Systems Immunology Modelling

From Mechanistic Details to Clinical Outcomes

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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 auto-immune 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

en.wikipedia.org/wiki/Rheumatoid_arthritis

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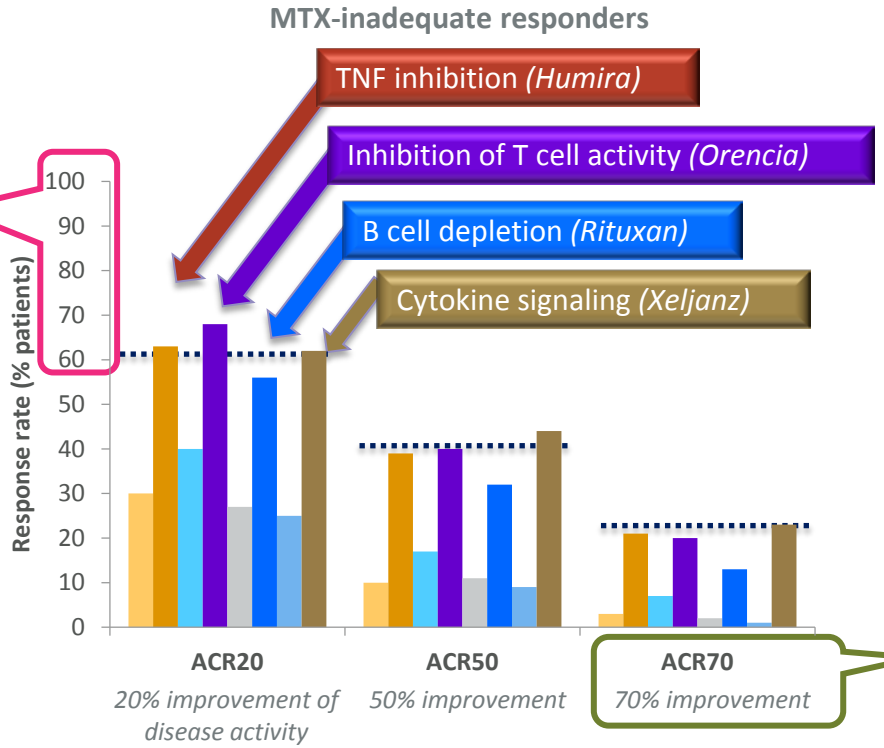
Treatment response in rheumatoid arthritis

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

Substantial portion of non-responders remaining



Low disease activity/ high remission only in minority of patients

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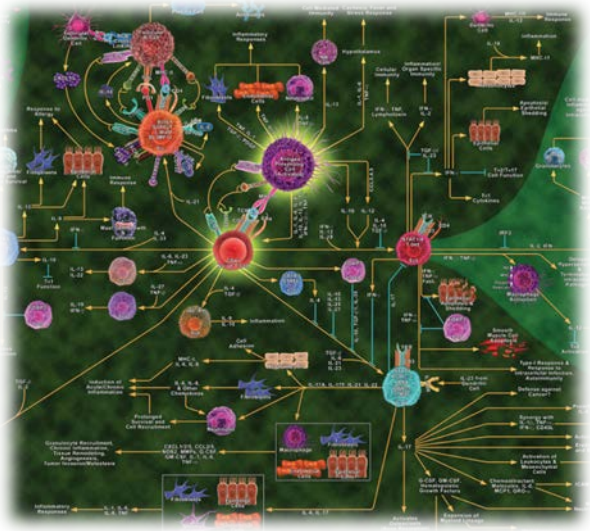
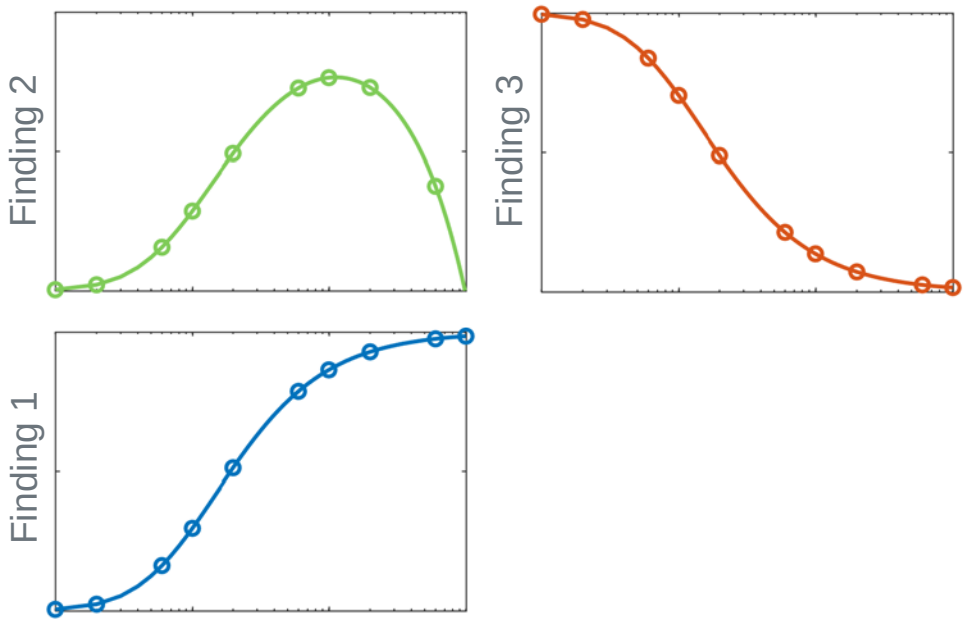
Immunology is very complex….



