

A photograph of a large, ornate library interior. In the foreground, a statue of a man in 18th-century attire stands on a pedestal, pointing towards the left. The background features a grand staircase with a decorative metal railing and a ceiling with a complex, repeating geometric pattern. Light enters through large windows with decorative panes.

"Cytokine signatures:
*Deconstructing immune mediated
inflammatory diseases?"*

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Veterinary and Life Sciences
Versus Arthritis Professor of Rheumatology
Muirhead Professor of Medicine
University of Glasgow, Scotland
Past-President, EULAR

Disclosures

- I have received research funding and honoraria from Abbvie, Amgen, BMS, Boehringer, Compugen, Causeway Therapeutics, Evelo, GSK, Cabaletta, Eli-Lilly, Pfizer, Novartis, Janssen, Roche, UCB
- I have research support from Versus Arthritis, MRC & Wellcome Trust



**PEOPLE
MAKE
GLASGOW**

Learning Objectives

- Explore the immunology and roles of targeted cytokines in therapeutics for rheumatic diseases

How do we break through the therapeutic ceiling in rheumatology...?

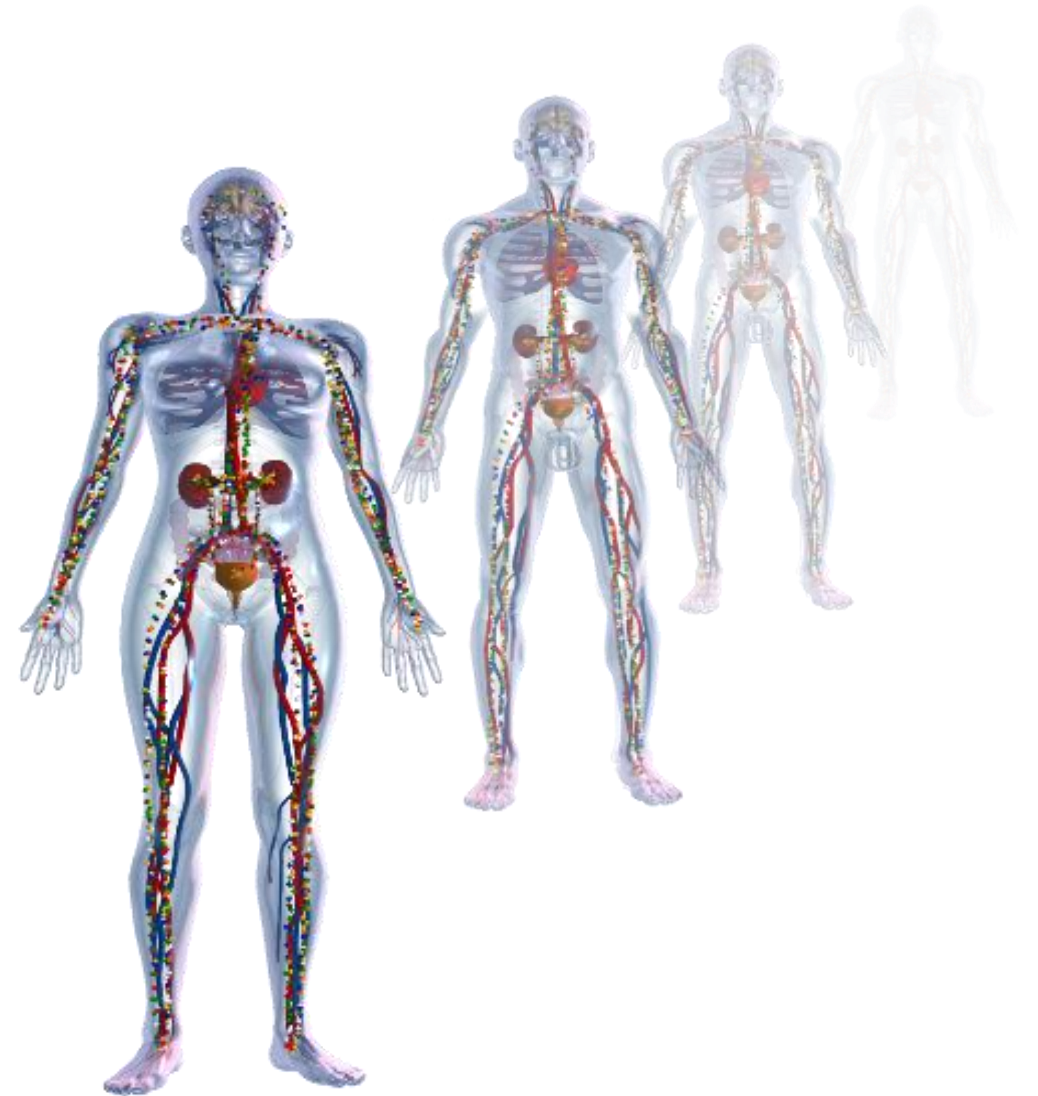


"Do you have a favourite saying?" asked the boy.
"Yes" said the mole.
"What is it?"
"If at first you don't succeed, have some cake."
"I see, does it work?"
"Every time"

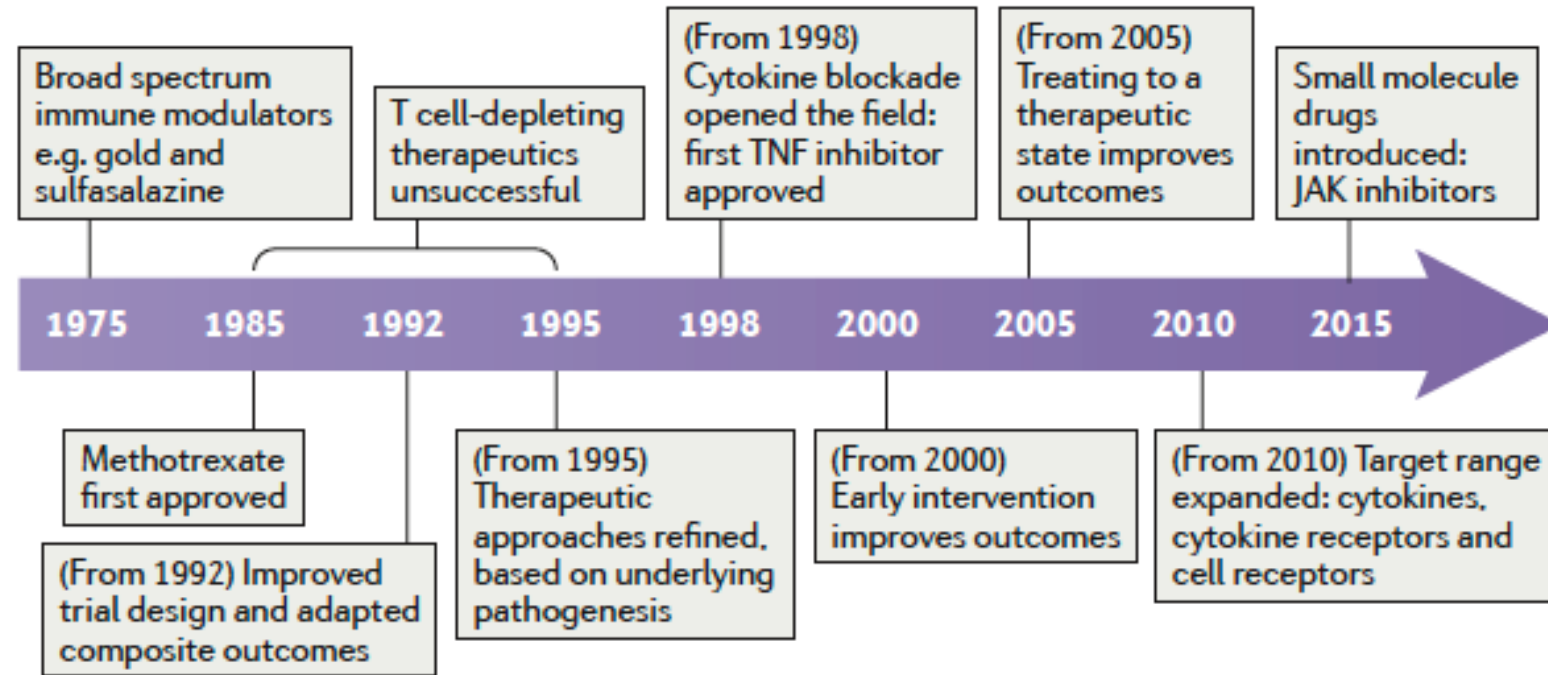


Harnessing cytokine signatures?

- Cytokine Therapeutics
- Cytokines – Drivers and Regulators?
- To a “cytokine centric” future?



Reflecting on therapeutic interventions...we shared our new medicines?

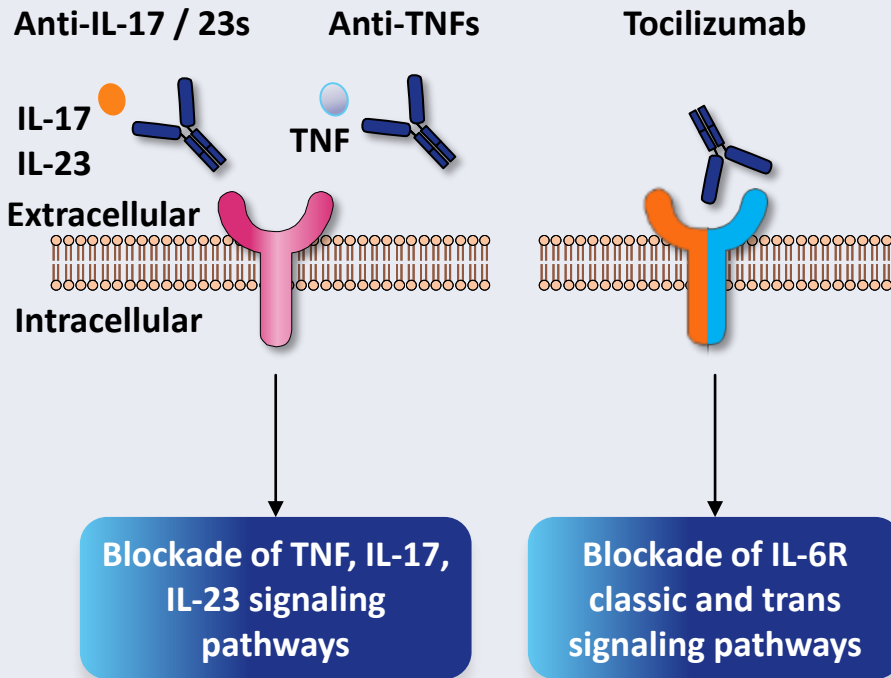


Biologics: molecular scalpels exquisitely target specific immune pathways

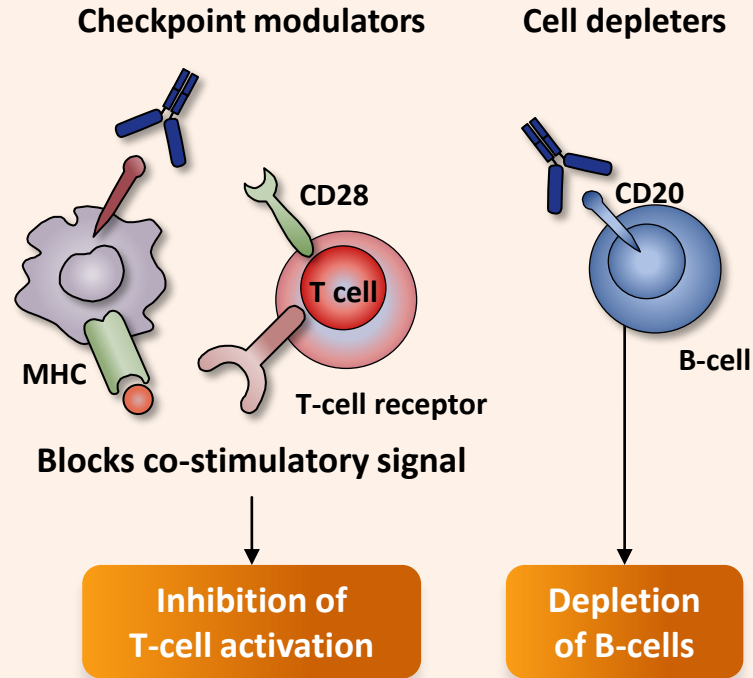


Cytokine therapeutics – from mono to poly targeting...

