



Systems Immunology Modelling

From Mechanistic Details to Clinical Outcomes

April 17th, 2019

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, disabling condition causing pain and joint deformation affecting 0.5 % to 1 % of the world population

- Infections can yield anti-citrullinated protein antibodies (ACPA)
- ACPAs target, for example, collagen in articular cartilage and initiate an autoimmune reaction
- Immune cells infiltrate the joints and release pro-inflammatory mediators
- Joint inflammation causes swelling and tenderness
- Disturbances in osteoclast and osteoblast activities causes bone deformation and stiffness that can become irrevocable

Healthy

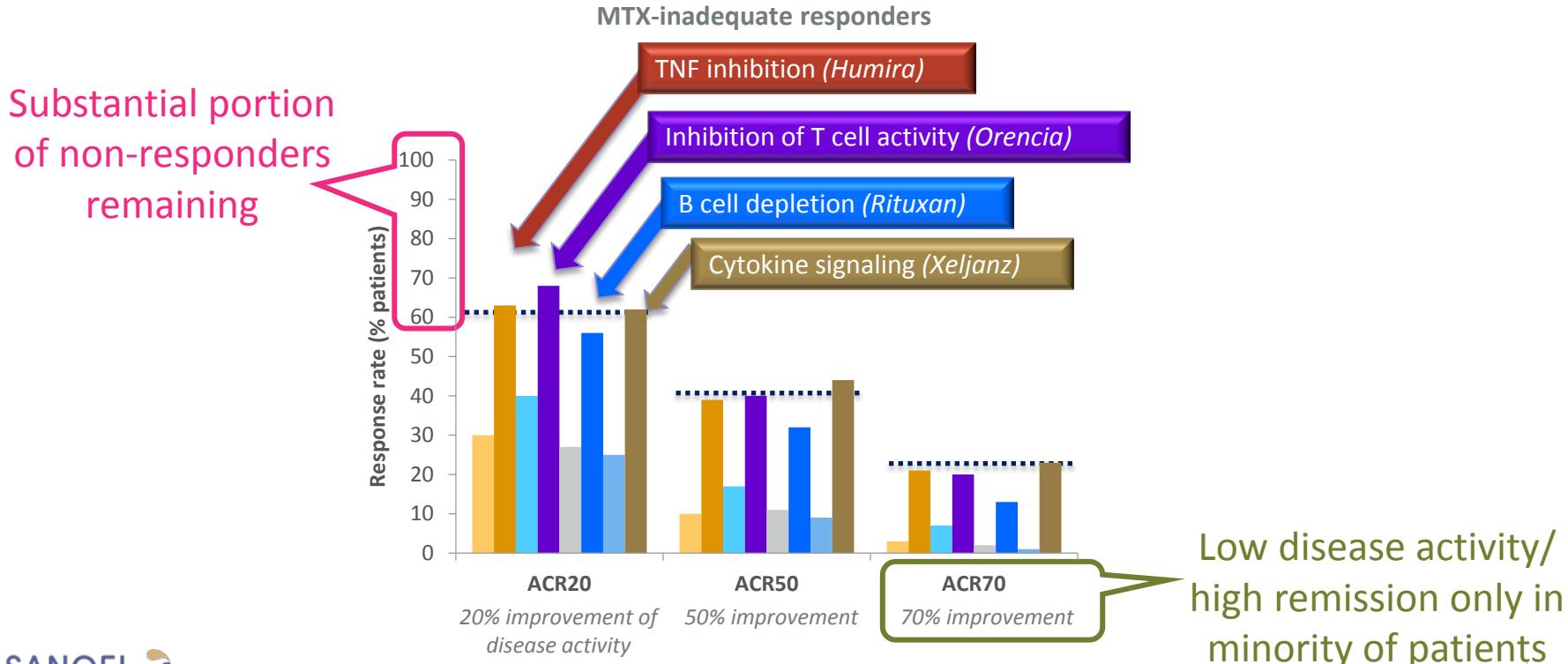


Arthritic



Treatment response in rheumatoid arthritis

RA patient's response rates remain stationary below a ~60% ceiling, despite different mechanisms of immunomodulation developed over the last 15 years.