biolegend.com Sep 2011

… while data sets are focused snapshots



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

Systems Immunology Modelling

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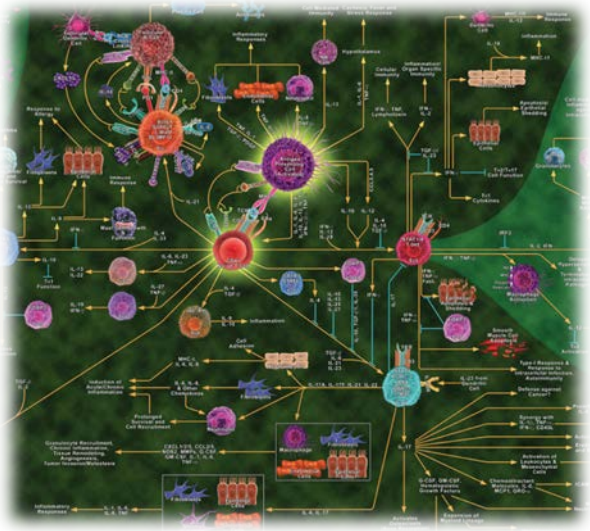

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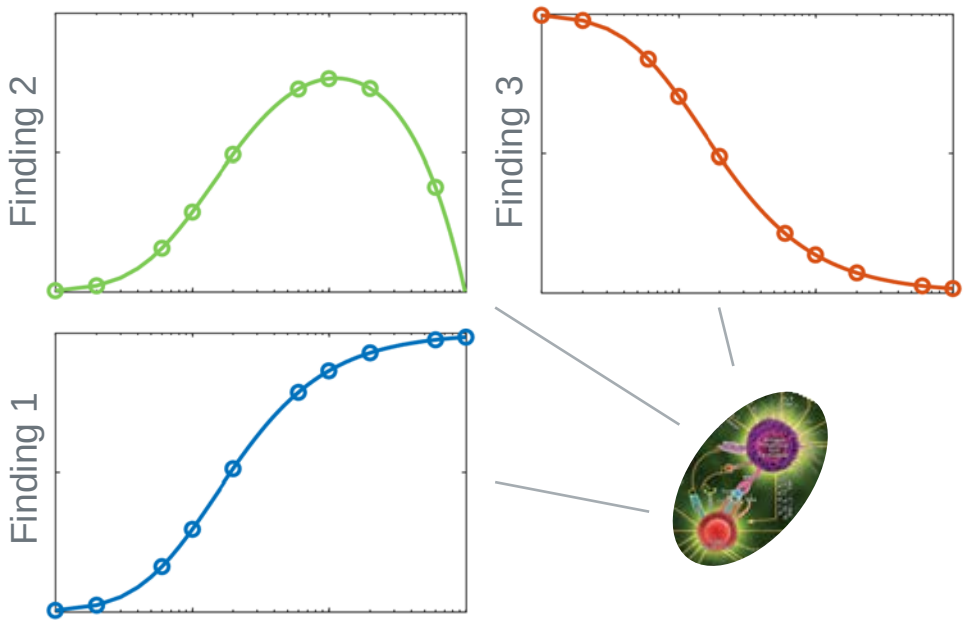


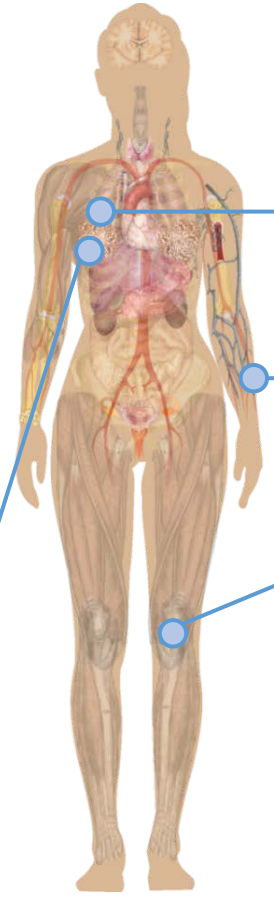
- **Q**uantitative **S**ystems **P**harmacology (**QSP**) modeling is a framework that consistently integrates all available data sources to conclude on biological mechanisms and to predict pharmacology

Scope and Modular Approach

Systems Immunology Modelling: Modules

Medications
Rheuma

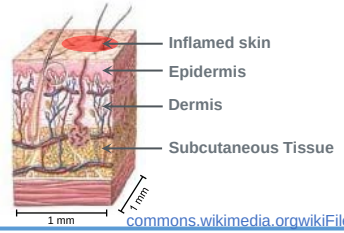
- Methotrexate
- Anti-TNF
- Anti IL-6R
- JAK inhibitors