Cytokine-targeting biologics

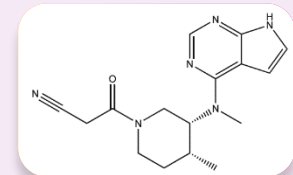


Cell-targeting biologics

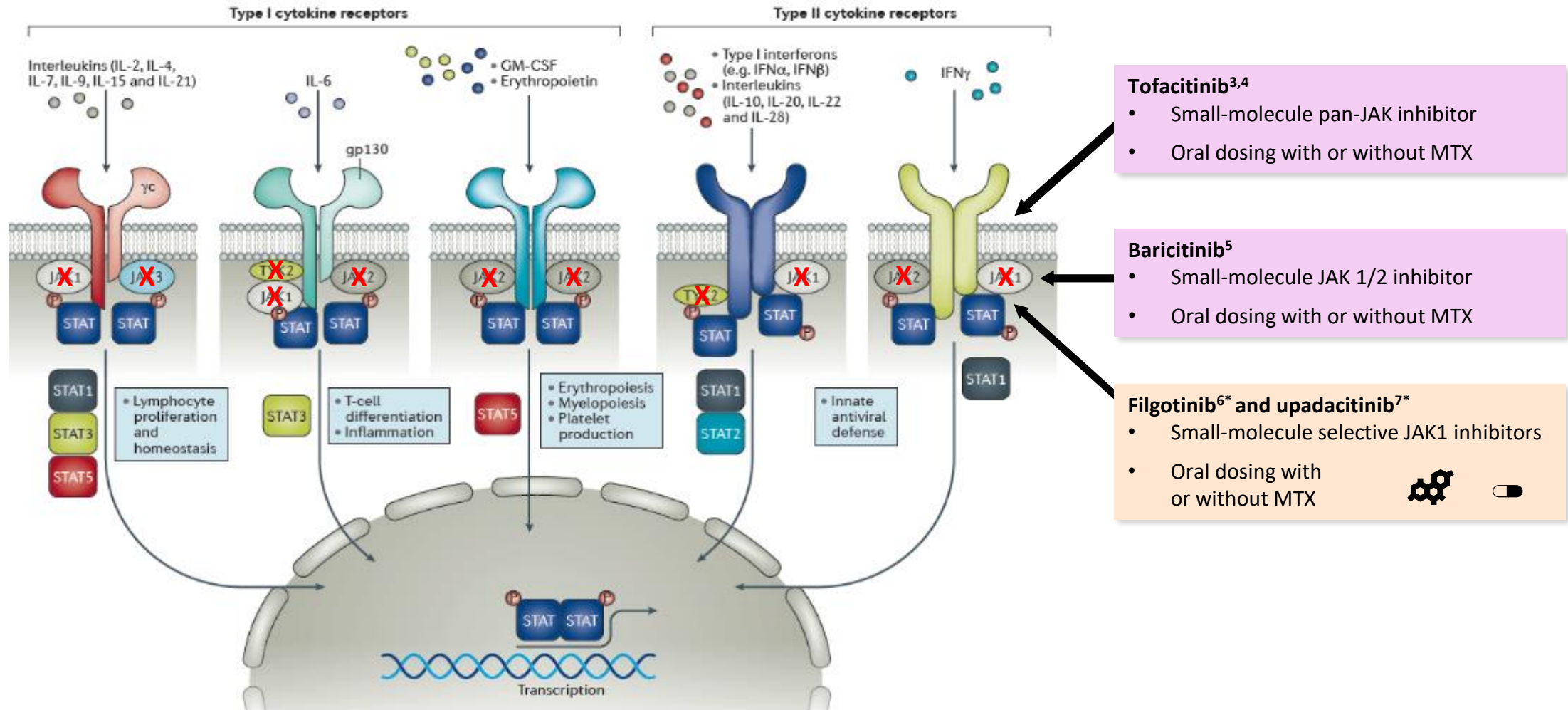


Cytokine-targeting SMEs

Tofacitinib, baricitinib, upaditinib...Tyk2i, BTK, RORg?

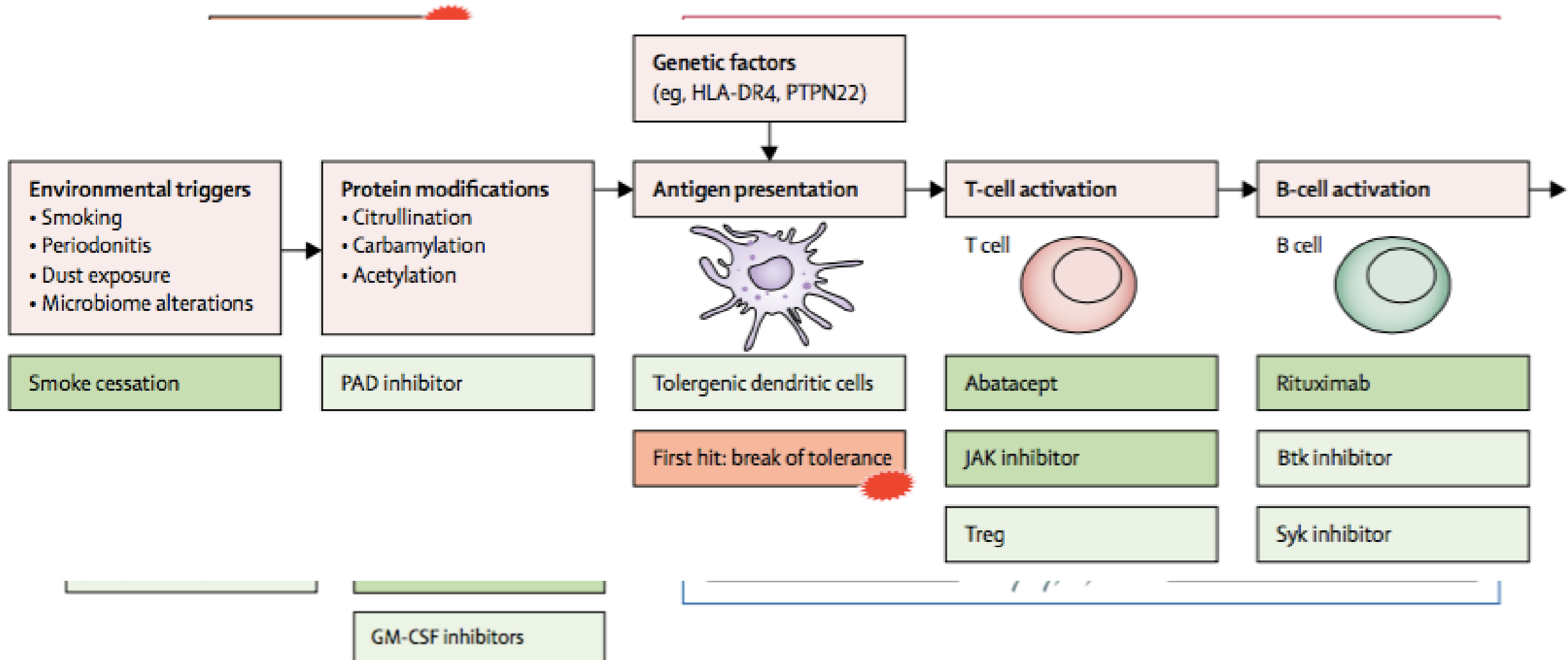


JAK family inhibitors – combination cytokine targeting

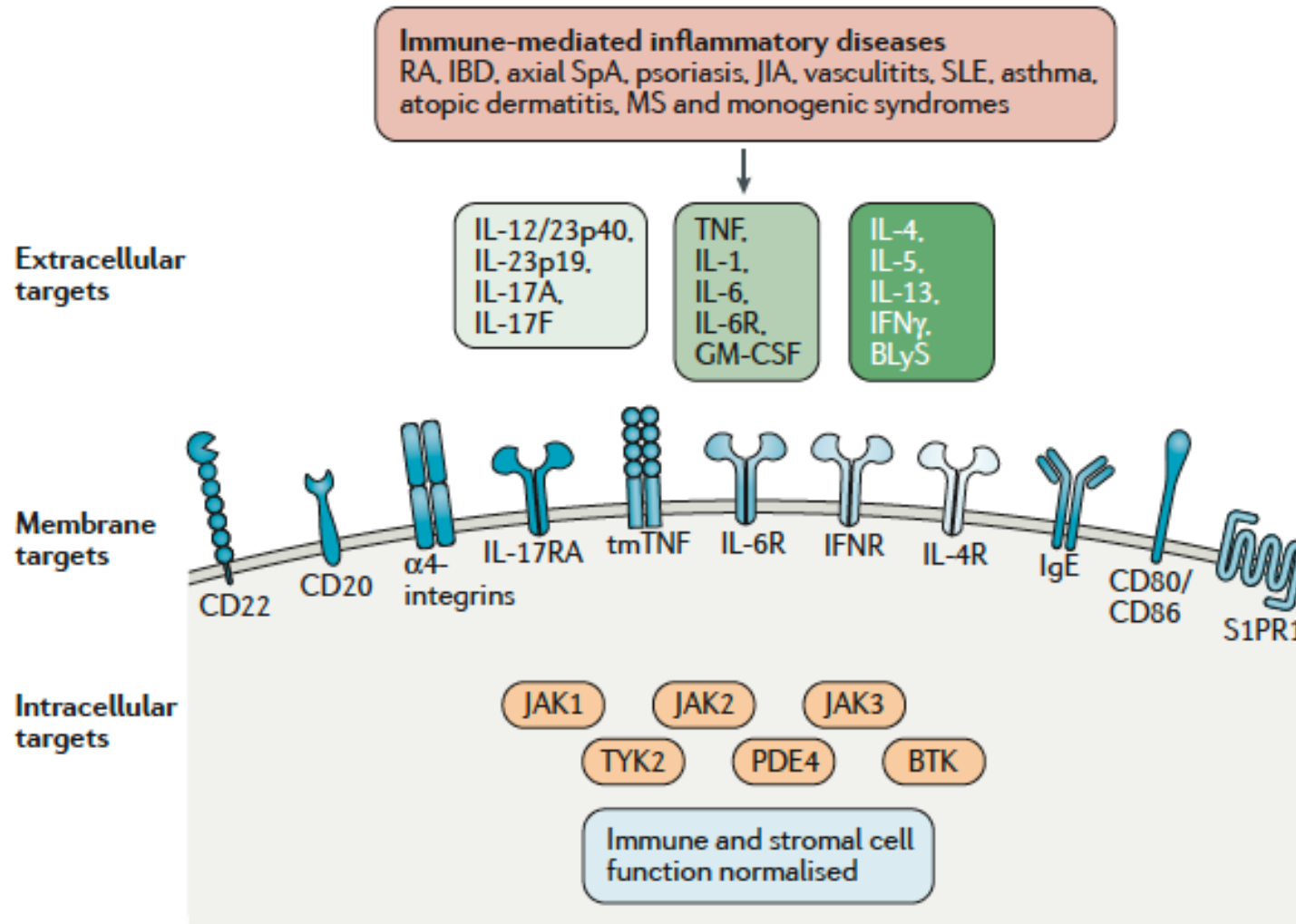


- Westhovens R et al. *Ann Rheum Dis* 2017;76:998–1008;
- Winthrop KL et al. *Nat Rev Rheumatol* 2017;13:234–43;
- Fleischmann R et al. *Lancet* 2017;390:457–66;
- Fleischmann R et al. *New Engl J Med* 2012;367:495–507;
- Fleischmann R et al. *Arthritis Rheumatol* 2017;69:506–17;
- Kavanaugh A et al. *Ann Rheum Dis* 2017;76:1009–19;
- Voss J. *Arthritis Rheumatol* 2013;65(Suppl10):2374.