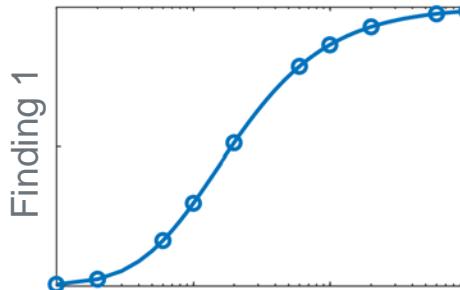
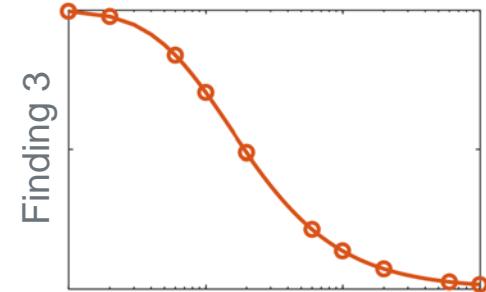
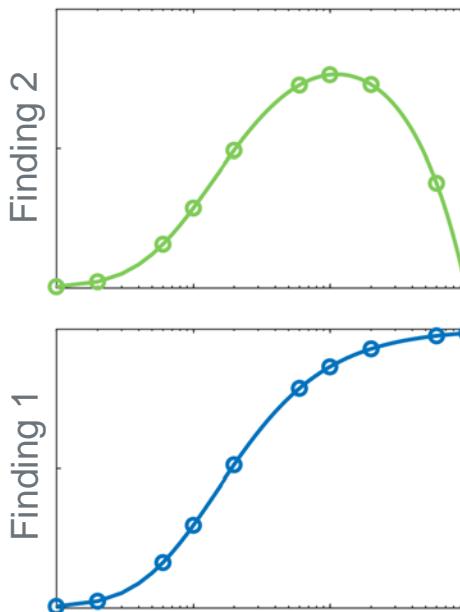


Systems Immunology Modelling

Immunology is very complex....



... while data sets are focused snapshots



- Line regression to interpolate within one data set to calculate, for example, EC50 values

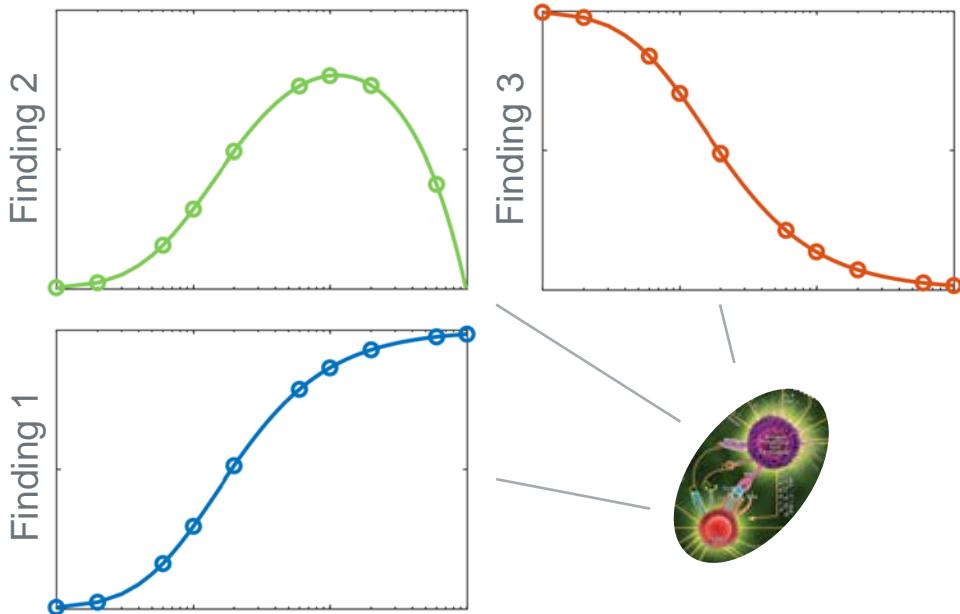
Systems Immunology Modelling

Immunology is very complex....



biolegend.com Sep 2011

... while data sets are focused snapshots



- Quantitative Systems Pharmacology (QSP) modeling is a framework that consistently integrates all available data sources to conclude on biological mechanisms and to predict pharmacology

Scope and Modular Approach

Systems Immunology Modelling: Modules

Medications

Rheuma

Methotrexate

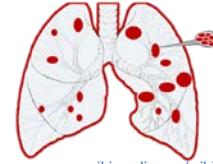
Anti-TNF

Anti IL-6R

JAK inhibitors



Immune response module



commons.wikimedia.org/wiki/File:Lungs_diagram_detailed.svg

Readouts: Disease Scores

Viral load

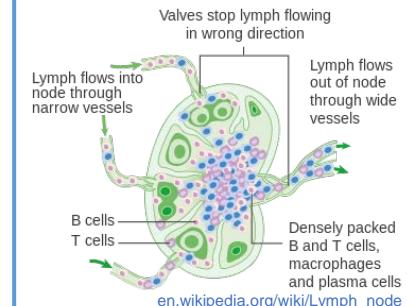
Bacterial load

Resp. time

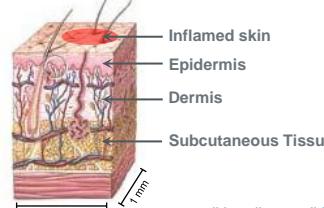
SPASI score

Barrier funct.

