methods

PhysioPD™ Research Platforms are mechanistic, quantitative models that elucidate the connection between mechanisms and outcomes.

- Rosa's PhysioPD Platforms are graphical, mathematical models of biology, a type of Quantitative Systems Pharmacology (QSP)
- PhysioPD Platforms combine **engineering approaches** and **scientific data analysis** to clarify complex physiology and drug interactions with each Platform designed and built to address specific drug development decisions
- PhysioPD Platforms are qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1)
- Simulated experiments are used to test hypotheses, explore mechanisms of action, evaluate likely efficacy of novel treatments, and provide comparisons to standard of care therapies (SOC)
- With client participation, Rosa has developed and conducted projects in Platforms containing detailed immunological function in a variety of indications, including:

Figure 1. Diagram of Rosa's Model Qualification Method[1] (MQM)

- B-Cell acute lymphoblastic leukemia (B-ALL)
- Melanoma
- Non-small cell lung cancer
- Non-Hodgkin's lymphoma
- Ewing's sarcoma
- Rheumatoid arthritis (RA)
- Acne
- Psoriasis
- Erythema
- Multiple sclerosis
- Alzheimer's disease
- Atopic dermatitis (AD)
- Skin aging
- Parkinson's disease
- Frontotemporal dementia
- Colitis
- Asthma
- COPD

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Systems Pharmacology 5, 43-53
2. Singh, I. et al. (2014) American Society of Clinical Pharmacology and Therapeutics Conference

Results: Immuno-Oncology

A B-ALL PhysioPD™ Research Platform helped to evaluate patient responses to blinatumomab treatment and the factors that influence these responses.[2]

- The Platform was developed to elucidate the factors influencing level of response to blinatumomab, a bispecific T-cell engager (BiTE®) antibody designed to direct cytotoxic T-cells to CD19-expressing B-cells

Figure 2. A B-ALL PhysioPD Research Platform focused on pathways critical to address scientific questions.

- The joint Rosa-client team agreed on a representation of the biology that focused on essential pathways in the bone marrow and plasma (Fig. 2)
- Parameters were based on data and scientific interpretations, and the Platform was qualified using agreed-upon criteria in the MQM framework
- Sensitivity analysis identified parameters driving response
- This led to insights for understanding patient variability (Fig. 3)

Figure 3. Response to therapy was sensitive to production rate of malignant B cell and the drug binding rate but not to baseline levels of malignant B cells.

Results: Rheumatoid Arthritis

An RA PhysioPD Platform was used to quantify benefits of bi-specific anti-TNFα/anti-Ang2 antibody.

- Quality of vasculature impacts immune cell infiltration in RA pathogenesis
- The client was interested in comparing an anti-TNFα/anti-Ang2 antibody against SOC anti-TNFα treatment

Figure 4. A focused RA PhysioPD Platform includes key TNFα and Ang2 effects in the context of disease.