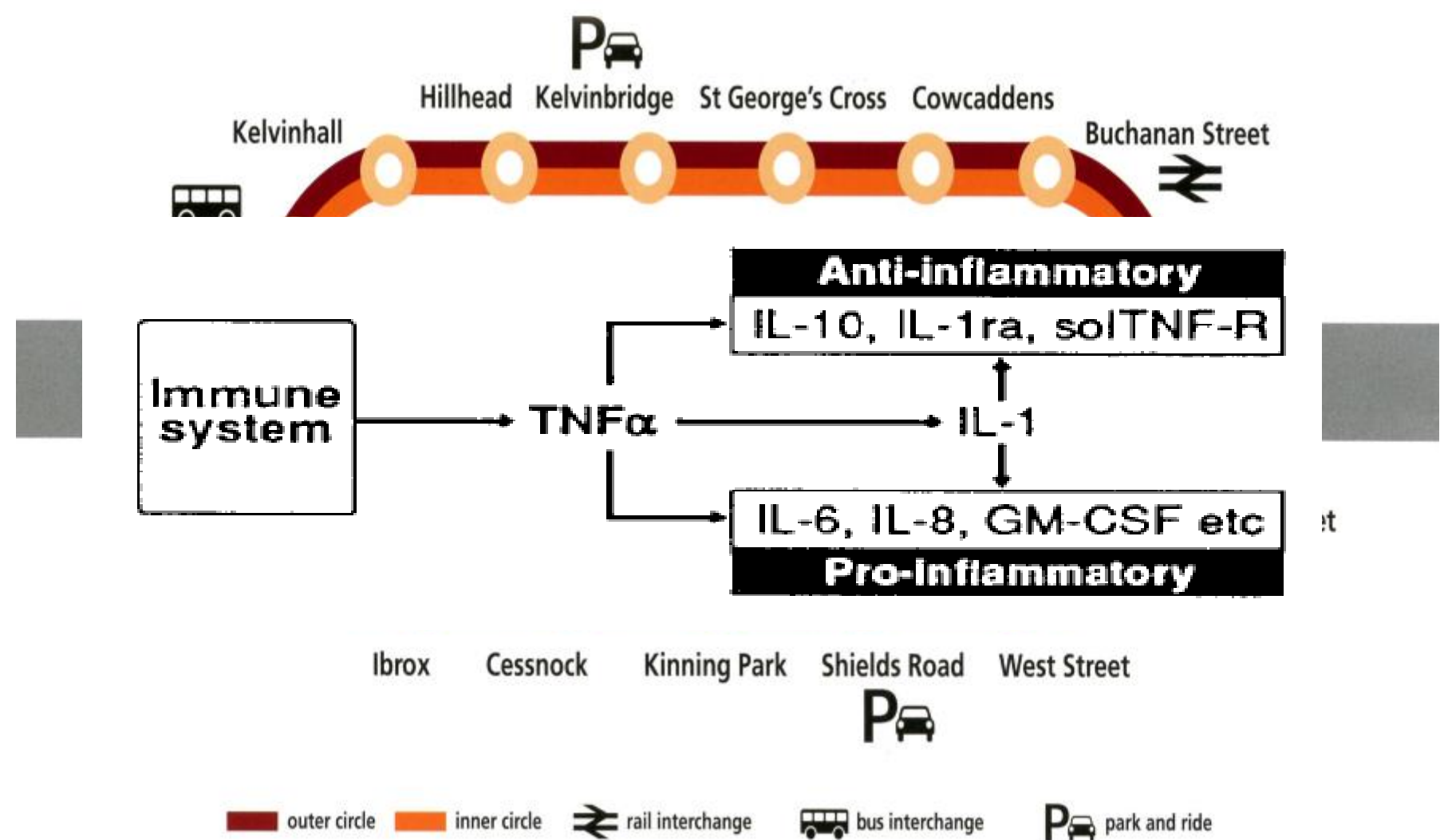
Pathogenetic lessons from cytokine therapies & vice versa?



However, we shared our new medicines, not always successfully!



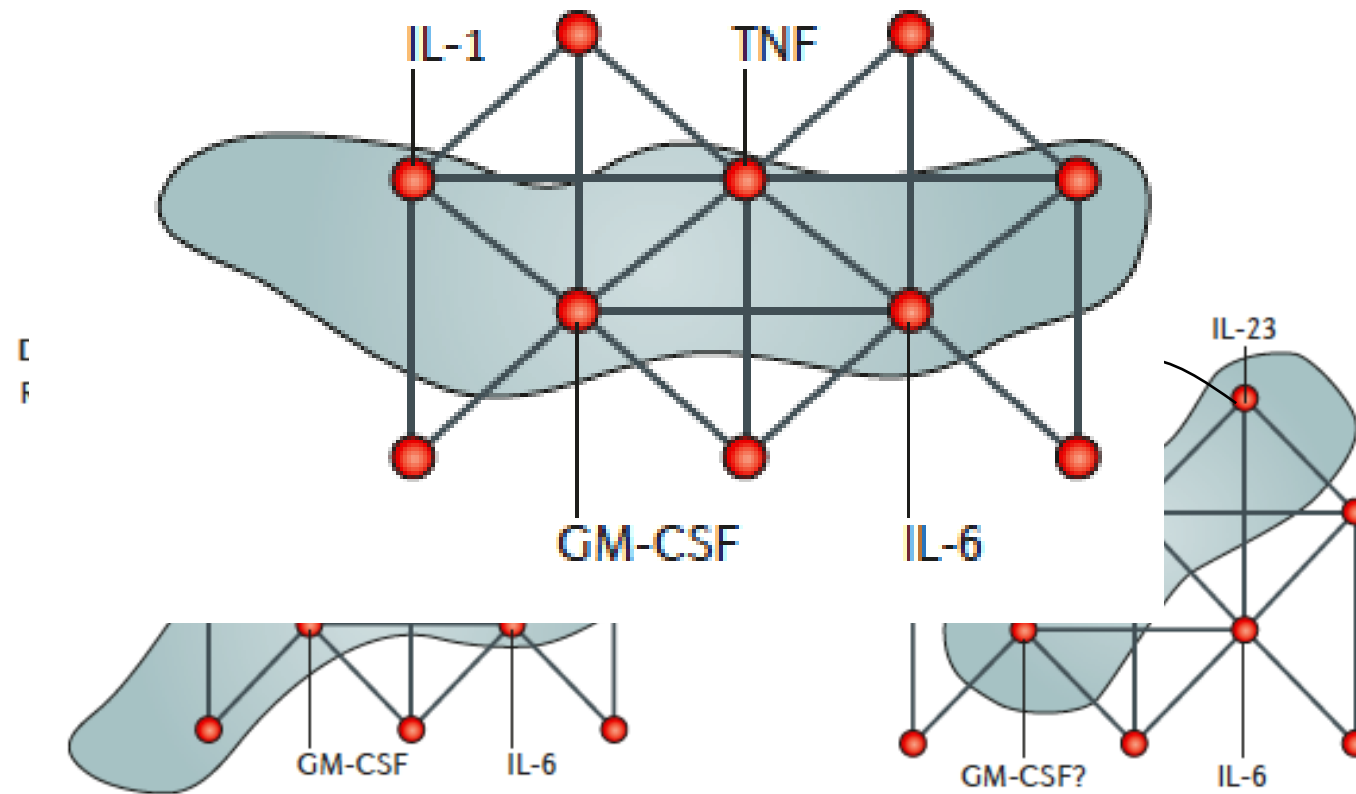
How do cytokine networks operate in IMIDs?



McInnes IB et al *Nature Rev Rheum* 2016;
see also Barabasi AL et al *Nature Rev Genetics* 2011: 12:56-67; Feldmann M et al *Cell* 1996 **85**:307

How do cytokine networks operate in IMIDs?

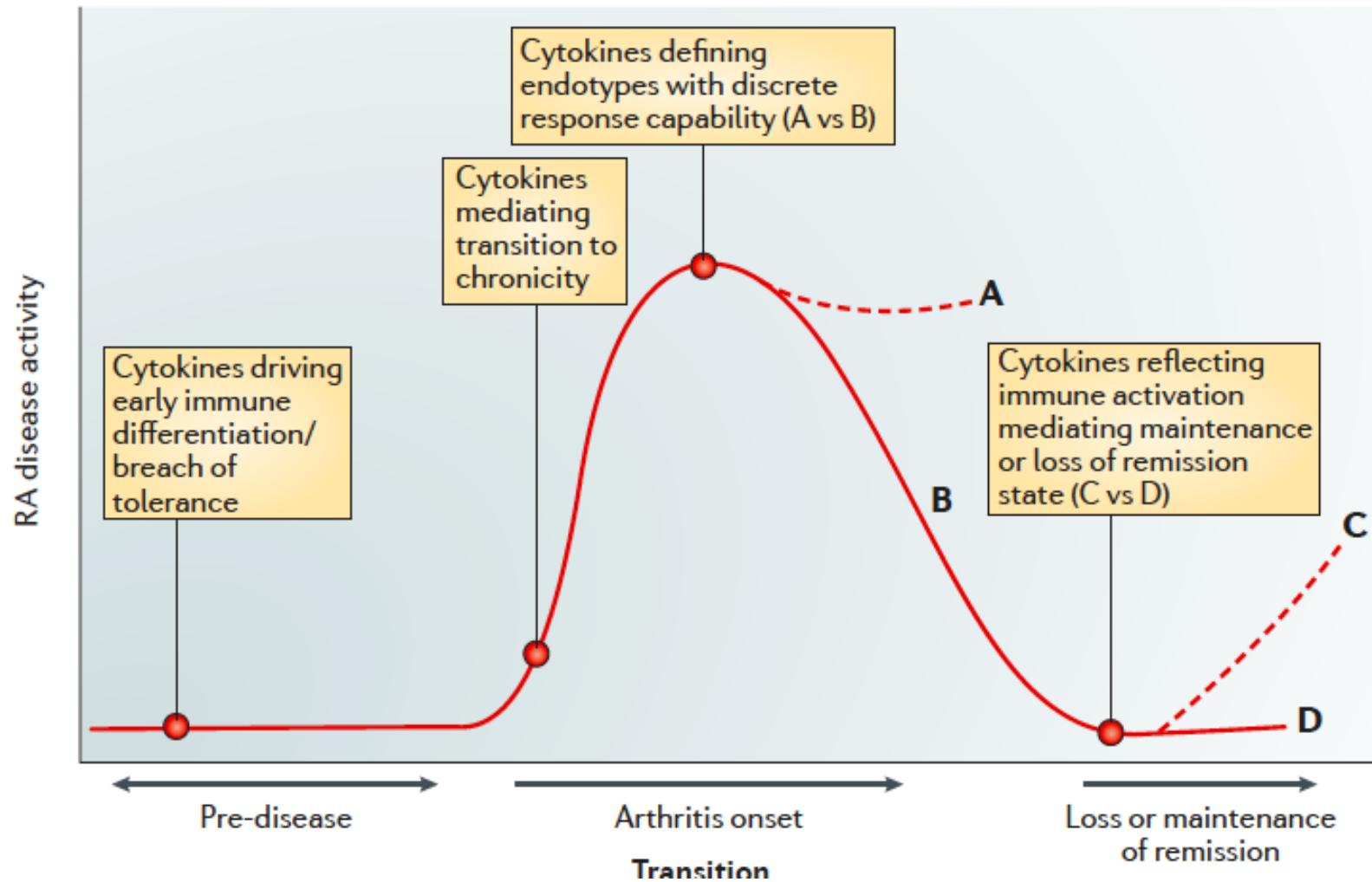
Defence functional module Gram-negative bacterial infection



Polling Question

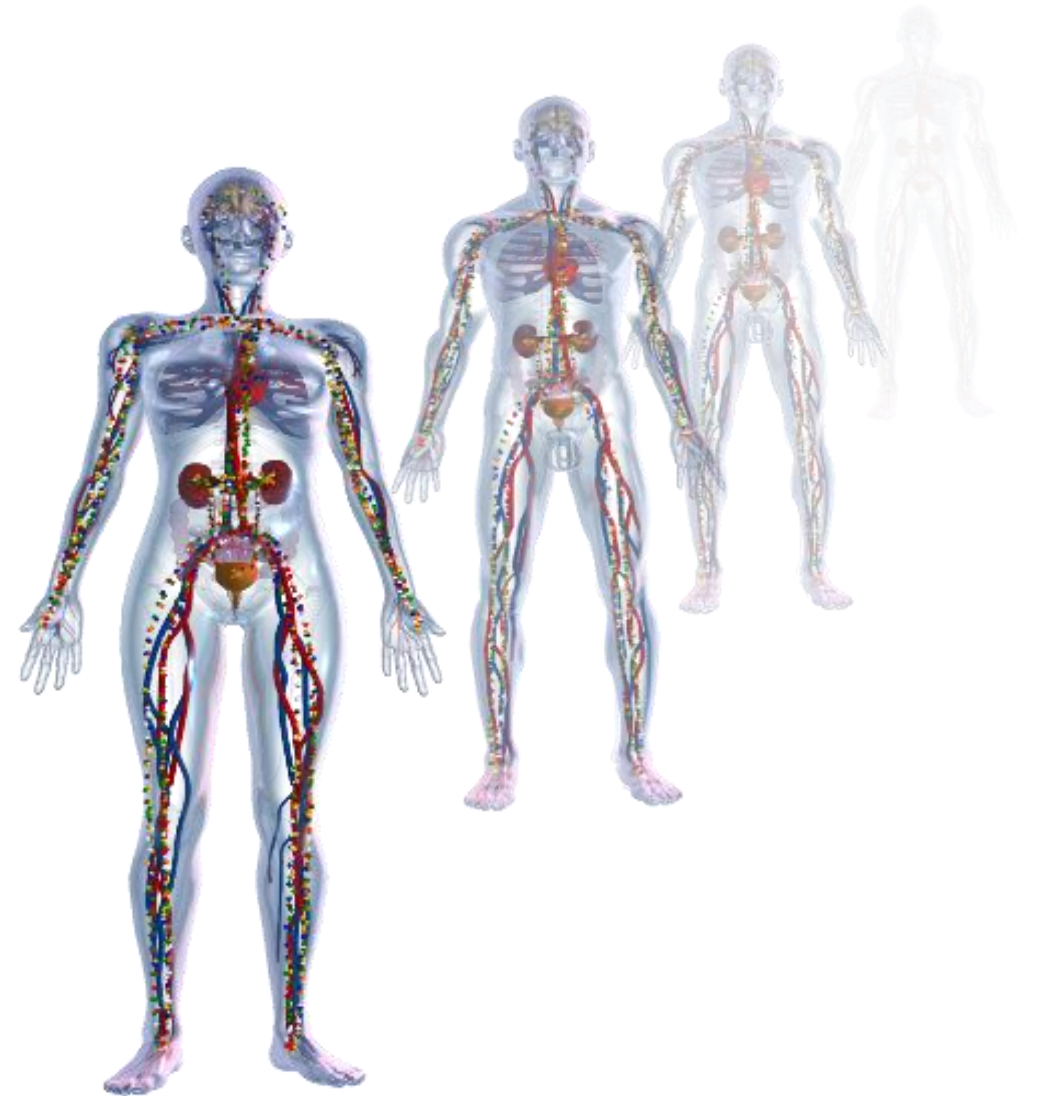
- Where are cytokines involved across the disease spectrum of RA?
 - A. Pre- disease
 - B. RA onset
 - C. Loss or maintenance of remission
 - D. All of the above

Over time does the immune system 'adapt' to the new scenario – why is arthritis chronic?