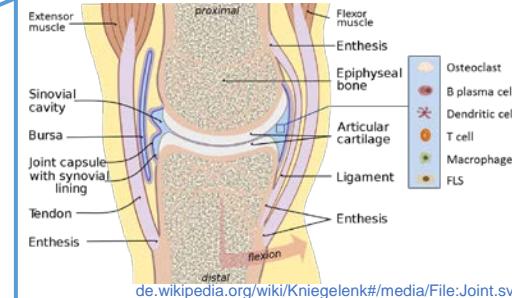
Draining lymph node module



Psoriatic skin module



Arthritic knee joint module



ACR score

DAS28-CRP

Cartilage destruct.

Bone metabolism

Systems Immunology Modelling: Modules

Medications

Rheuma

Methotrexate

Anti-TNF

Anti IL-6R

JAK inhibitors

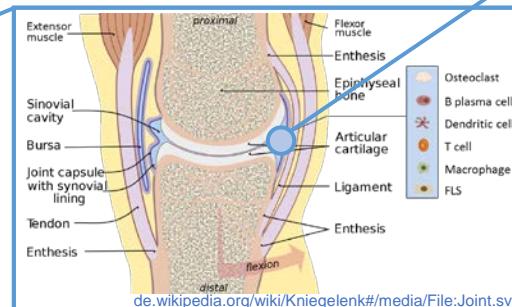
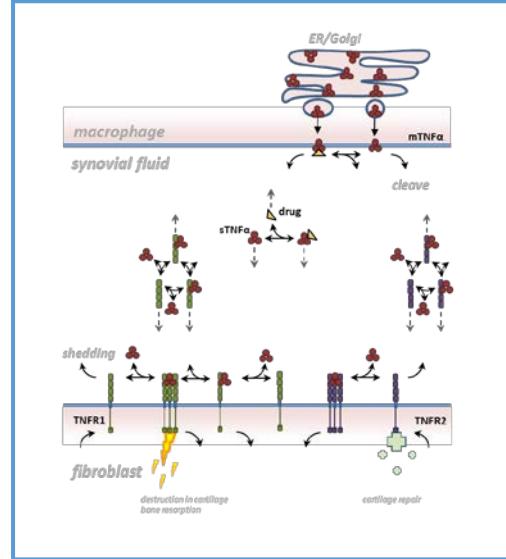
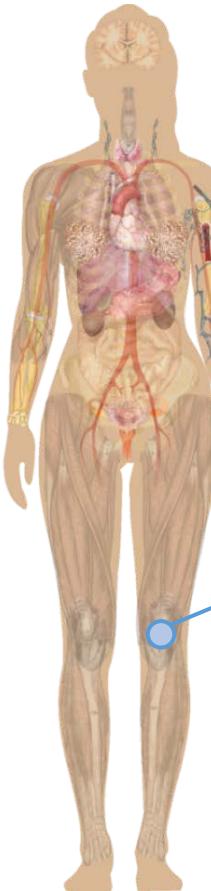
Psoriasis

Methotrexate

Anti-TNF

Anti-IL23

Anti-IL17



Cells

Macrophage

Th1

FLS

Treg

Mediators

TNF

IFNγ

CXCL13

MMP1

Disease Scores

ACR score

DAS28-CRP

Cartilage destruct.

Bone metabolism

Implementing Mechanistic Details

Systems Immunology Modelling: Modules

Legend:

Therapies

Cell

Mediator

Receptor

Biomarker

Therapies:

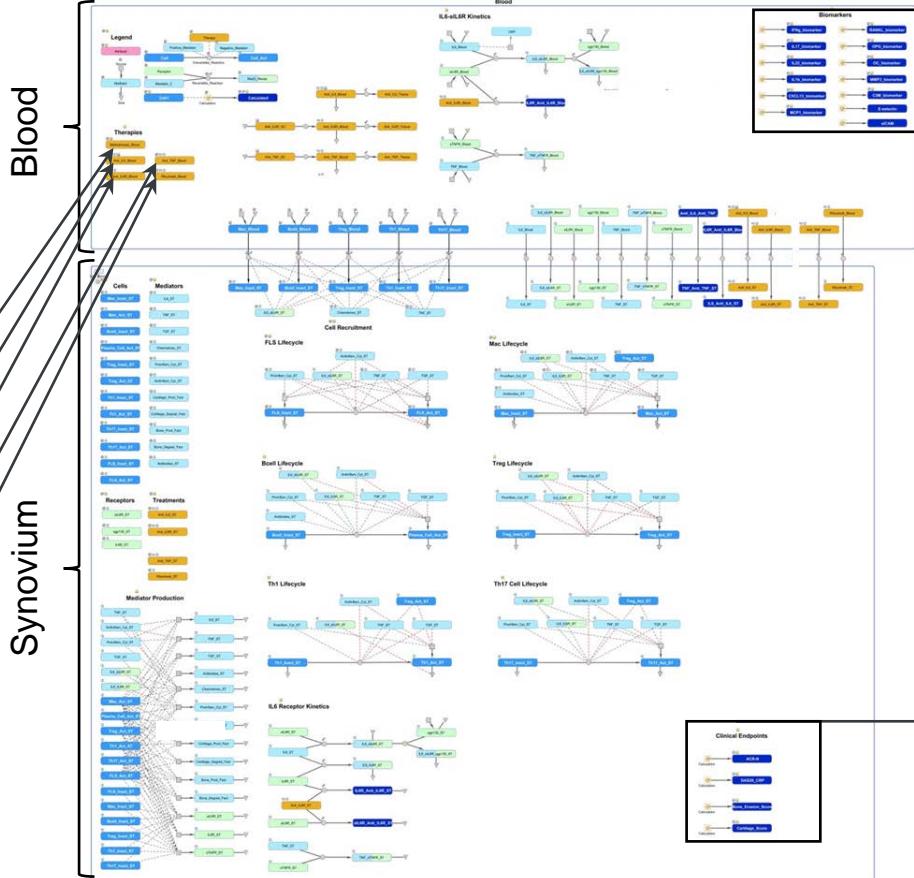
Methotrexate

Sirukumab

Sarilumab

Anti-TNF

Baricitinib



Output:

IFN- γ

IL17

IL22

IL-1 β

CXCL-13

MCP-1

RANKL

OPG

OC

MMP3

ACR-N

C2M

E-selectin

sICAM

CRP

DAS28 -CRP

Bone erosion

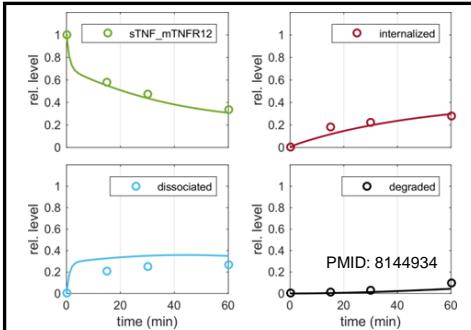
Cartilage dest

Model scope: Molecular mechanistic links

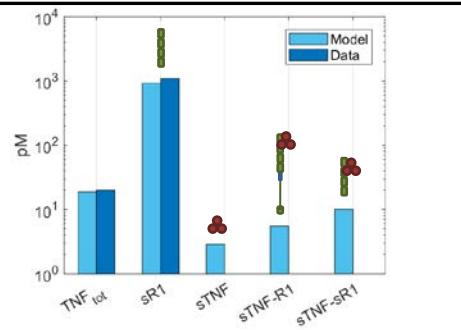
Cell distribution

Cell type	Baseline Density, cells /mm ³ , mean (range)	Selected References
FLS	634 (320-1040)	Smeets 2002 PMID 12905468; Wijbrandts 2008 PMID 18055470; Gerlag 2004 PMID 15593225; Kraan 2002 PMID 12209505
Macrophages	708 (220-1643)	Smeets 2003 PMID 12905468; Wijbrandts 2008 PMID 18055470; Gerlag 2004 PMID 15593225; Kraan 2002 PMID 12209505; Mulherin 1996 PMID 8546720; Veale 1993 PMID 7686370; Izquierdo 2009 PMID 1843860
CD3+ T cell	317 (47-823)	Smeets 2003 PMID 12905468; Wijbrandts 2008 PMID 18055470; Gerlag 2004 PMID 15593225; Kraan 2002 PMID 12209505; Mulherin 1996 PMID 8546720; Veale 1993 PMID 7686370; Izquierdo 2009 PMID 1843860
CD4+ T cell	274 (219-390)	Mulherin 1996 PMID 8546720; Veale 1993 PMID 7686370; Yamada 2008 PMID 18063670; Leijo 2010 PMID 20583102; Cosimi 2011 PMID 21381000
• Tregs	11% of CD4+ (2.4-26%)	Moradi 2014 PMID 24742142; Morita 2016 PMID 2722457
• Th17	2% of CD4+ (0.5-9%)	Yamada 2008 PMID 18063670; Leijo 2010 PMID 20583102; Cosimi 2011 PMID 21381000
• Th1	30% of CD4+ (5-61%)	Mulherin 1996 PMID 8546720; Wijbrandts 2008 PMID 18055470; Kraan 2002 PMID 12209505; Veale 1993 PMID 7686370; Izquierdo 2009 PMID 1843860
B cells	230 (47-521)	

