Evaluation of Novel Anti-TNFα and IL-6R Therapies in a Rheumatoid Arthritis (RA) Quantitative Systems Pharmacology (QSP) Platform.

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Introduction

- **RA** is a common **autoimmune disease** associated with **progressive disability,** systemic complications, early death, and socioeconomic costs.
- RA is characterized by **synovial inflammation** and **hyperplasia**, autoantibody production, cartilage and bone destruction, and systemic features.
- **Anti-TNFα, anti-IL-6,** and **anti-IL-6 receptor (IL-6R) therapies** are approved for use in RA**.**
- A significant number of patients do not respond to treatment. Therefore, the **development of new treatment approaches is warranted.**

Objectives

- Support the development of **novel anti-TNFα and IL-6R therapies for RA**
- Gain a deeper understanding of the **key biological pathways impacting clinical response** to anti-TNFα or anti-IL-6R
- **Identify** RA patient **phenotypes with optimal response** to therapy

Methods

PhysioPD™ Research Platforms are mechanistic, QSP models that allow investigation of the connection between mechanisms and outcomes.

- Rosa and Sanofi developed a QSP model of RA, **the RA PhysioPD Platform**, using **engineering approaches** and **scientific data analysis** to clarify complex physiology and drug mechanism of action
- The RA Platform was qualified in accordance with **Rosa's Model Qualification Method[1] (MQM)** (Figure 1)
- The RA Platform represents mechanistically the **physiology of a single RA joint** (Figure 2) including:
  - Fibroblast-like synoviocytes (FLS), immune cells, cytokines, chemokines, and their regulation
  - Standard therapies (adalimumab, sarilumab, sirukumab, methotrexate [MTX], baricitinib)
  - Clinical outcomes (DAS28-CRP score)

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

RA PhysioPD Platform Overview

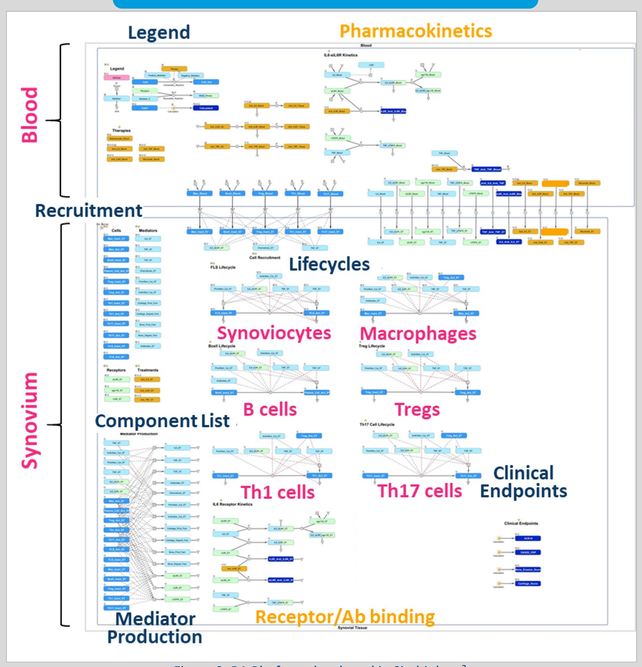

Figure 2. RA Platform developed in Simbiology[2]

Platform Qualification

The reference virtual patient (VP) is representative of an average moderate/severe MTX-inadequate responder RA patient with stable, chronic disease

- Cell numbers in blood and synovium were calibrated to match the average from several published studies for moderate/severe RA patients (Figure 3)
- Synovial mediator levels, determined by clearance rates, cell numbers, and cell-type specific production rates also matched reported literature averages

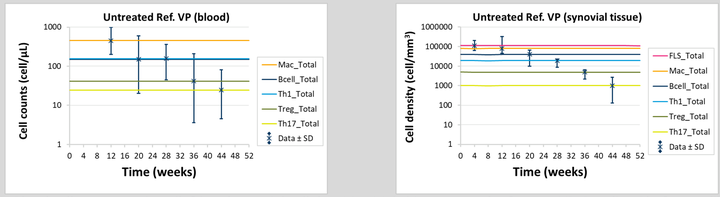

Figure 3. Blood cell concentrations (left) and synovial cell densities (right) in untreated reference VP. Baseline Platform calibration represents a dynamic equilibrium that reflects stable, chronic disease. Data values are plotted at arbitrary time points.