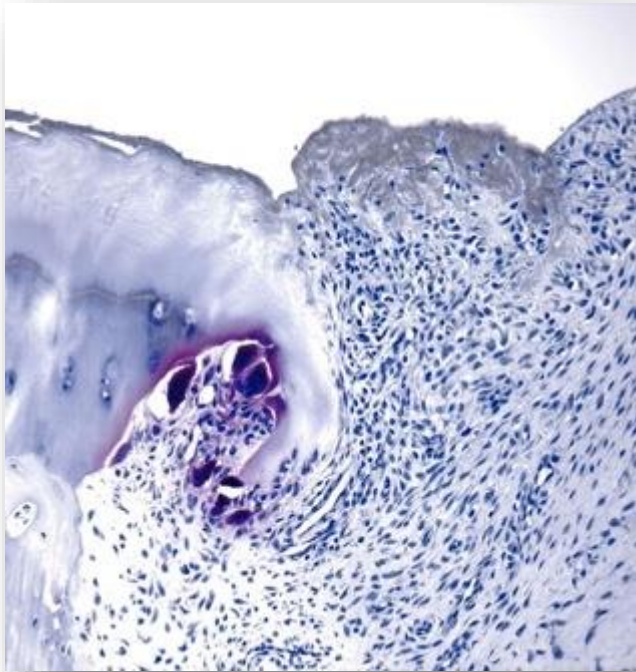


Harnessing cytokine signatures?

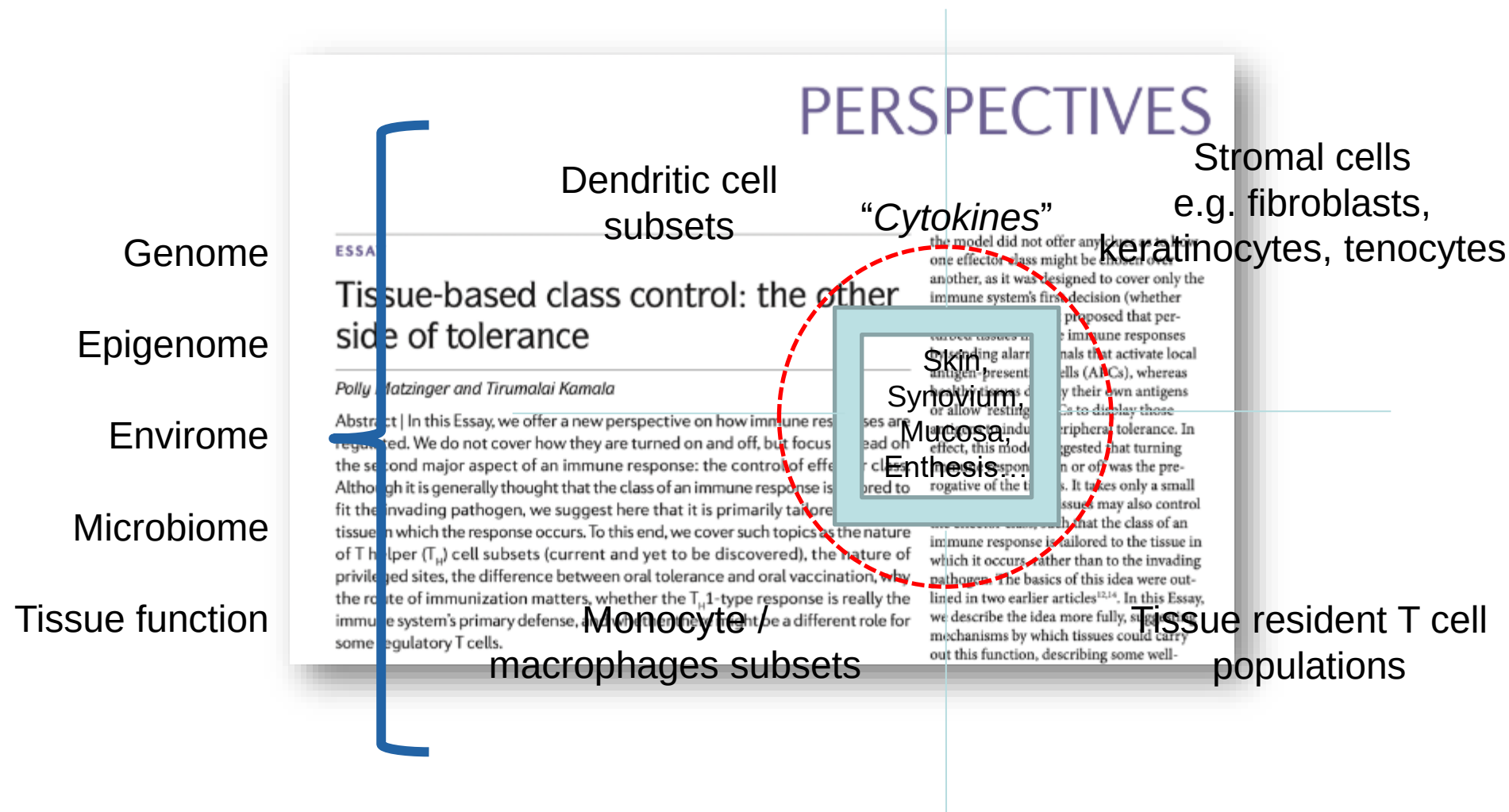
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- Cytokines – Drivers and Regulators?
- To a “cytokine centric” future?



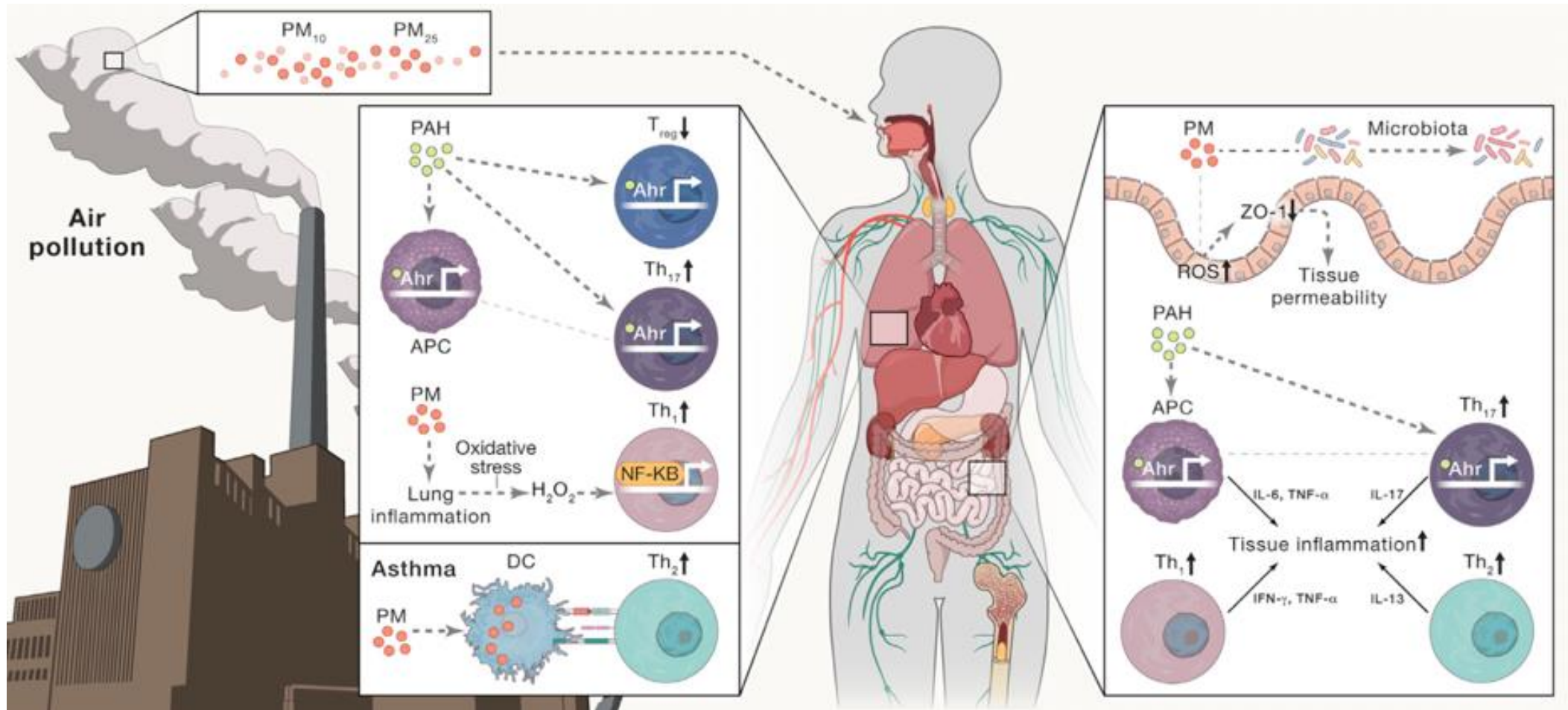
From organ pathology to accepting and resolving molecular complexity?