Dynamical binding data



Cellular response



Model scope



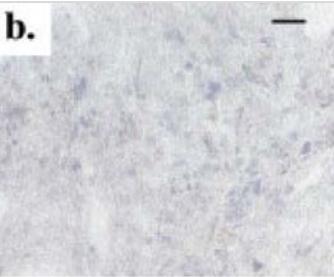
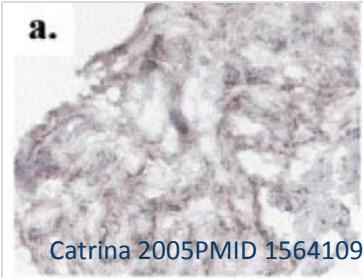
Cell-specific production rates

Cell Type	Mediator	Rate
Cell	sTNF	2.0E-03
Cell	IL-6	1.0E-03
Cell	IL-8	1.0E-03
Cell	IL-10	1.0E-03
Cell	IL-12	1.0E-03
Cell	IL-13	1.0E-03
Cell	IL-17	1.0E-03
Cell	IL-23	1.0E-03
Cell	IL-27	1.0E-03
Cell	IL-31	1.0E-03
Cell	IL-33	1.0E-03
Cell	IL-34	1.0E-03
Cell	IL-35	1.0E-03
Cell	IL-36	1.0E-03
Cell	IL-37	1.0E-03
Cell	IL-38	1.0E-03
Cell	IL-39	1.0E-03
Cell	IL-40	1.0E-03
Cell	IL-41	1.0E-03
Cell	IL-42	1.0E-03
Cell	IL-43	1.0E-03
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Cell	IL-337	1.0E-03</

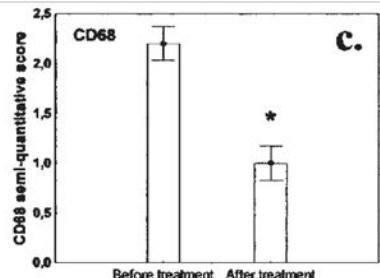
Simulating Clinical Study Data

Serial biopsies from RA-patients

Example: Anti-TNF treatment



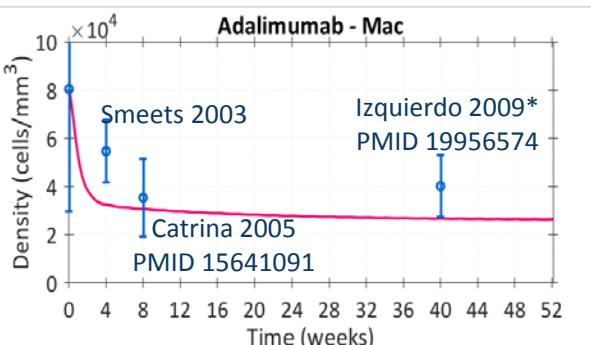
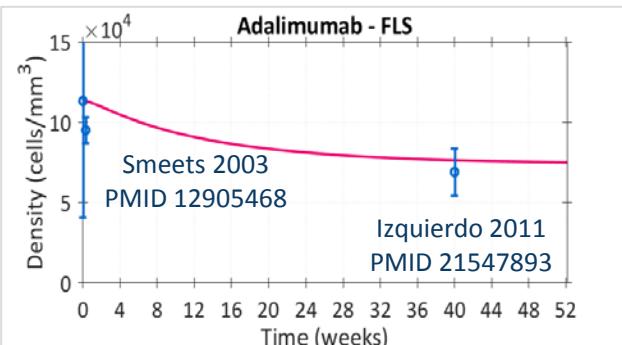
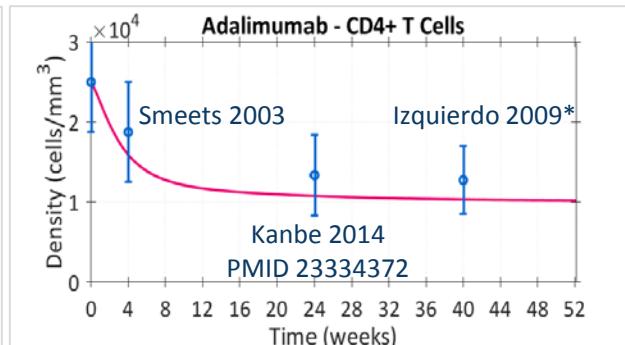
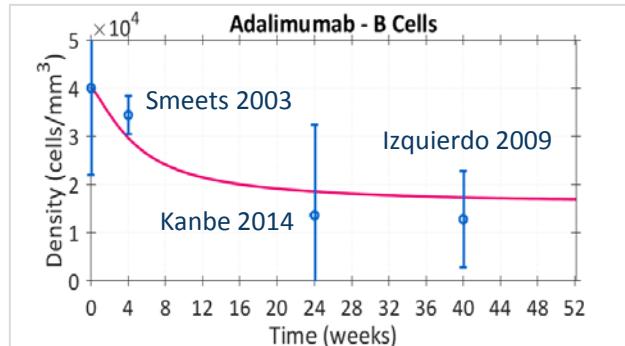
Catrina 2005 PMID 15641091