Immune response module

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

Psoriatic skin module



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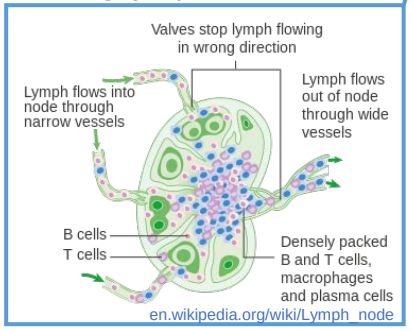
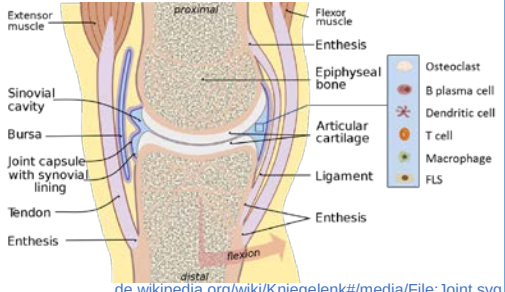
Draining lymph node module



en.wikipedia.org/wiki/Lymph_node

Arthritic knee joint module



de.wikipedia.org/wiki/Kniegelenk#/media/File:Joint.svg

Readouts:
Disease Scores

- Viral load
- Bacterial load
- Resp. time
- SPASI score
- Barrier funct.
- ACR score
- DAS28-CRP
- Cartilage destruct.
- Bone metabolism

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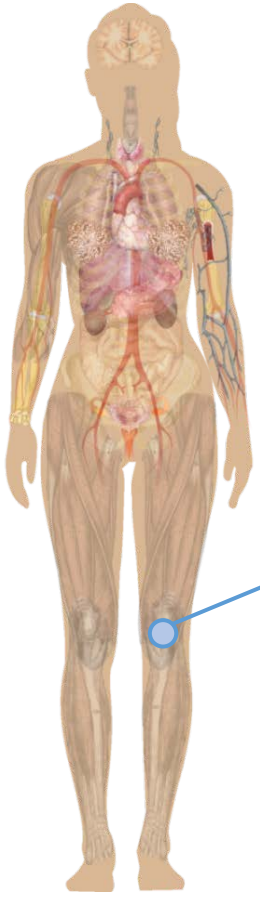
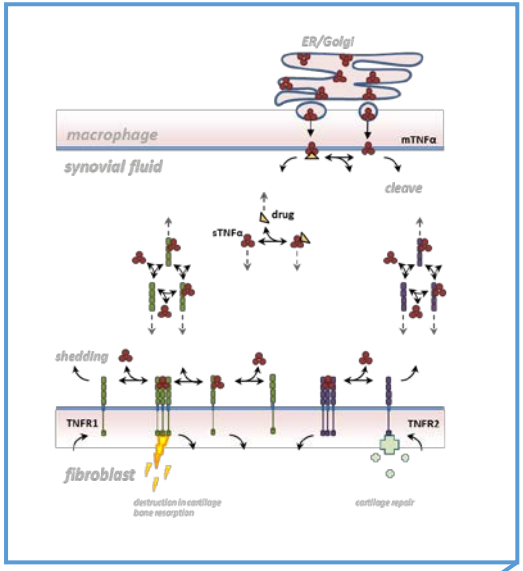
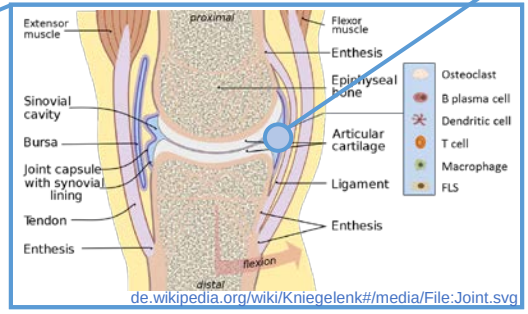
Systems Immunology Modelling: Modules

Medications

Rheuma	Psoriasis
Methotrexate	Methotrexate
Anti-TNF	Anti-TNF
Anti IL-6R	Anti-IL23
JAK inhibitors	Anti-IL17







de.wikipedia.org/wiki/Kniegelenk#/media/File:Joint.svg

Cells

- Macrophage
- Th1
- FLS
- Treg

Mediators

- TNF
- IFNγ
- CXCL13
- MMP1

Disease Scores

- ACR score
- DAS28-CRP
- Cartilage destruct.
- Bone metabolism

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Implementing Mechanistic Details

Systems Immunology Modelling: Modules

Legend:

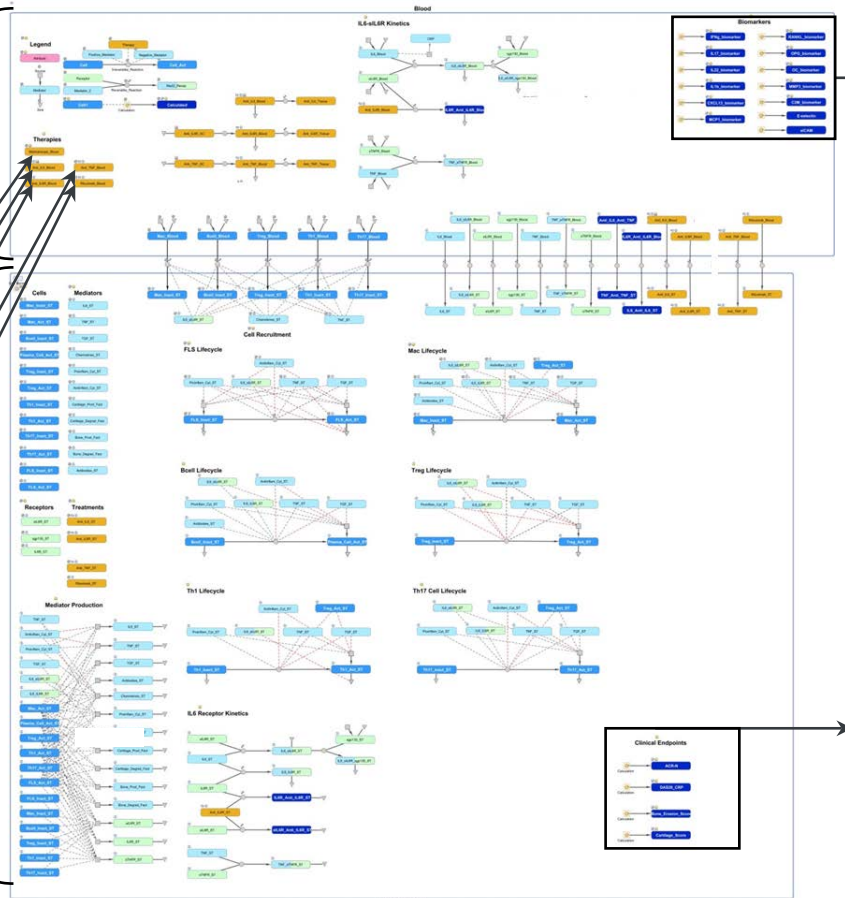
- Therapies
- Cell
- Mediator
- Receptor
- Biomarker

Therapies:

- Methotrexate
- Sirukumab
- Sarilumab
- Anti-TNF
- Baricitinib

Blood

Synovium



Output:

- IFN-γ
- IL17
- IL22
- IL-1β
- CXCL-13
- MCP-1
- RANKL
- OPG
- OC
- MMP3
- C2M
- E-selectin
- sICAM
- CRP
- ACR-N
- DAS28 -CRP
- Bone erosion
- Cartilage dest

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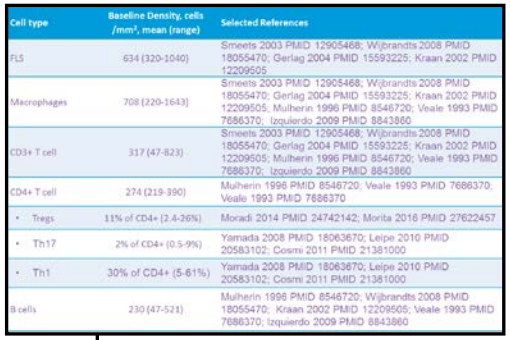
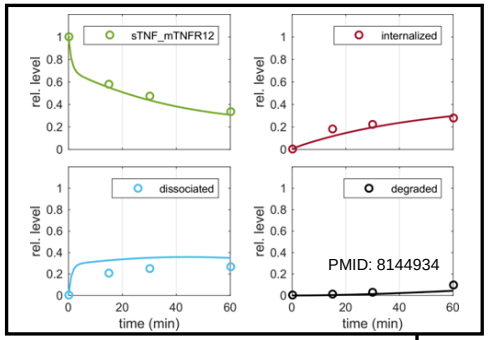
Model scope: Molecular mechanistic links