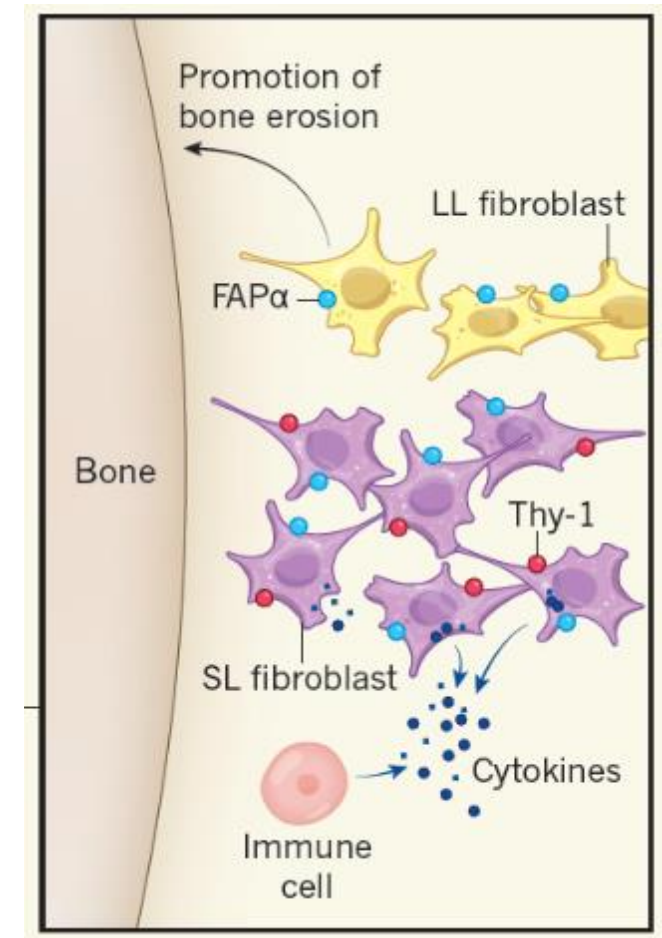
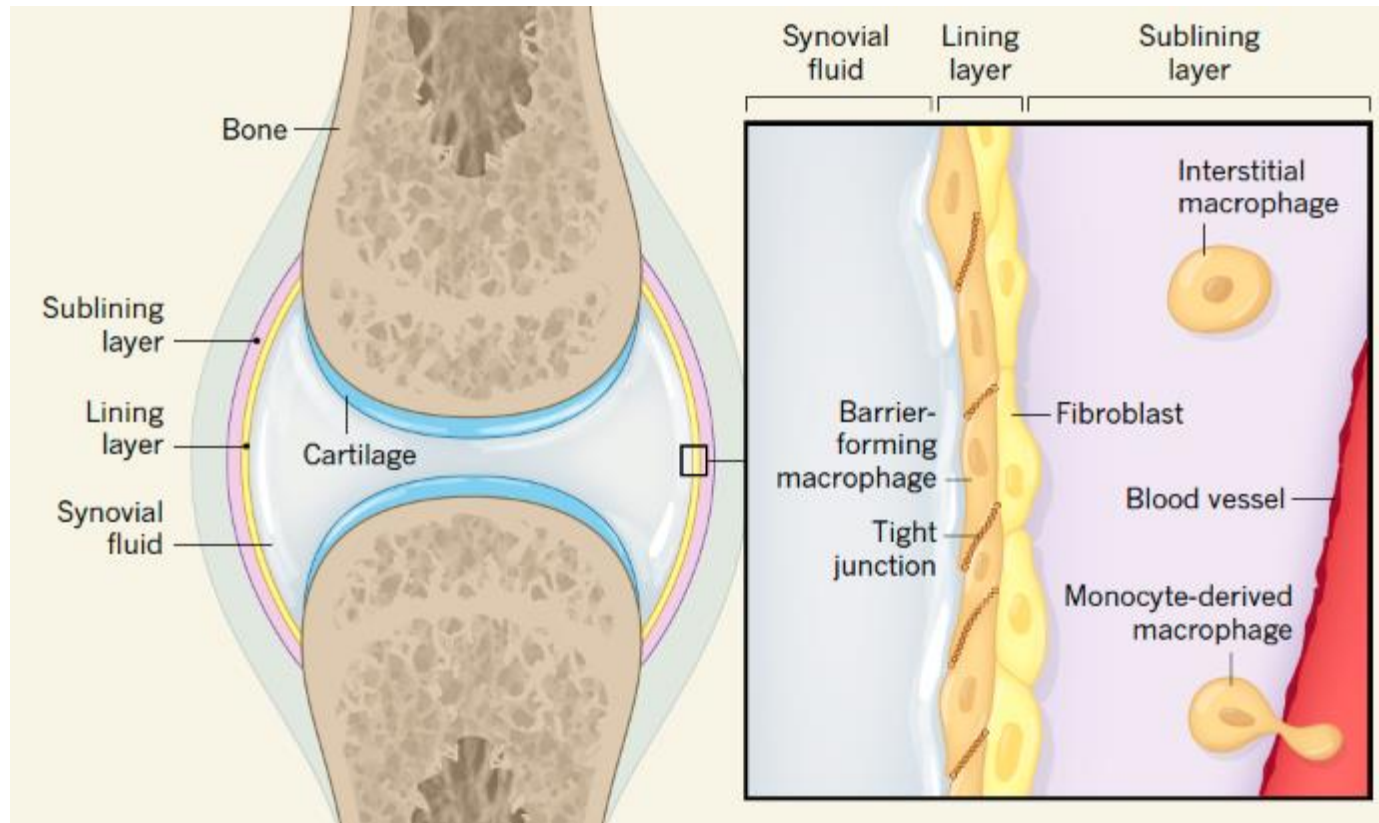
Does the tissue differentially define the pathology in disease?



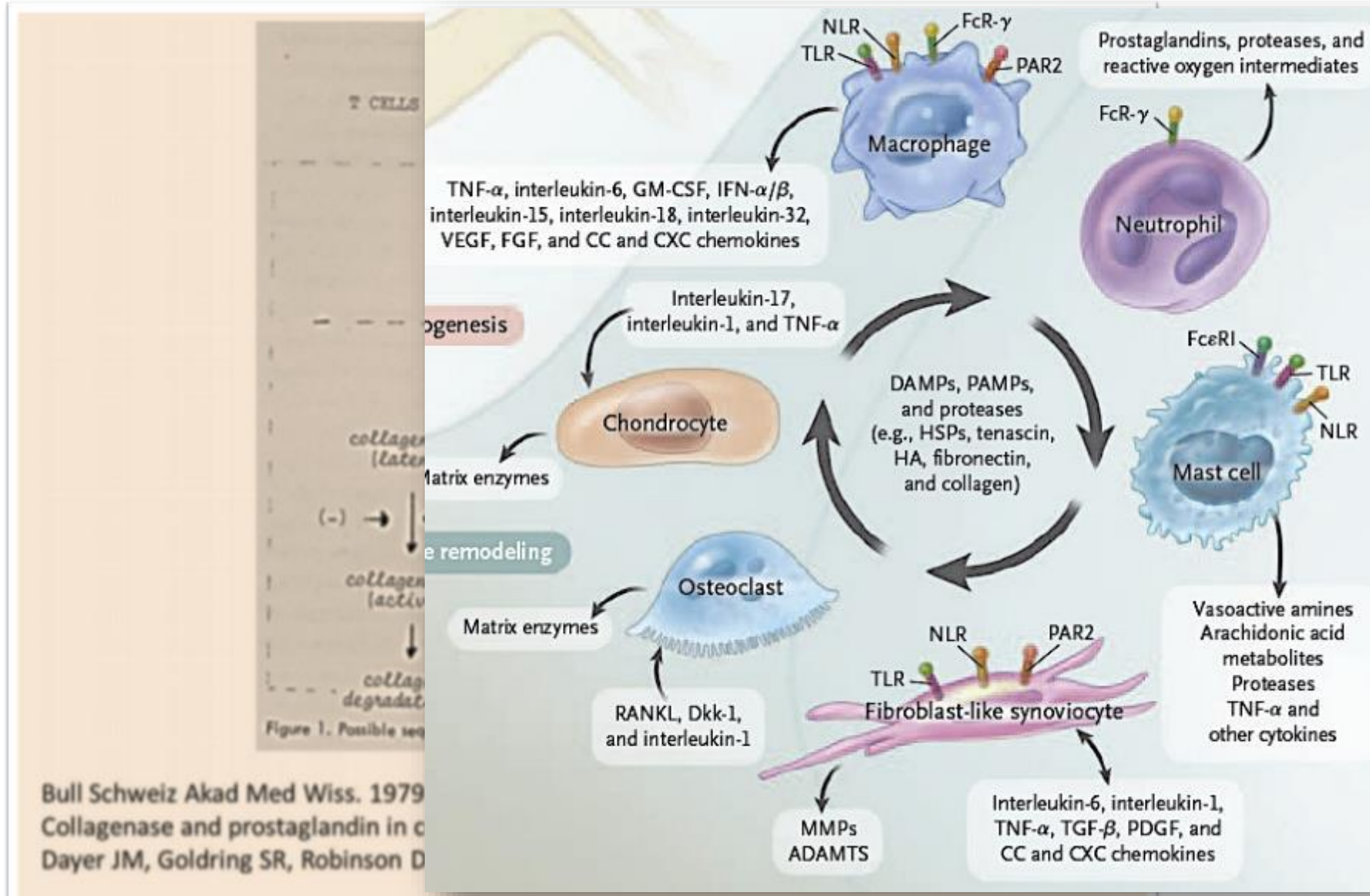
Consider the decisions tissues make in response to challenge?
– cytokine pathways are central



Reimagining the structure of the synovium – FLS and macrophages to the fore

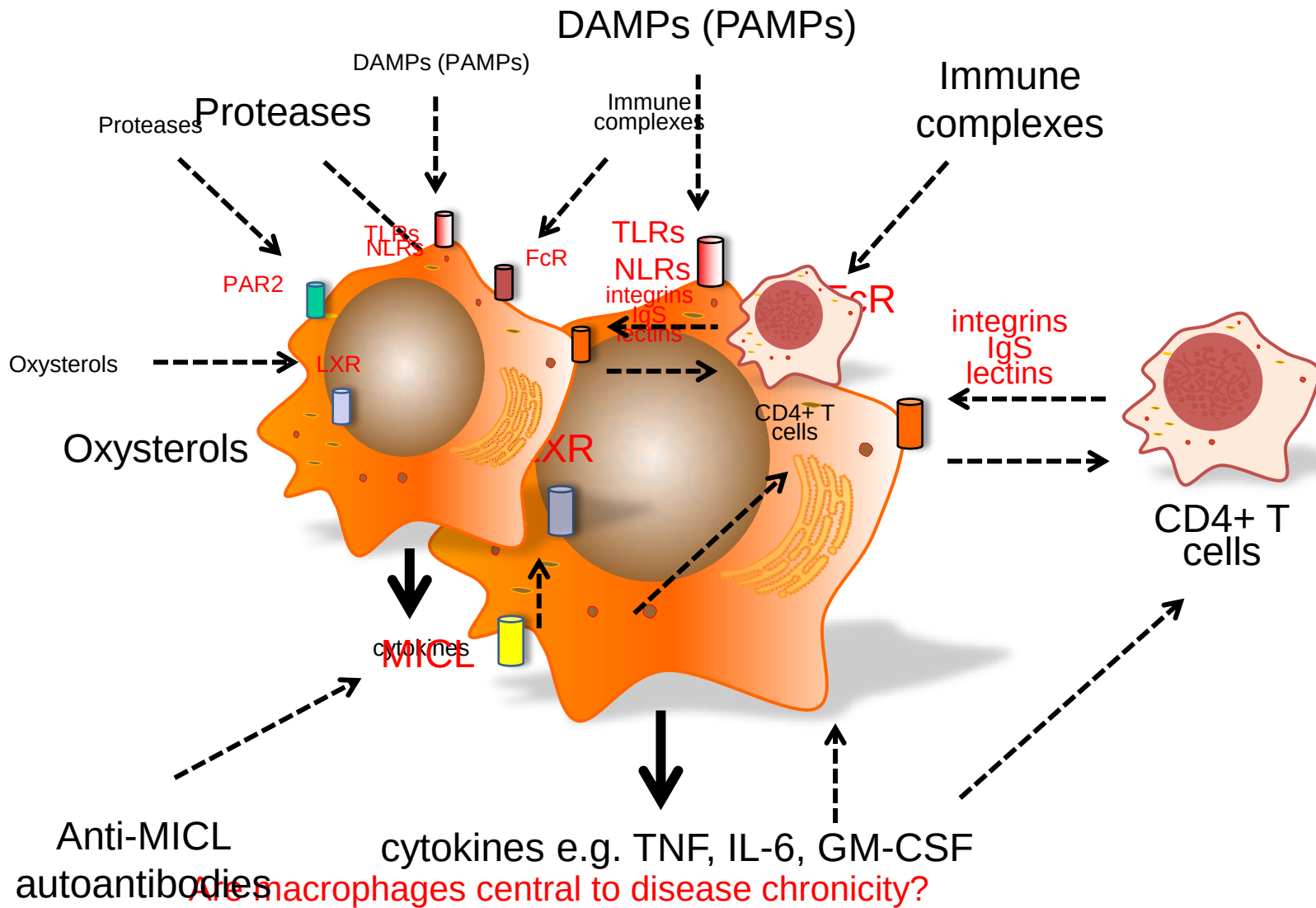


Using RA as an example – how does chronicity occur?