- The RA Platform focused on aspects of pathophysiology expected to be affected by TNFα and Ang2 (Fig. 4)
- Simplifying assumptions, such as grouping of immune cells, limited complexity and facilitated timely insights
- The Platform reproduced relevant outcomes, such as untreated progression and response to anti-TNFα
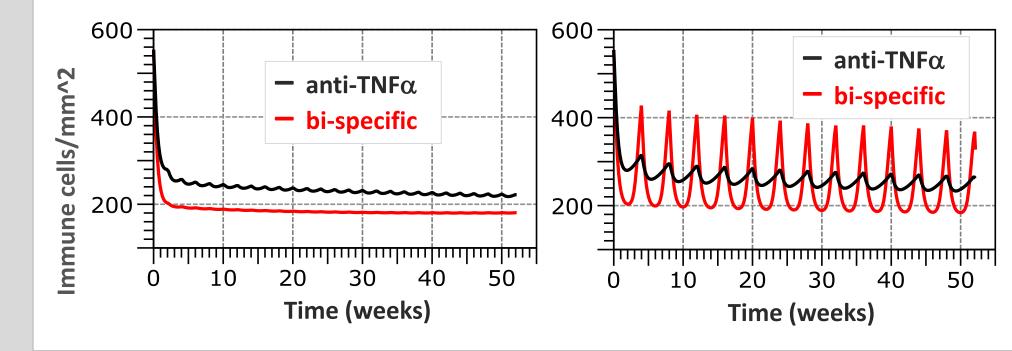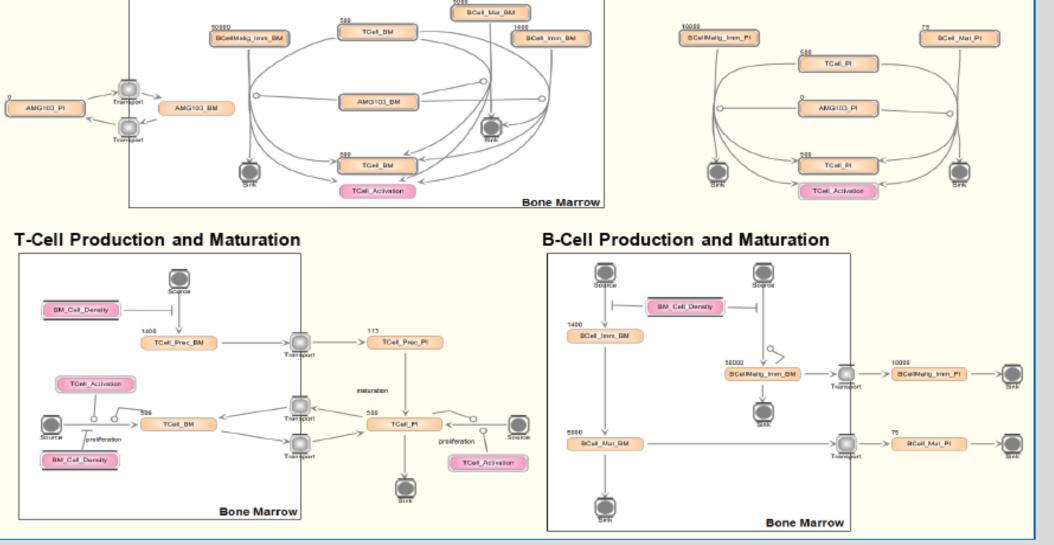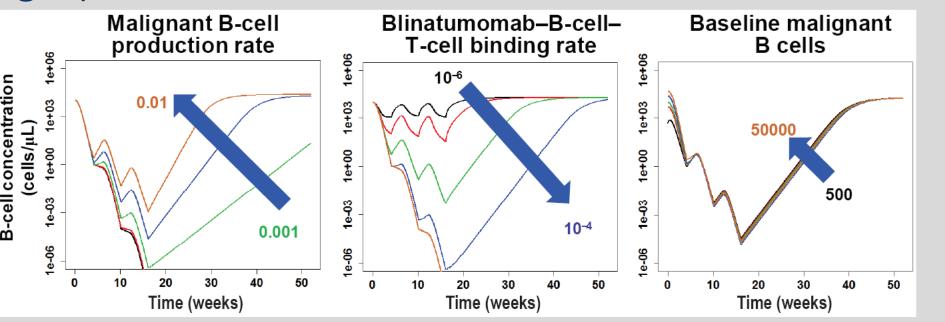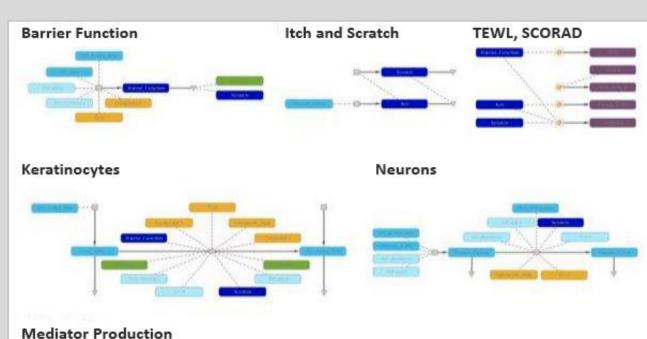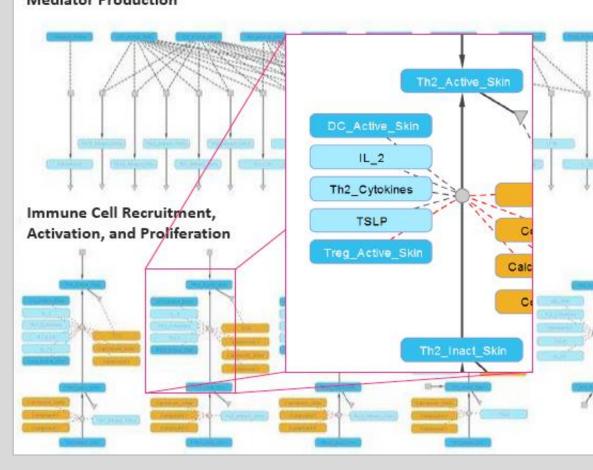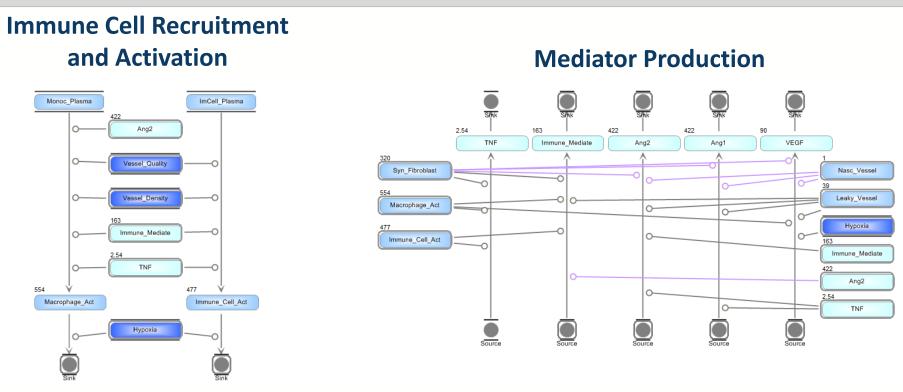- Prospective simulations supported insights into likely response to the bi-specific vs. anti-TNFα (Fig. 5)