- Pink lines: simulation results
- Blue circles: mean \pm SD (error bars) with corresponding reference

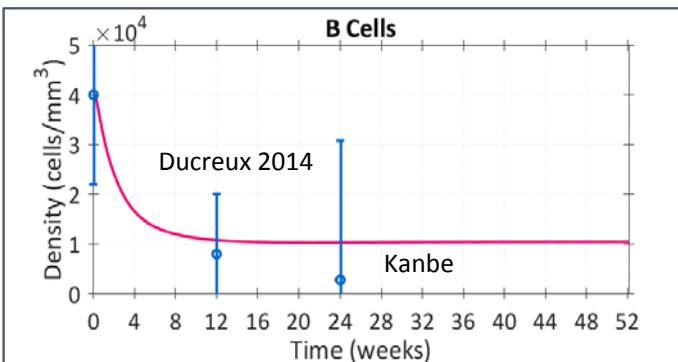
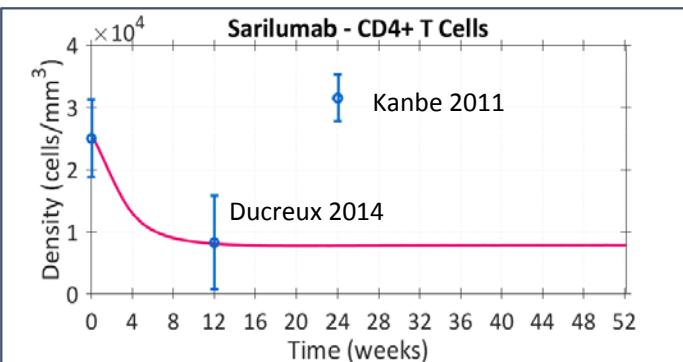
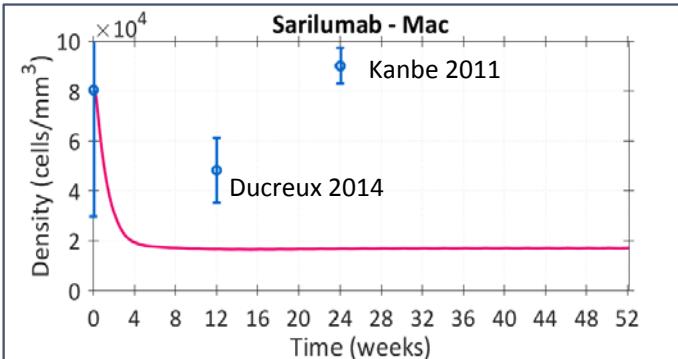
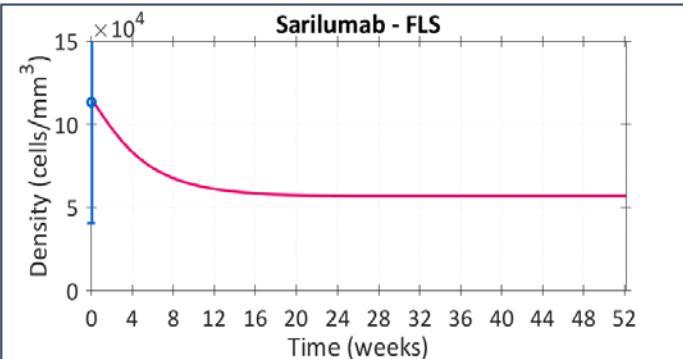
Table 3 Comparison of immunohistology of synovium by treatment of golimumab Kanbe 2014 PMID 23334372

