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 (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)

RA PhysioPD Platform Overview

![RA PhysioPD Platform Overview](Image)

Legend

- Blood
- Recruiting
- Lifecycles
- Synovocytes
- Macrophages
- Component List
- Clinical Endpoints
- Mediator Production
- Receptor/Ab binding

RA Platform developed in Simulays®

References


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Platform Qualification

![Platform Qualification](Image)

The reference virtual patient (VP) is representative of an average moderate/severe RA inadequately responders RA patient with 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

![Serial histological studies from biopsies of patients were used to quantify cellular responses to therapies](Image)

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![Reference VP response matches average clinical response to anti-TNFα and anti-IL-6R measured in large clinical trials](Image)

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

- Dennis et al. 2014 identified synovial phenotypes which may predict response to anti-TNFα or anti-IL-6R therapies

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<tr>
<th>Phenotype</th>
<th>Synovial</th>
<th>Hematological</th>
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<tr>
<td>MTX</td>
<td>Low</td>
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<tr>
<td>Anti-TNFα</td>
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Platform Qualification - Table 1.

![Four alternate VPs with diverse phenotypes were created to explore response to anti-TNFα and anti-IL-6R therapies](Image)

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![The alternate VPs cover a range of responses to the various therapies](Image)

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

![Conclusions](Image)

Conclusions

- The most sensitive pathways for baseline DAS28-CRP (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

- 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-6 than to anti-TNFα therapies

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

Figure 4. Reduction in synovial FLS, macrophages, CD4+ T-cells and B cells in anti-TNFα treated reference VP. Simulations (pink line) of 100 mg sirukumab Q2W or 4 mg baricitinib QD in reference VP

Figure 5. Reduction in synovial FLS, macrophages, CD4+ T-cells and B cells in anti-TNFα treated reference VP. Simulations (pink line) of 100 mg sirukumab Q2W + MTX on a MTX background treatment compared to published data (△ mean ± SD)

Figure 6. Reduction in DAS28-CRP in reference VP treated with anti-TNFα or anti-IL-6R (left) or anti-TNFα + MTX (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 (△ mean ± SD)

Figure 7. Analysis of the most sensitive pathways for DAS28-CRP in the untreated reference VP. Ranking of the 30 most sensitive pathways affecting baseline DAS28-CRP levels. The bars are color-coded to identify parameters regulating a specific cell type (via legend) or mediator (darker, in dark red)

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 26 weeks in all VPs treated with adalimumab, sarilumab or sirukumab alone (left) or with MTX (right)

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 DAS28-CRP levels. The bars are color-coded to identify parameters regulating a specific cell type (via legend) or mediator (darker, in dark red)