Serial histological studies from biopsies of patients were used to qualify cellular responses to therapies

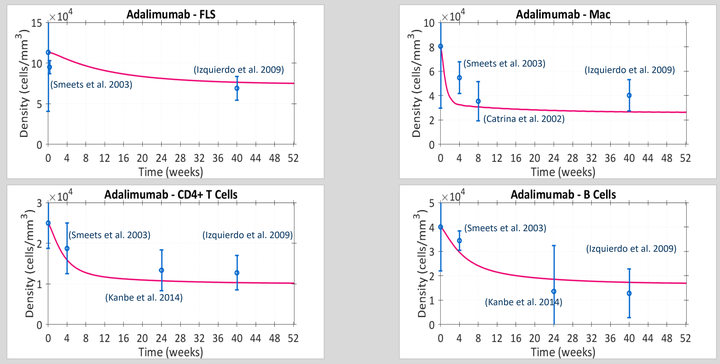

Figure 4. Reduction in synovial FLS, macrophages, CD4⁺ T cells and B cells in anti-TNFα treated reference VP. Simulations (pink line) of 40 mg Q2W adalimumab treatment in reference VP compared to published data (ϕ: mean ± SD)

Reference VP response matches average clinical response to anti-TNFα and anti-IL-6R measured in large clinical trials

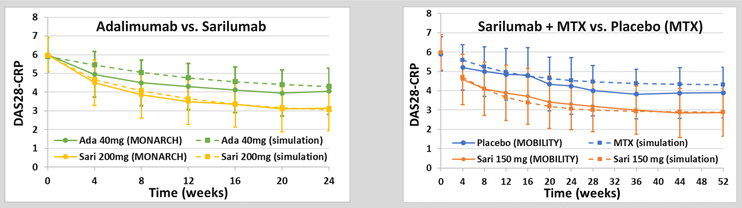

Figure 5. Reduction in DAS28-CRP in reference VP treated with anti-TNFα or anti-IL-6R (left) or anti-IL-6R + MTX (right). Simulations in reference VP (dashed lines) of 40 mg Q2W adalimumab, 200 mg sarilumab Q2W or 150 mg sarilumab Q2W + MTX vs. clinical score from the MONARCH (Burmester et al. 2017) and MOBILITY trials (Genovese et al. 2015) (ϕ: mean ± SD)

Reference VP has an average clinical response to all implemented test therapies in combination with MTX

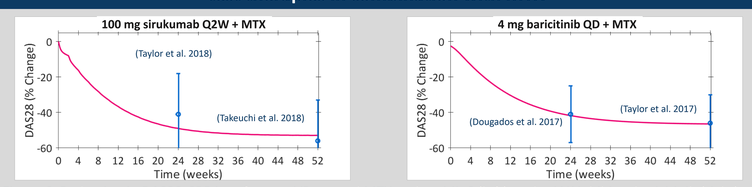

Figure 6. Reduction in DAS28-CRP in reference VP treated MTX and anti-IL-6 (left) or the JAK inhibitor baricitinib (right). Simulations (pink line) of 100 mg sirukumab Q2W or 4 mg baricitinib QD in reference VP on a MTX-background treatment compared to published data (ϕ: mean ± SD)

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Alternate Virtual patients

Specific RA synovial phenotypes have differential response to anti-TNFα vs. anti-IL-6R therapies

- Dennis et al. 2014 identified phenotypes which may predict response to anti-TNFα and anti-IL-6R therapies (Table 1)