	CD68	CD20	CD4	CD8
Control (<i>n</i> = 10)	41 (4.5)	35 (7.4)	26 (6.7)	18 (6.5)
Golimumab (<i>n</i> = 10)	11 (5.9)*	12 (5.6)*	17 (6.8)*	7.5 (4.2)*



Serial biopsies from RA-patients

Example: Predicting cell density response to anti-IL6R treatment

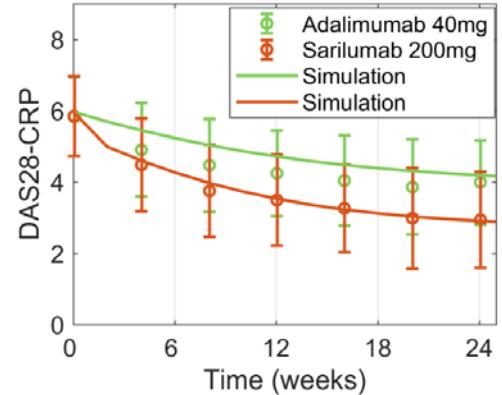
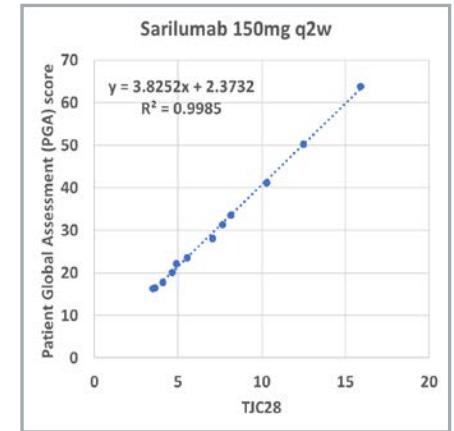
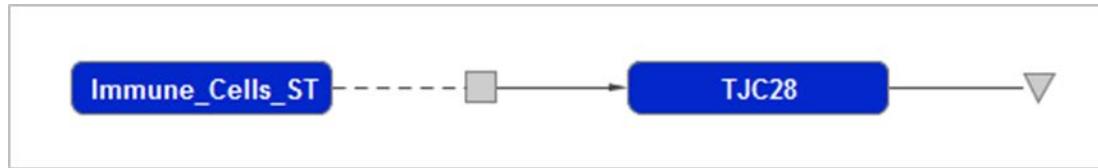


- Blue circles: mean \pm SD (error bars) with corresponding reference
- Pink lines: simulation results

- The model describes/predicts cell density changes during treatment
- Using data from different studies can yield data inconsistencies

Translating the cellular level into disease activity

- EULAR guidelines: $DAS28-CRP = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.36 * \log_N([CRP] + 1) + 0.014 * GH + 0.96$
- CRP is a blood biomarker that is released by the liver depending on blood IL-6 and TNF levels
- The number of tender joints correlates with the patient global assessment (PGA)
- 75 % of the tender joints are also swollen (SJC28, internal study data)
- Infiltration of activated immune cells relates well to disease activity



Disease Subtypes

Simulating disease subtypes

Dennis 2014 PMID 25167216

Phenotype	Myeloid	Lymphoid	Low inflammation	Fibroid
Defining gene clusters (microarrays)	chemotaxis, TNF α and IL-1 β production, phagocytosis, mononuclear cells proliferation	B and/or T lymphocyte activation and differentiation, Ig production, IL-17 signaling	inflammatory response and wound response processes	TGF β & bone morphogenetic protein signaling, endocytosis
Synovial cell infiltration (histology, FACS)	<ul style="list-style-type: none">• T cells: +++• B cells: +• Mac.: +++• Fibroblasts: ++	<ul style="list-style-type: none">• T cells: ++• B cells: +++• Mac.: +++• Fibroblasts: +	<ul style="list-style-type: none">• T cells: ++• B cells: -• Mac.: ++• Fibroblasts: ++	<ul style="list-style-type: none">• T cells: ++• B cells: -• Mac.: ++• Fibroblasts: +++
Serum biomarker baseline levels	<ul style="list-style-type: none">• sICAM: high• CXCL13: low	<ul style="list-style-type: none">• sICAM: low• CXCL13: high	<ul style="list-style-type: none">• sICAM: low• CXCL13: med	<ul style="list-style-type: none">• sICAM: low• CXCL13: low