Cell distribution

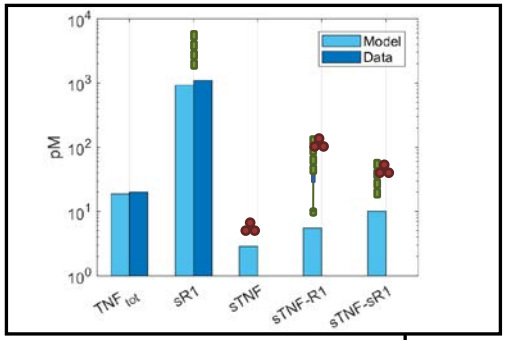


Cell type	Baseline Density, cells /mm², mean (range)	Selected References
FLS	634 (320-1040)	Smeets 2003 PMID 12905468; Wijbrandts 2008 PMID 18055470; Gerlag 2004 PMID 15593225; Kraan 2002 PMID 12209505
Macrophages	708 (220-1643)	Smeets 2003 PMID 12905468; Wijbrandts 2008 PMID 18055470; Gerlag 2004 PMID 15593225; Kraan 2002 PMID 12209505; Mulherin 1996 PMID 8546720; Veale 1993 PMID 7686370; Izquierdo 2009 PMID 8843860
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 8843860
CD4+ T cell	274 (219-390)	Mulherin 1996 PMID 8546720; Veale 1993 PMID 7686370; Veale 1993 PMID 7686370
• Tregs	11% of CD4+ (2.4-26%)	Moradi 2014 PMID 24742142; Morita 2016 PMID 27622457
• Th17	2% of CD4+ (0.5-9%)	Yamada 2008 PMID 18063670; Leipe 2010 PMID 20583102; Cosmi 2011 PMID 21381000
• Th1	30% of CD4+ (5-61%)	Yamada 2008 PMID 18063670; Leipe 2010 PMID 20583102; Cosmi 2011 PMID 21381000
B cells	230 (47-521)	Mulherin 1996 PMID 8546720; Wijbrandts 2008 PMID 18055470; Kraan 2002 PMID 12209505; Veale 1993 PMID 7686370; Izquierdo 2009 PMID 8843860

Dynamical binding data



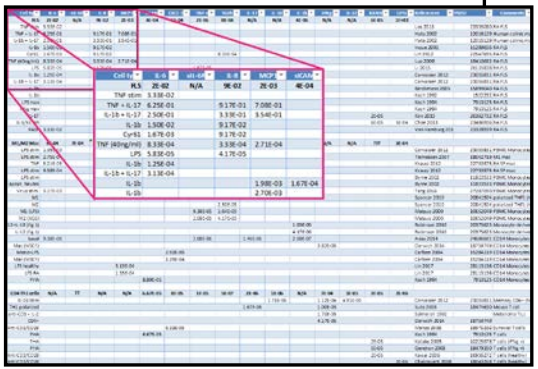
Cellular response



Model scope

Cell → Mediator → Effect

Cell-specific production rates



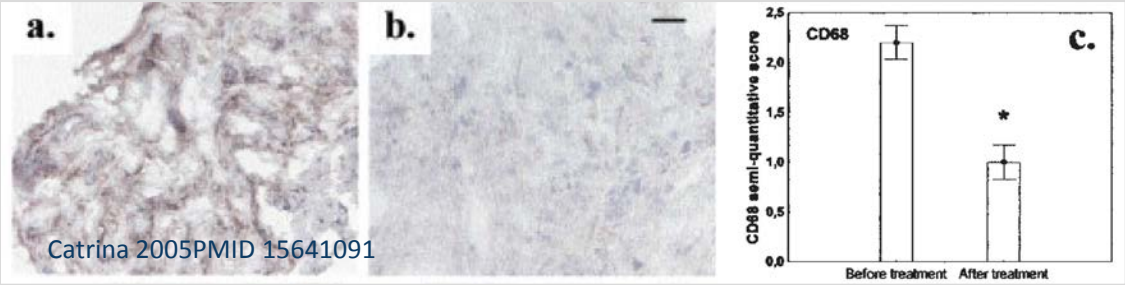
Mediator levels

Reference	PMID	Description	Tissue	Disease status	Assay	Amount	SD-range	Units	Amount in Model Units	Model Units	Figure or Table
Wright 2012	22179732	synovial TNFa	synovial fluid	RA	Luminex	20.0	0-4000	pg/ml	0.39	pM	Fig. 1
Perry 2010	10.2217/ijr.10.51	synovial TNFa	synovial fluid	RA	ELISA	15.2	12-18.9	pg/ml	0.30	pM	Table 3
Andres Cerezo 2017	28448508	synovial TNFa	synovial fluid	RA	ELISA	21.0	≥25	pg/ml	0.41	pM	Sup Table 2
ig 2010	20439268	synovial TNFa	synovial fluid	RA	ELISA	65.0	45-170	pg/ml	1.26	pM	Fig. 5
ig 2010	20439268	synovial TNFa	synovial fluid	RA	ELISA	10.0	5-30	pg/ml	0.19	pM	Fig. 5
Raza 2005	15987480	synovial TNFa	synovial fluid	RA	Luminex	10.0	0-100	pg/ml	0.19	pM	Fig. 2
Cañete 2000	10733472	synovial TNFa	synovial fluid	RA	ELISA	62.0	≥57	pg/ml	1.20	pM	Table 3
Horiuchi 1999	10670749	synovial TNFa	synovial fluid	RA	ELISA	19.5	± 15.1	pg/ml	0.38	pM	Table 1
Horiuchi 1999	10670749	synovial TNFa	synovial fluid	OA	ELISA	4.8	± 3.0	pg/ml	0.09	pM	Table 1
Robbens 2000	11125512	synovial TNFa	synovial fluid	RA	ELISA	101.0	58-160	pg/ml	1.96	pM	Table 1
Laffassio 1998	9743215	synovial TNFa	synovial fluid	RA	ELISA	100.7	39.9–254.1	pg/ml	1.96	pM	Table 3
Westacott 1990	1709873	synovial TNFa	synovial fluid	RA	RIA	390.0	± 40	pg/ml	7.57	pM	Table 2
Feldmann 1990	1709872	synovial TNFa	synovial fluid	RA	Biol. Assay	4,000.0	0-20 ng/ml	pg/ml	77.67	pM	Fig. 1
							Median	62.00	pg/ml Median	1.20	pM
Wright 2012	22179732	blood TNFa	plasma	RA	Luminex	5	0-420	pg/ml	0.10	pM	Text
Perry 2010	10.2217/ijr.10.51	blood TNFa	plasma	RA	ELISA	94	22-544	pg/ml	1.83	pM	Table 1
Kyrmanescu 2005	16286991	blood TNFa	serum	RA	ELISA	202	± 53	pg/ml	3.92	pM	Table 1
Panicourt 1993	8457224	blood TNFa	serum	RA	ELISA	31.6	± 21.3	pg/ml	0.61	pM	Table 1
Chen 2011	21801431	blood TNFa	serum	RA	ELISA	22	± 2.4	pg/ml	0.43	pM	Table 2
Herrera 2001	11406520	blood TNFa	serum	RA	ELISA	41	± 2.4	pg/ml	0.80	pM	Text
Feldmann 1990	1709872	blood TNFa	serum	RA	Biol. Assay	6000	1-20 ng/ml	pg/ml	116.50	pM	Fig. 1
Panayi 1992	1358037	blood TNFa	serum	RA	Biol. Assay	800	100-8000	pg/ml	15.53	pM	Fig. 1
							Median	31.60	pg/ml Median	0.61	pM