Table 1. Characteristics of the four major phenotypes of RA synovium identified

Phenotype	Lymphoid	Myeloid	Low inflammation	Fibroid
Defining gene clusters (microarrays)	B and/or T lymphocyte activation and differentiation, Ig production, IL-17 signaling	chemotaxis, TNFα and IL-1β production, phagocytosis, mononuclear cells proliferation	inflammatory response and wound response processes	TGFβ & bone morphogenetic protein signaling, endocytosis
Synovial cell infiltration (histology, FACS)	• T cells: ++ • B cells: +++ • Mac.: +++ • Fibroblasts: +	• T cells: +++ • B cells: + • Mac.: +++ • Fibroblasts: ++	• T cells: ++ • B cells: - • Mac.: ++ • Fibroblasts: ++	• T cells: ++ • B cells: - • Mac.: ++ • Fibroblasts: +++
Serum biomarkers	• sICAM: low • CXCL13: high	• sICAM: high • CXCL13: med	• sICAM: low • CXCL13: med	• sICAM: low • CXCL13: low

Four alternate VPs with diverse phenotypes were created to explore response to anti-TNFα and anti-IL-6R therapies

Table 2. Characteristics of the different VP phenotypes created and their relative response to therapies

VP phenotype	Response to therapy		
	MTX	Anti-TNFα	Anti-IL-6R
Reference VP	±	++	+++
Anti-TNF-IR #1*	±	±	+++
Anti-TNF-IR #2	±	±	+++
Anti-IL-6-IR #1	±	+++	+

*** IR : inadequate-responder**

The alternate VPs cover a range of responses to the various therapies

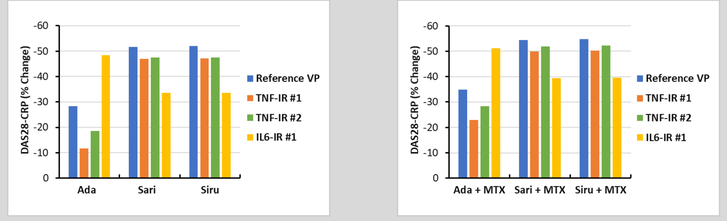

Figure 8. Clinical response of the five VPs to anti-TNFα, anti-IL-6R and anti-IL-6 therapies with or without MTX. % change in DAS28-CRP at 24 weeks in all VPs treated with adalimumab, sarilumab or sirukumab alone (left) or with MTX (right)

Sensitivity analysis highlights the role of IL-6 as a major driver of RA pathophysiology

- A sensitivity analysis of the untreated reference VP was performed by modifying each parameter by ± 10% and measuring the impact after 52 weeks
- The most sensitive pathways for baseline DAS28-CRP (as a measure of disease severity) were:
  - Cytokine regulation of B cell & FLS clearance
  - Macrophage recruitment and clearance
  - Treg proliferation and clearance
  - TNFα and other proinflammatory cytokines

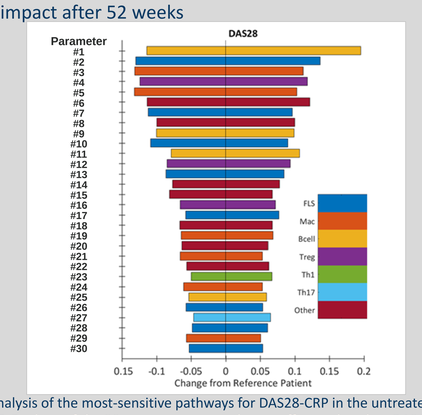

Figure 9. Analysis of the most-sensitive pathways for DAS28-CRP in the untreated reference VP. Ranking of the 30 most-sensitive pathways affecting baseline DAS-28 CRP levels. The bars are color-coded to identify parameters regulating a specific cell type (see legend) or mediator (Other, in dark red)

Conclusions

- Anti-TNFα inadequate responders could benefit from switching to novel anti-TNFα or anti-IL-6R therapies, in particular in patients developing anti-drug antibodies
- IL-6 pathways are key disease drivers in a majority of the VPs phenotypes resulting in more patients responding to anti-IL-6R than to anti-TNFα therapies

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