Figure 5. Head-to-head simulations comparing efficacy for bi-specific antibody to anti-TNFα. The relative efficacy varied across VPs (results not shown).

Results: Atopic Dermatitis

Research in the Atopic Dermatitis PhysioPD Platform helped prioritize compounds and identified opportunities for competitive differentiation.

- Client needed to prioritize assets for development for AD
- Because of the broad set of targets, a relatively detailed AD PhysioPD Platform was developed (Fig. 6)

Figure 6. An AD PhysioPD Platform provides a graphical and mathematical model of disease processes and involvement of targets. The SCORAD ("SCORing Atopic Dermatitis") clinical score was implemented by quantifying immunological markers such as cell and mediator concentrations and correlating those with outcome.

- Qualification included comparison of known protocols to expected results (Fig. 7)
- All targets were contextualized within the same pathophysiology framework
- Platform development clarified pathophysiology and enabled exploration of each target's contribution
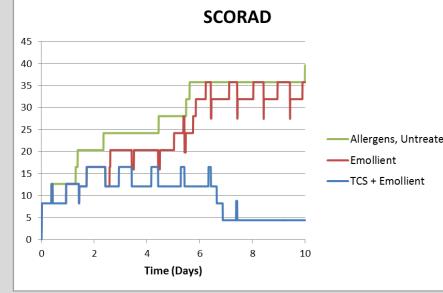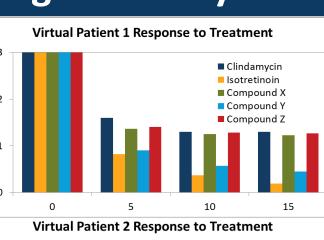

Figure 7. Left: The efficacy of T2 cell activation of a compound under consideration. Right: SCORAD under allergen challenge, Emollient, and topical corticosteroid (TCS) + Emollient treatment.

Results: Acne

Analysis in Acne PhysioPD™ Platform identified pathways most likely involved in target efficacy.
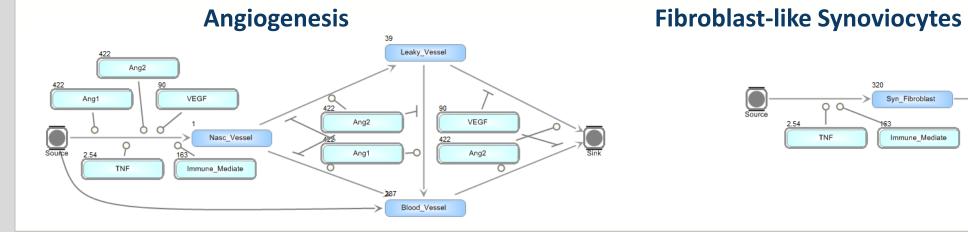
- An Acne PhysioPD Platform included the pathways involved in pathophysiology and response to SOCs
- The Platform enabled comparison of novel compounds to SOCs in a range of VPs with different pathophysiologies (Fig. 8)

Figure 8. VP responses to SOC and novel compounds.

Conclusions

- The complexity of the immune system does not preclude mechanistic modeling
- Use of QSP in immunology R&D requires careful scoping of models to ensure the appropriate level of detail
- Rosa's Immunology PhysioPD Platforms have been used effectively to elucidate the mechanisms of pathogenesis and treatment and to support development decisions

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