Simulating Clinical Study Data

Serial biopsies from RA-patients

Example: Anti-TNF treatment

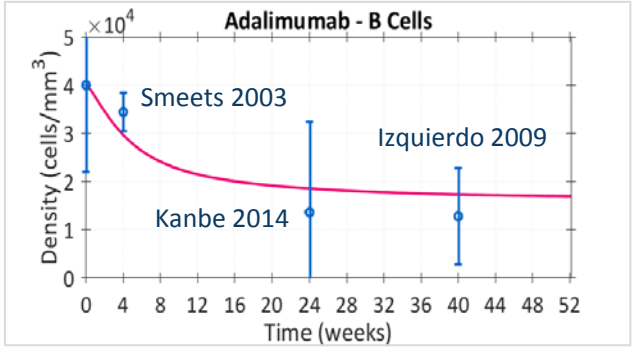


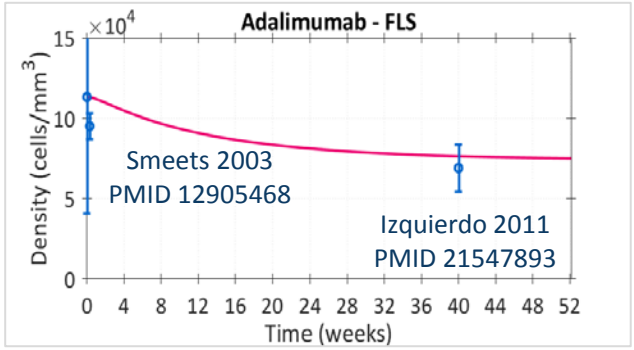
Catrina 2005PMID 15641091

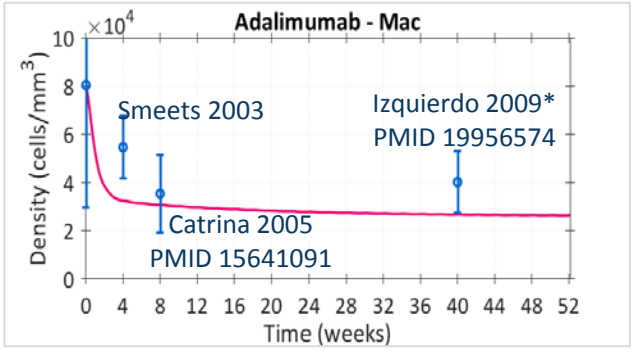
- Pink lines: simulation results
- Blue circles: mean ± SD (error bars) with corresponding reference

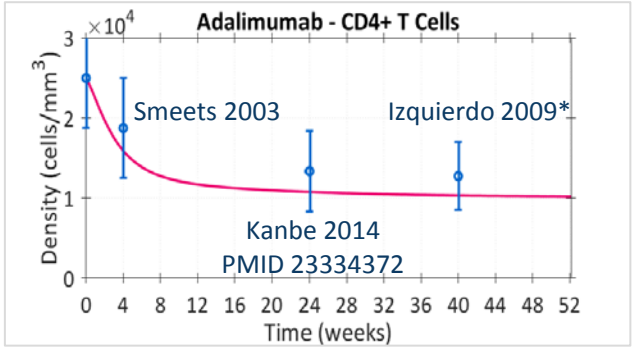
Table 3 Comparison of immunohistology of synovium by treatment of golimumab Kanbe 2014PMID 23334372