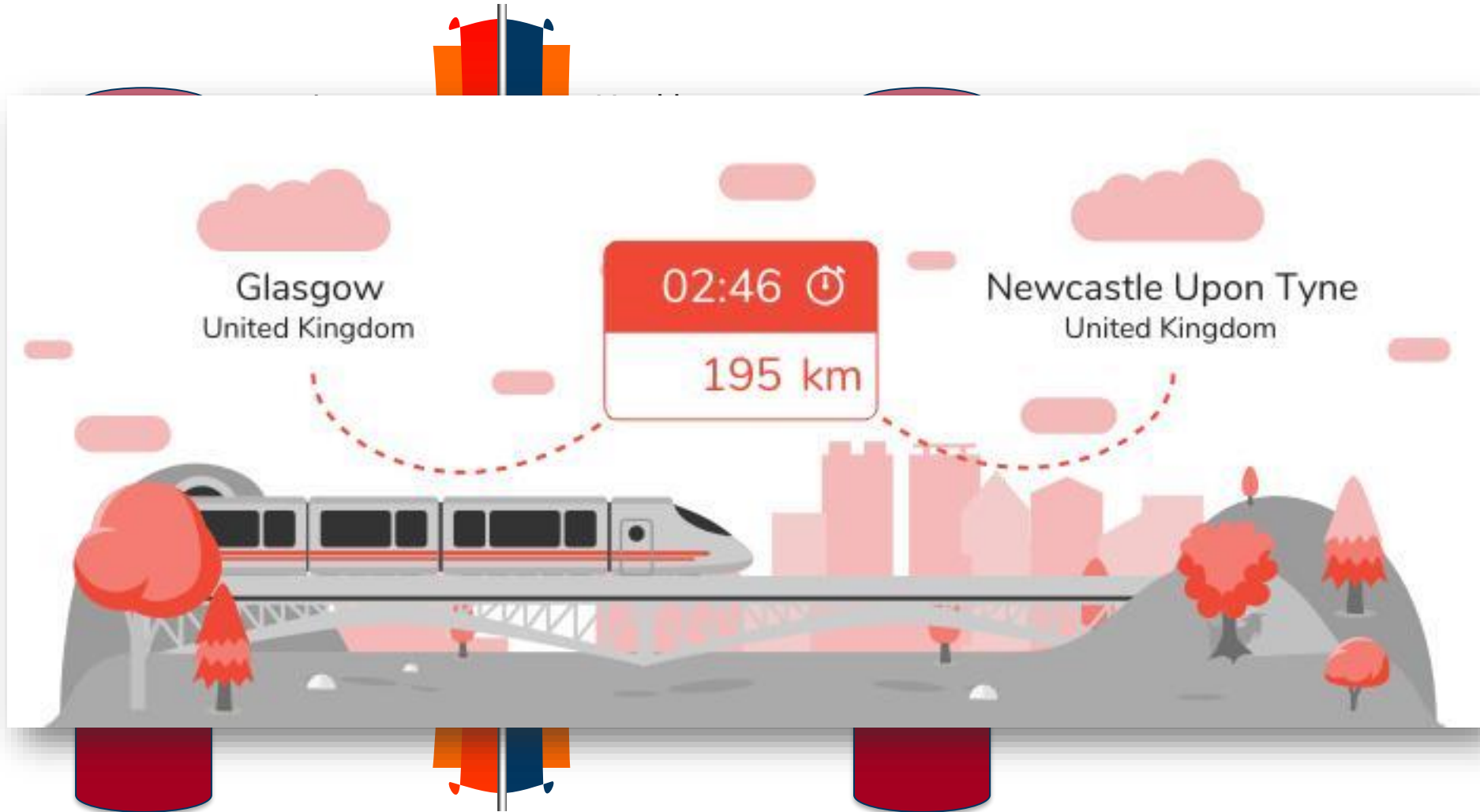


gift of Jean Michel-Dayer

What drives cytokine release in RA synovitis?



Why study active disease?



What about synovial tissue macrophages in distinct disease states?

Dr Alivernini and Prof Ferraccioli (Catholic University of the Sacred Heart, Rome)



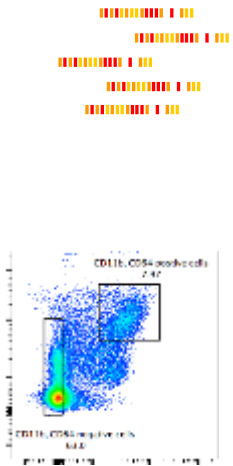
Liberase (150 μ g/ml)



1.5 h, 37°C



RNAseq (Glasgow Polyomics)



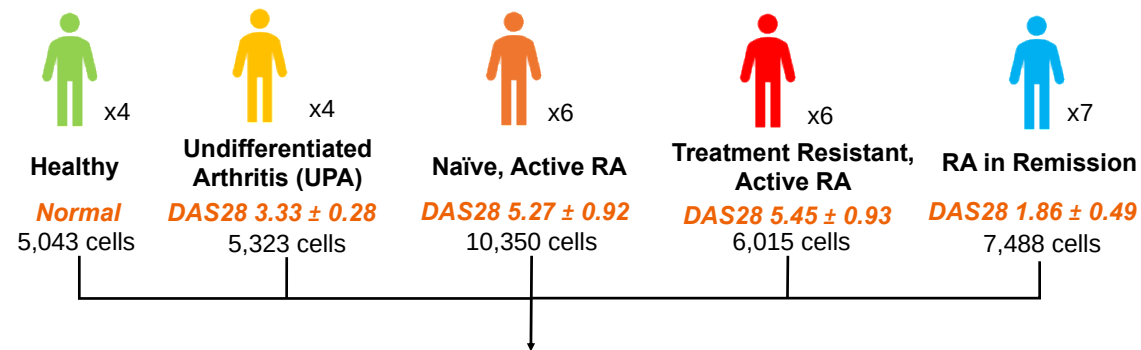
Sorting

Phenotyping

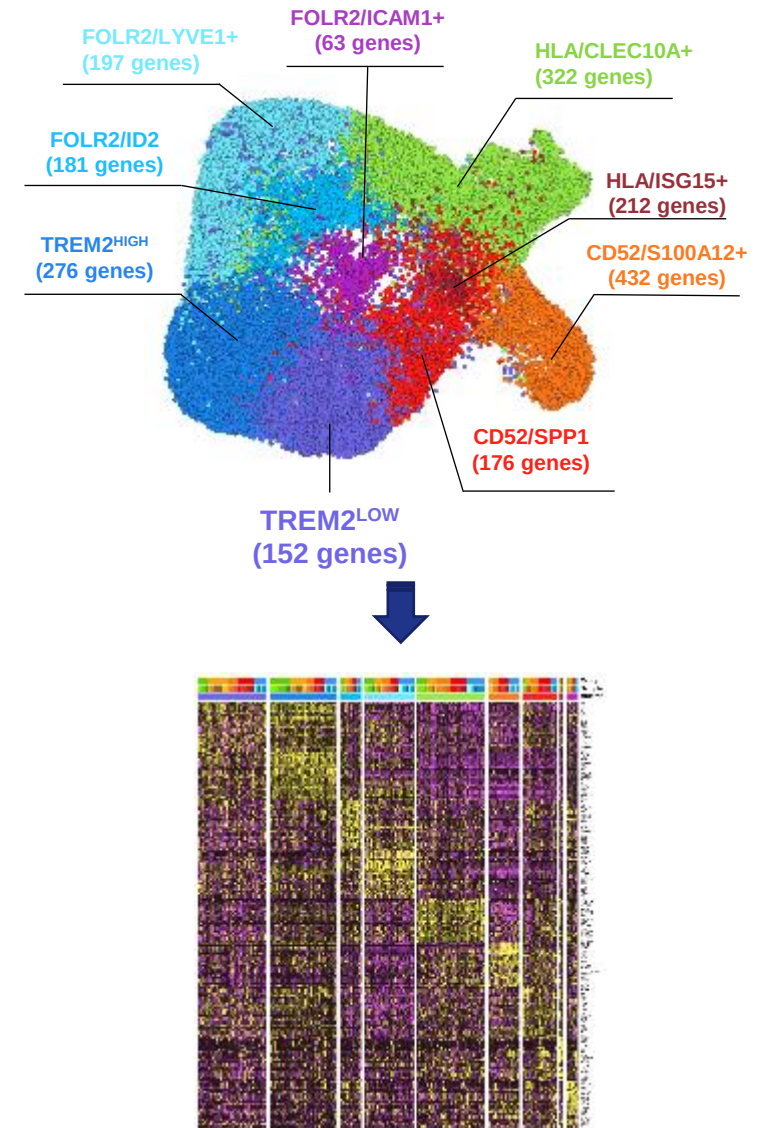
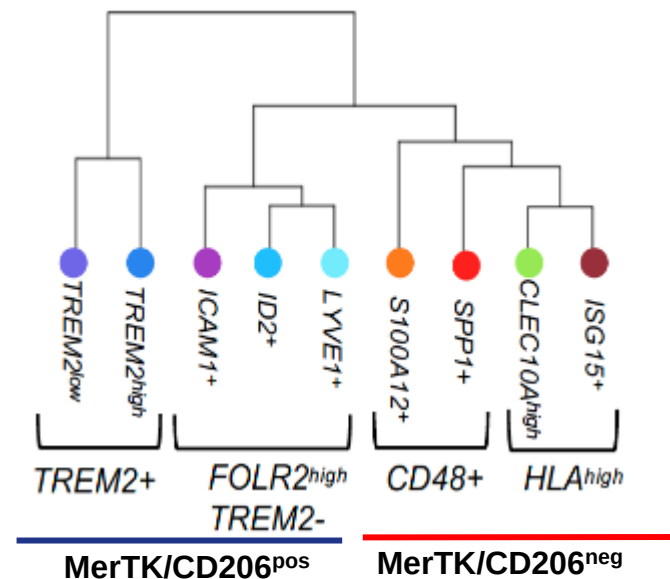
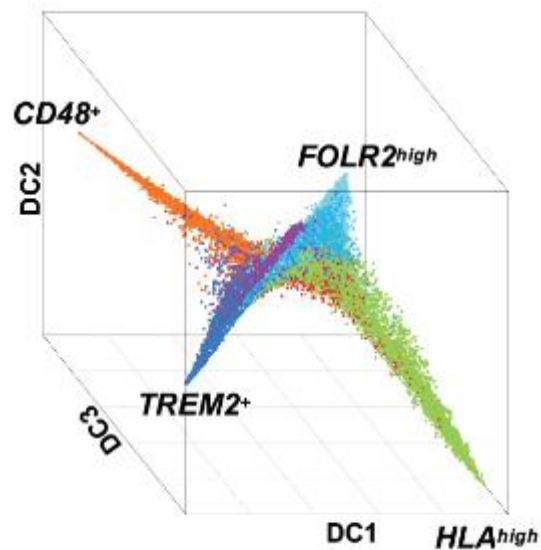
Staining with the following antibody panel

1	Live _ Dead marker	APC/Cy7
2	CD45	BV 711
3	Dump Channel	FITC
4	CD64	BV 510
5	CD11b	AF 700
6	CD206	BV 421
7	HLA-DR	BV 785
8	MERTK R	PE
9	CD163	PerCP/Cy5.5
10	IL-13Ra	APC
11	IL-4Ra	PE/CY7

Novel taxonomy of human synovial tissue macrophages

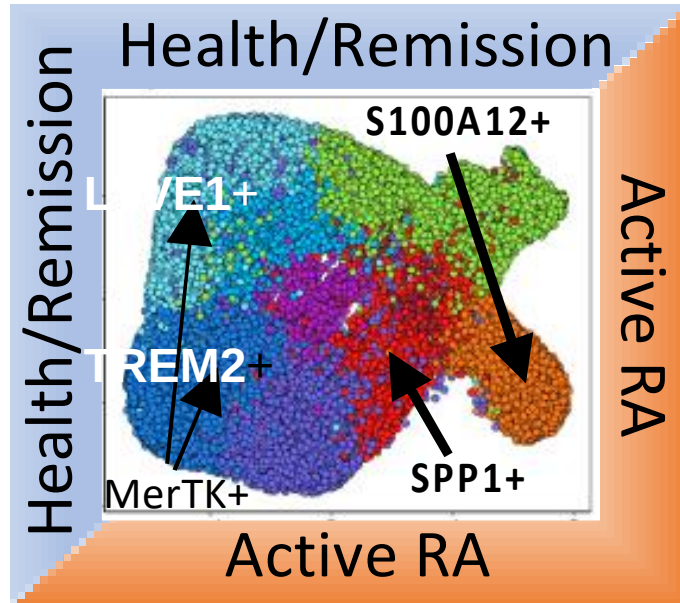


In total - 34,219 synovial macrophages profiled from 27 patients, across 5 conditions