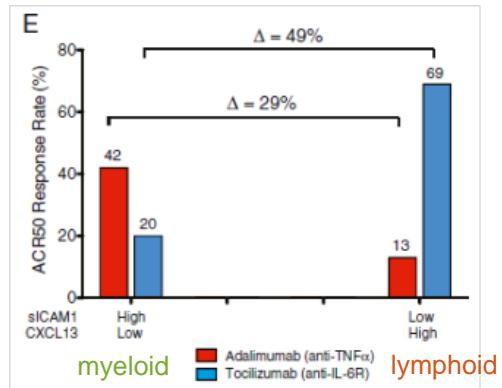
Identify preliminary disease subtypes for evaluation in QSP model

- Published literature disease subtypes
- sICAM and CXCL13 are potential biomarkers for identifying subtypes

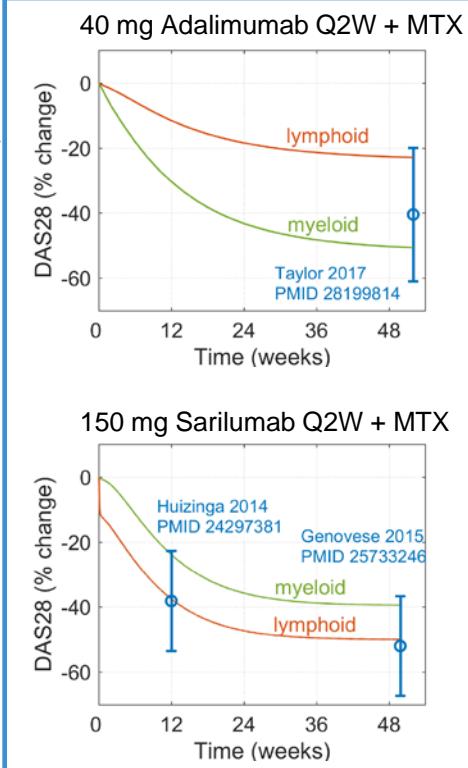
Simulating disease subtypes

Hypothesis

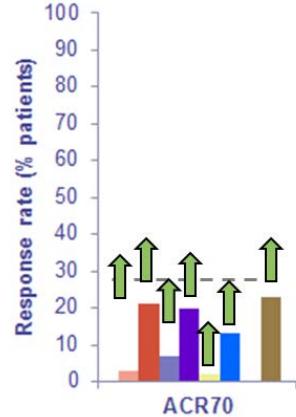
Myeloid	Lymphoid
• T cells: +++	• T cells: ++
• B cells: +	• B cells: +++
• Mac.: +++	• Mac.: +++
• Fibroblasts: ++	• Fibroblasts: +
• sICAM: high	• sICAM: low
• CXCL13: low	• CXCL13: high



QSP model simulations



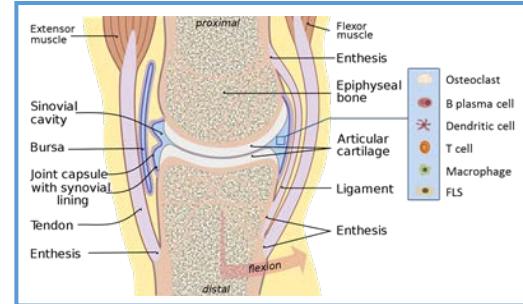
- Simulations reflect data variability
- Subtypes respond differently to treatment
- Guiding patient to their individual medication may increase response rate
- Predictive blood biomarkers are perhaps different from sICAM and CXCL13 → Additional analysis needed



Summary and conclusion

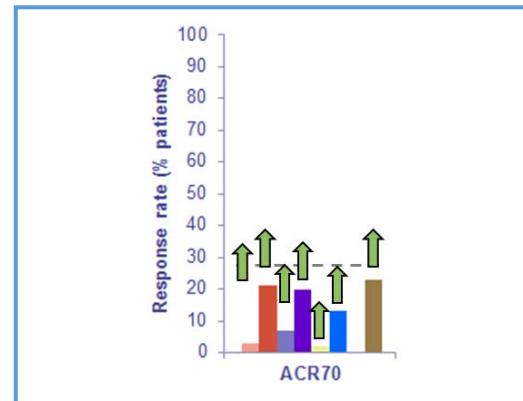
Core elements of QSP model development:

- **Focus** on the project scope and key mechanisms of the pathophysiology
- **Incorporate** latest mechanistic data
- **Validate** model using clinical data
- **Explore** patient variability and disease subtypes



Achievements

- **Illuminating** the mode of action of key anti-inflammatory drugs
- **Evaluating** disease subtypes and their response to drugs
- **Predicting** optimal dosing regimens and treatment combinations
- **Suggesting** clinical biomarkers for target engagement, treatment synergies and patient response



Thank you for your attention!