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









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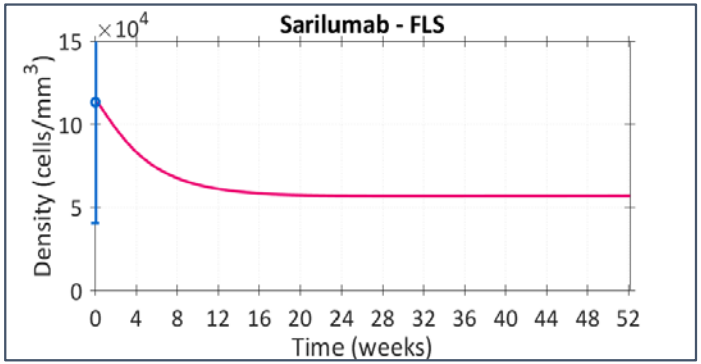
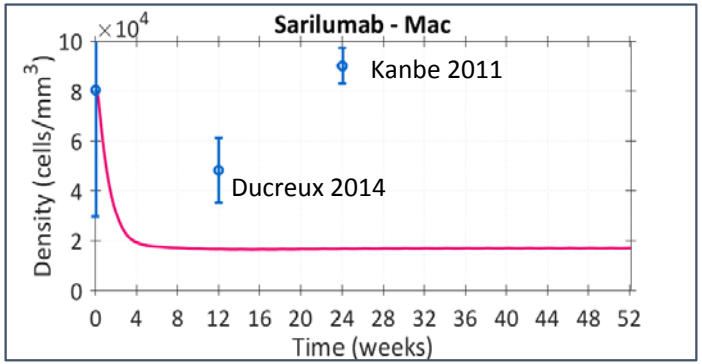
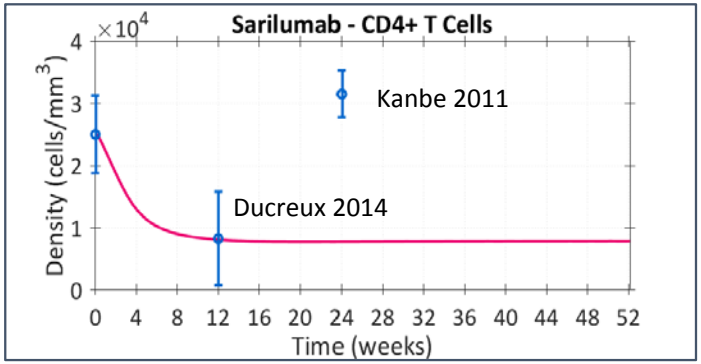
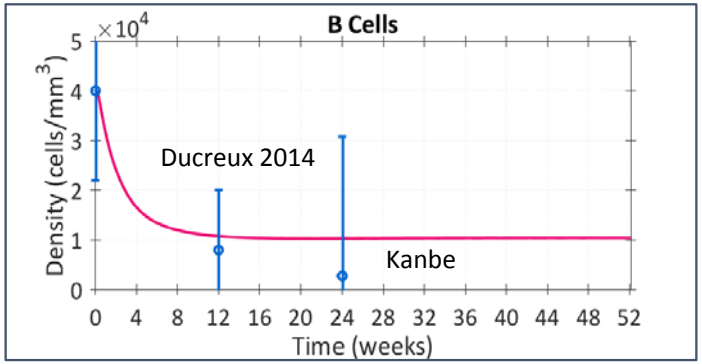
Serial biopsies from RA-patients

Example: Predicting cell density response to anti-IL6R treatment









- Blue circles: mean ± 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

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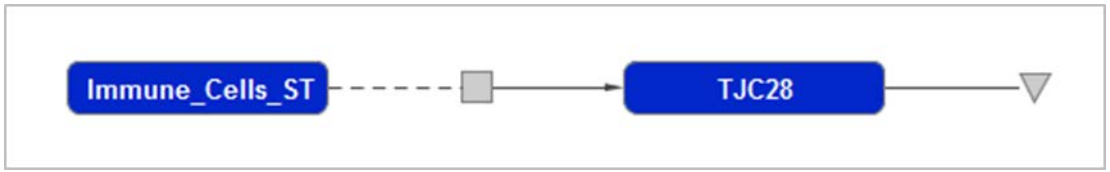
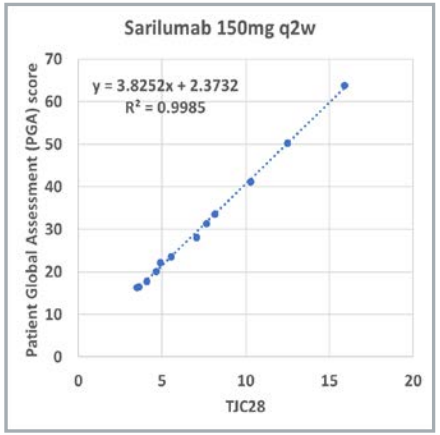
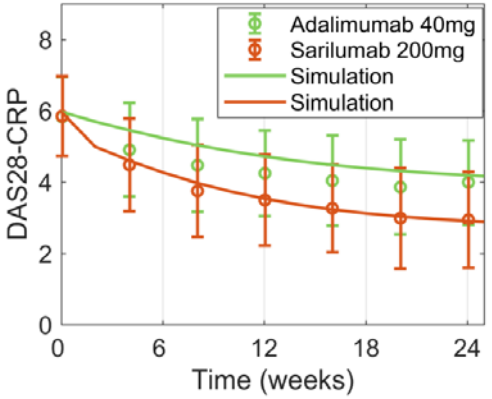
Translating the cellular level into disease activity