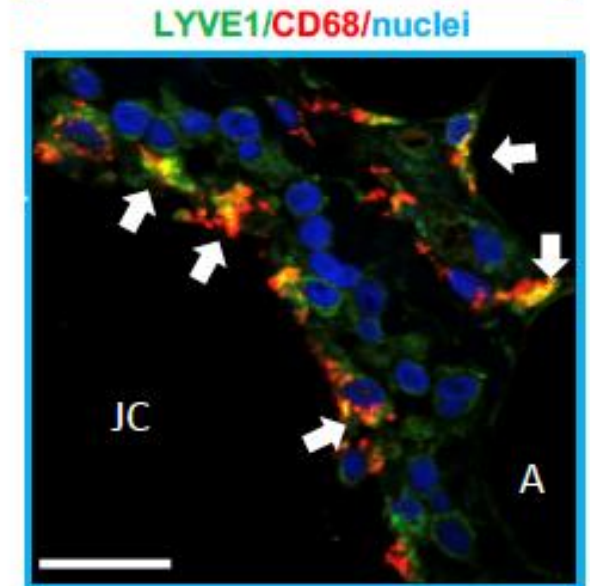
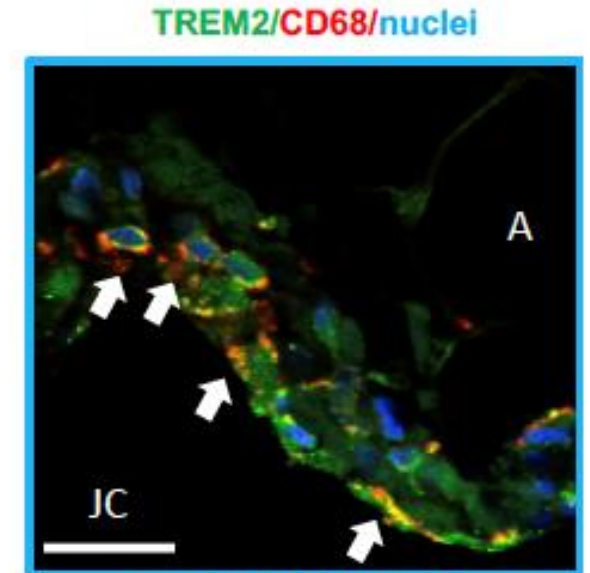
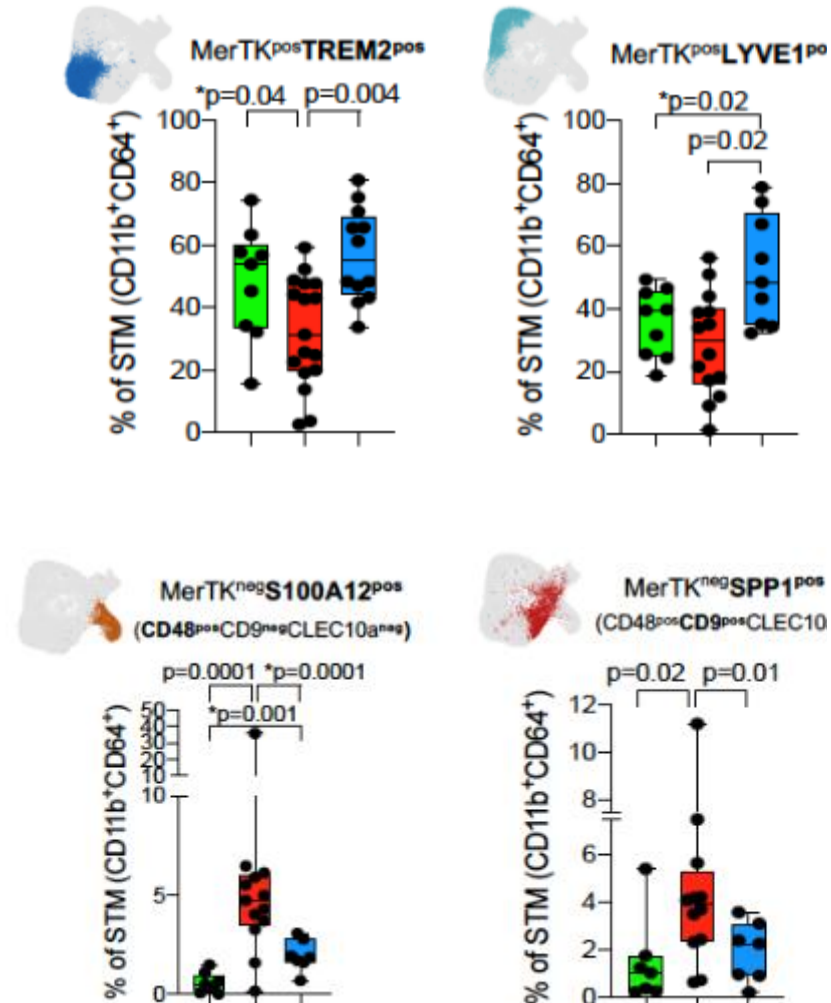


MerTK positive clusters: TREM2^{pos} / LYVE1^{pos} dominate in health and remission
while MerTK negative clusters: SPP1^{pos} / S100A12^{pos} dominate in active RA

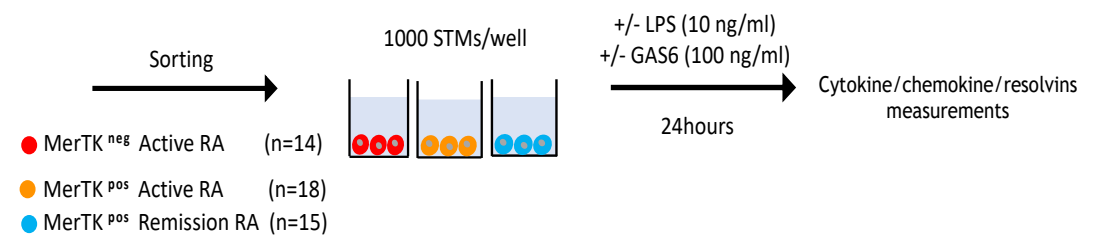
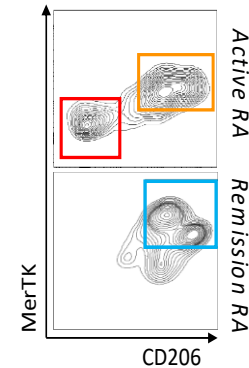
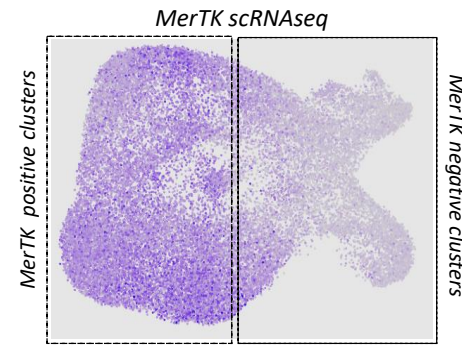
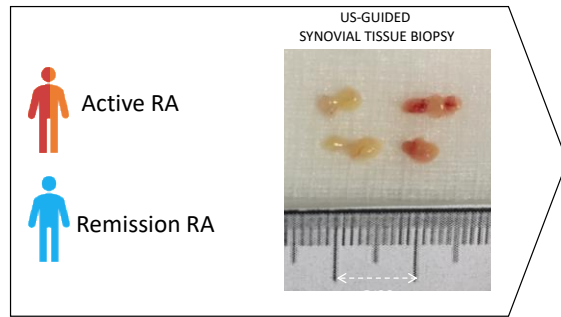
- Healthy
- Active RA
- Remission RA



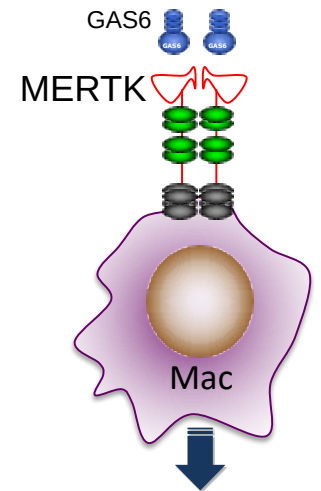
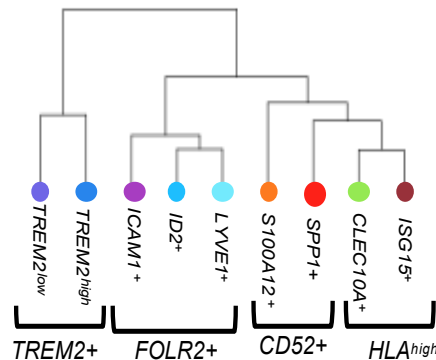
Validated by flow cytometry
and immunohistochemistry



MerTK^{neg} STM populations produce **pro-inflammatory** mediators, while MerTK^{pos} STMs produce inflammation **resolving** mediators

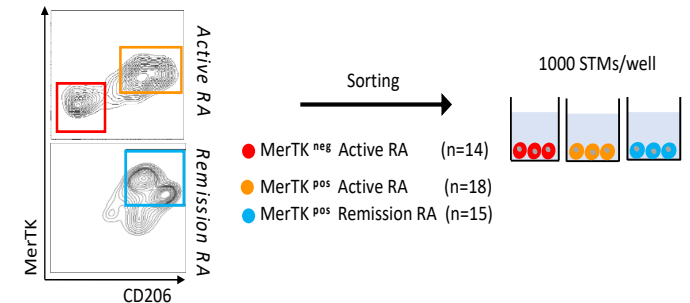
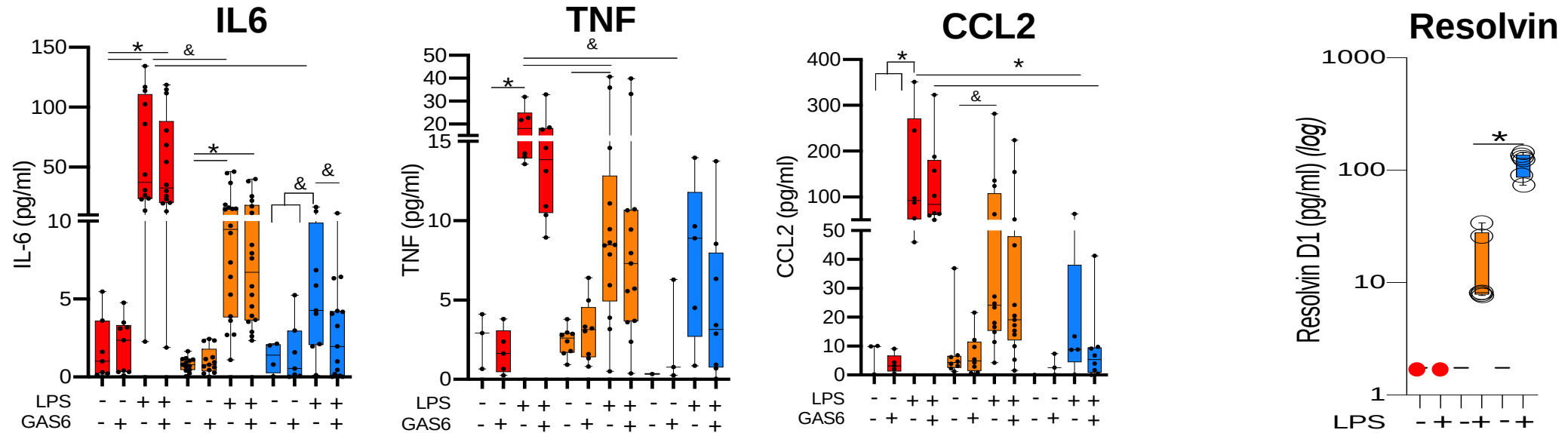


MerTK^{pos} MerTK^{neg}

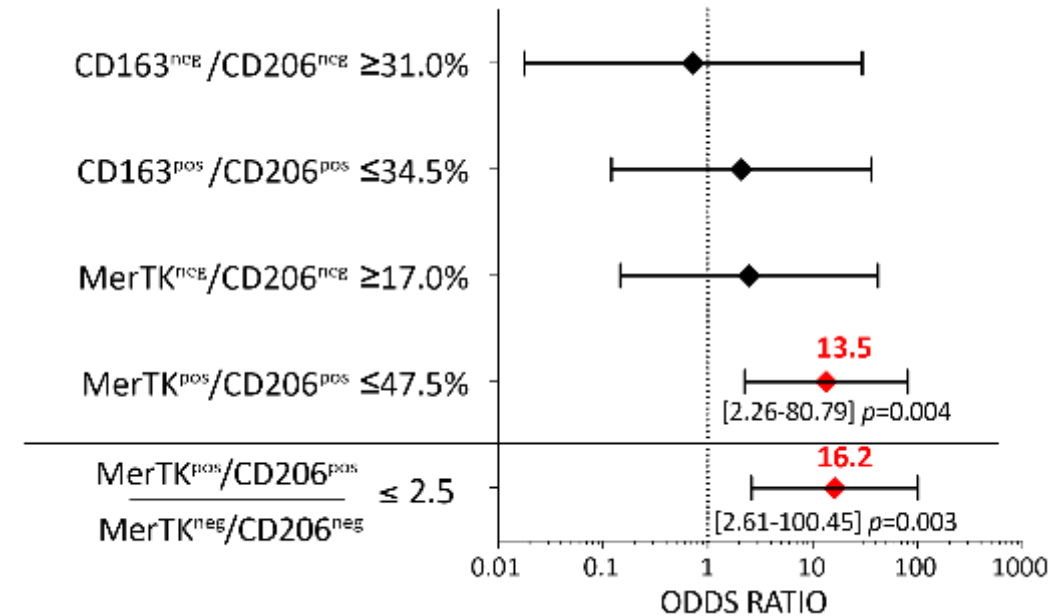
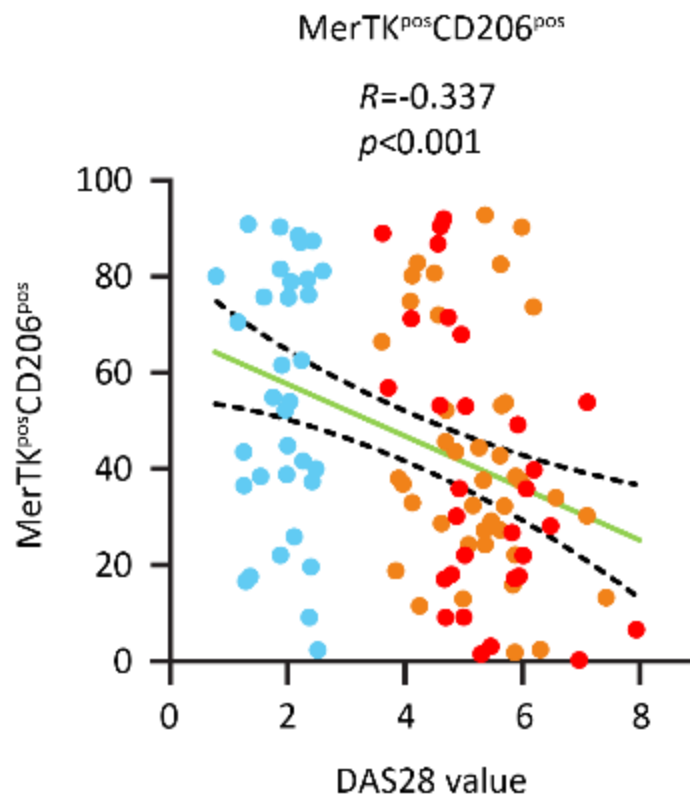