- 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







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Disease Subtypes

Simulating disease subtypes

Dennis 2014 PMID 25167216

Phenotype	Myeloid	Lymphoid	Low inflammation	Fibroid
Defining gene clusters (microarrays)	chemotaxis, TNFα and IL-1β production, phagocytosis, mononuclear cells proliferation	B and/or T lymphocyte activation and differentiation, Ig production, IL-17 signaling	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 biomarker baseline levels	• sICAM: high • CXCL13: low	• sICAM: low • CXCL13: high	• sICAM: low • CXCL13: med	• sICAM: low • CXCL13: low

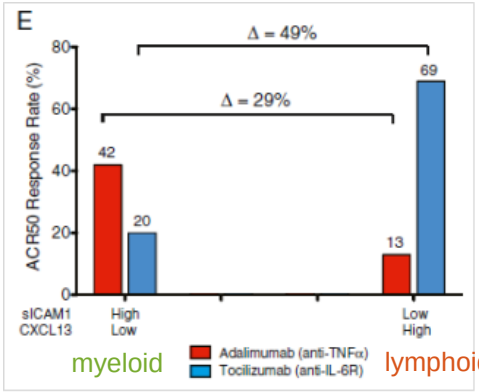
Identify preliminary disease subtypes for evaluation in QSP model

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

Simulating disease subtypes

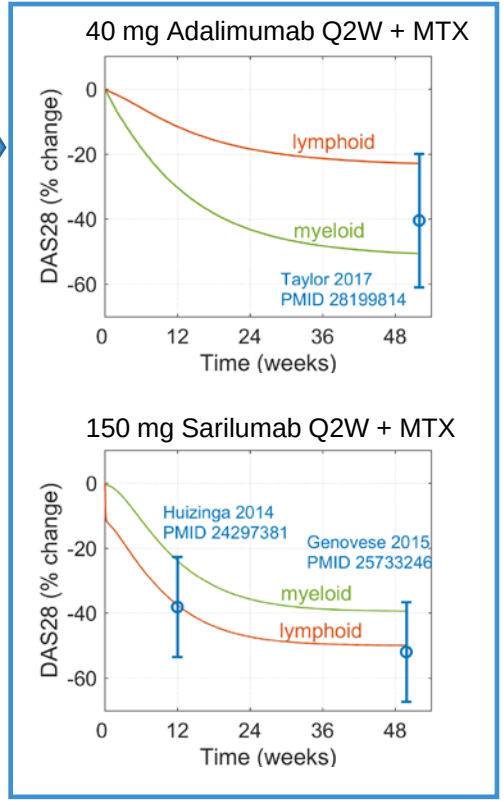
Hypothesis

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

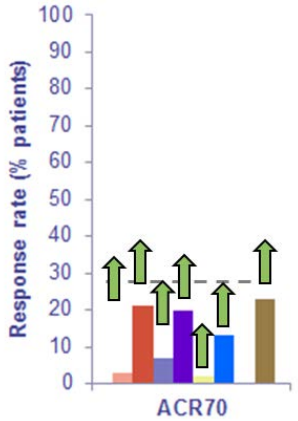


Dennis 2014 PMID 25167216

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

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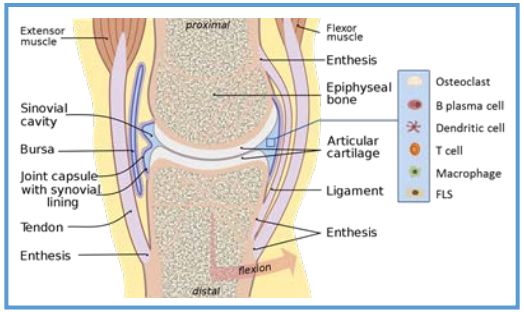
Summary and conclusion

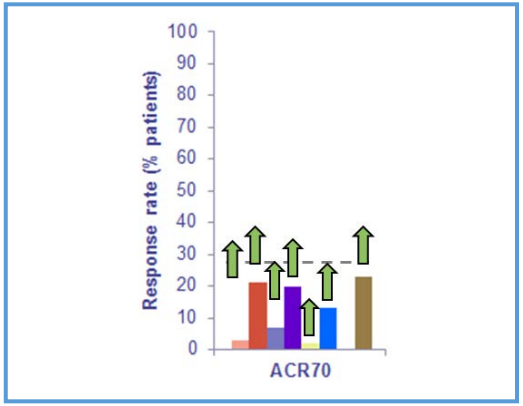
Core elements of QSP model development:

- **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



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Thank you for your attention!