Resolution of tissue inflammation
Tissue homeostasis
Tissue remodeling
Tissue spatial organization

MerTK^{neg} STM populations produce **pro-inflammatory** mediators, while MerTK^{pos} STMs produce inflammation **resolving** mediators

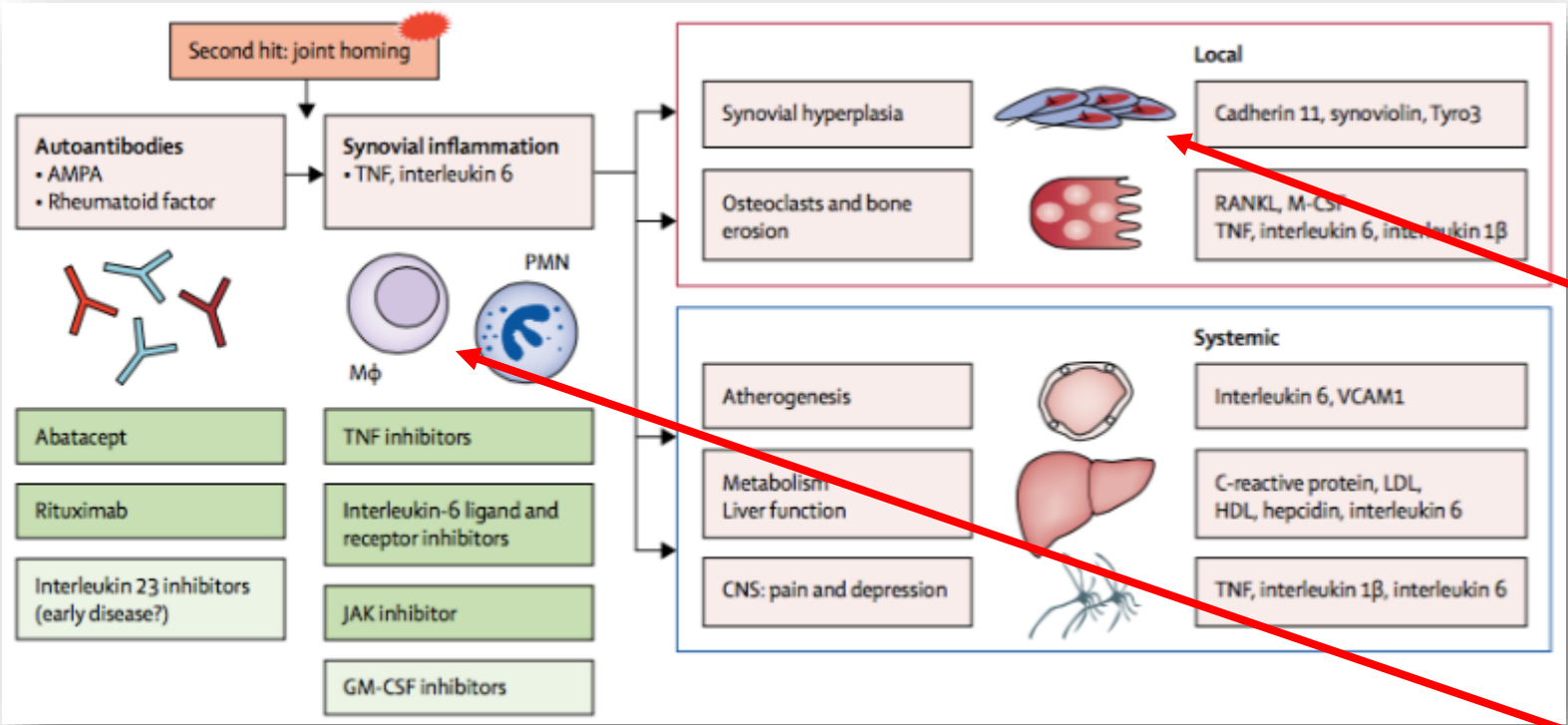


RA patients in disease remission who do not flare after treatment cessation have high proportion of MerTK^{pos} synovial macrophages



OCCURRENCE of FLARE

Looking to the future in IMID therapeutics to target cytokine networks?



FLS subsets.

New candidate SMEs



Macrophage subsets

Cytokines regulate inflammation distinctively across different tissues...

Target	Disease domain of SpA																		
	Peripheral arthritis						Skin (PASI 75) ¹	Nails ^{2–7,a}	Enthesitis ^{1,b}	Dactylitis ^{1,b}	Axial disease (ASAS40)								
	Arthritis (ACR70) ¹		Physical function (HAQ) ¹		X-ray damage (PsA-mSvdHS) ¹														
TNF															Axial PsA ^{8,c} + axSpA ²				
IL-17A															Axial PsA ⁹ + axSpA ³				
TNF/IL-17A																			
CD80/86															AS ^{10,d}				
IL-6															AS ¹¹				
IL-23-p19	GUS	RIS	GUS	RIS			GUS	RIS	GUS	RIS	GUS	RIS	GUS	RIS	GUS – Axial PsA ^{12,e}		RIS – AS ¹³		
JAK															AS ¹⁴				
PDE-4															AS ^{15,f}				

^aEfficacy demonstrated in nail psoriasis or patients with PsA with nail psoriasis; ^bDifferent instruments used in studies; ^cAs judged on evidence in axial SpA; ^dOpen-label study – no major clinical response observed; ^eAssessed with BASDAI in patients with active PsA with imaging-confirmed sacroiliitis from DISCOVER-1&2; ^fNo significant difference vs placebo (ASAS20)

Cytokines in different tissues: Interconnectivity of the brain and peripheral inflammation?

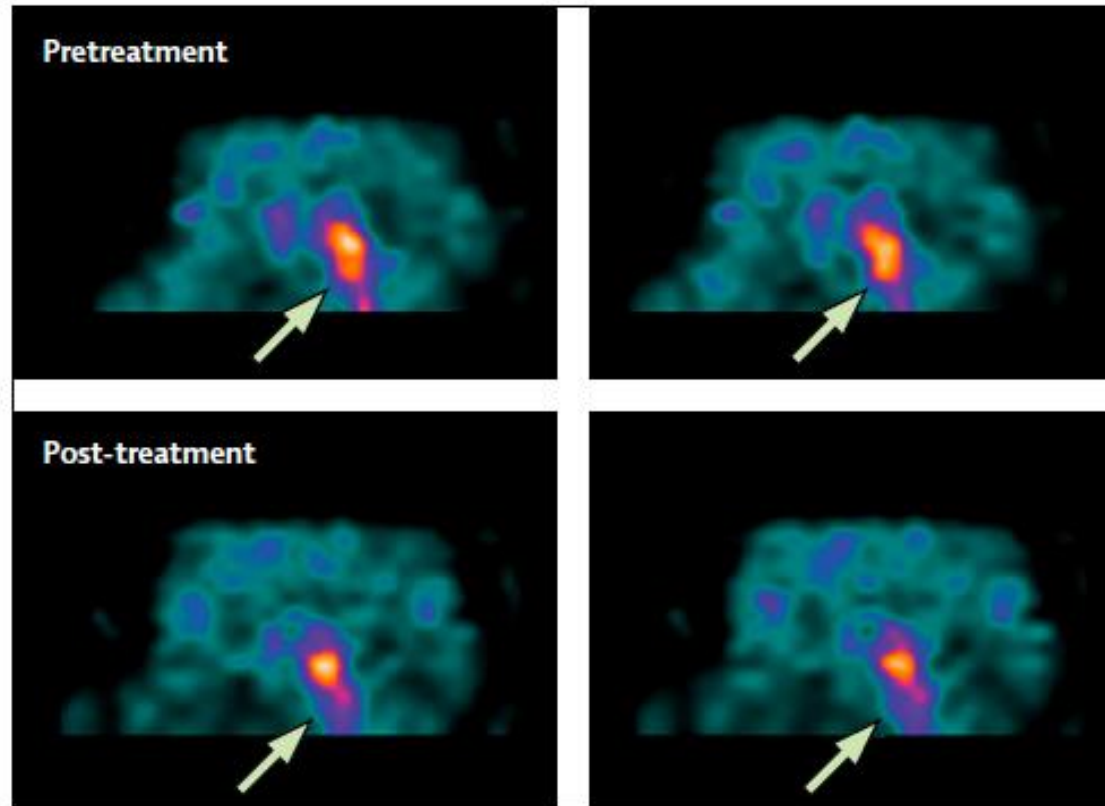
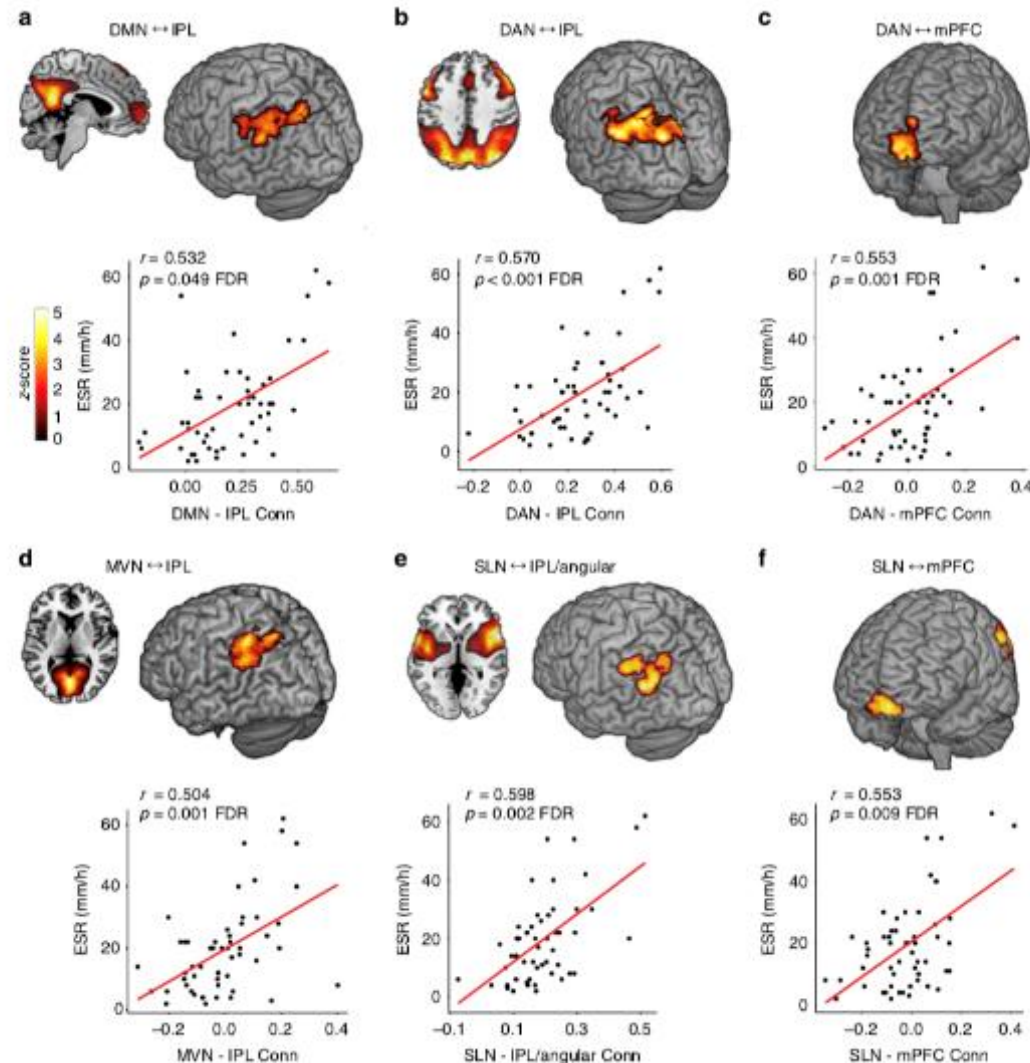


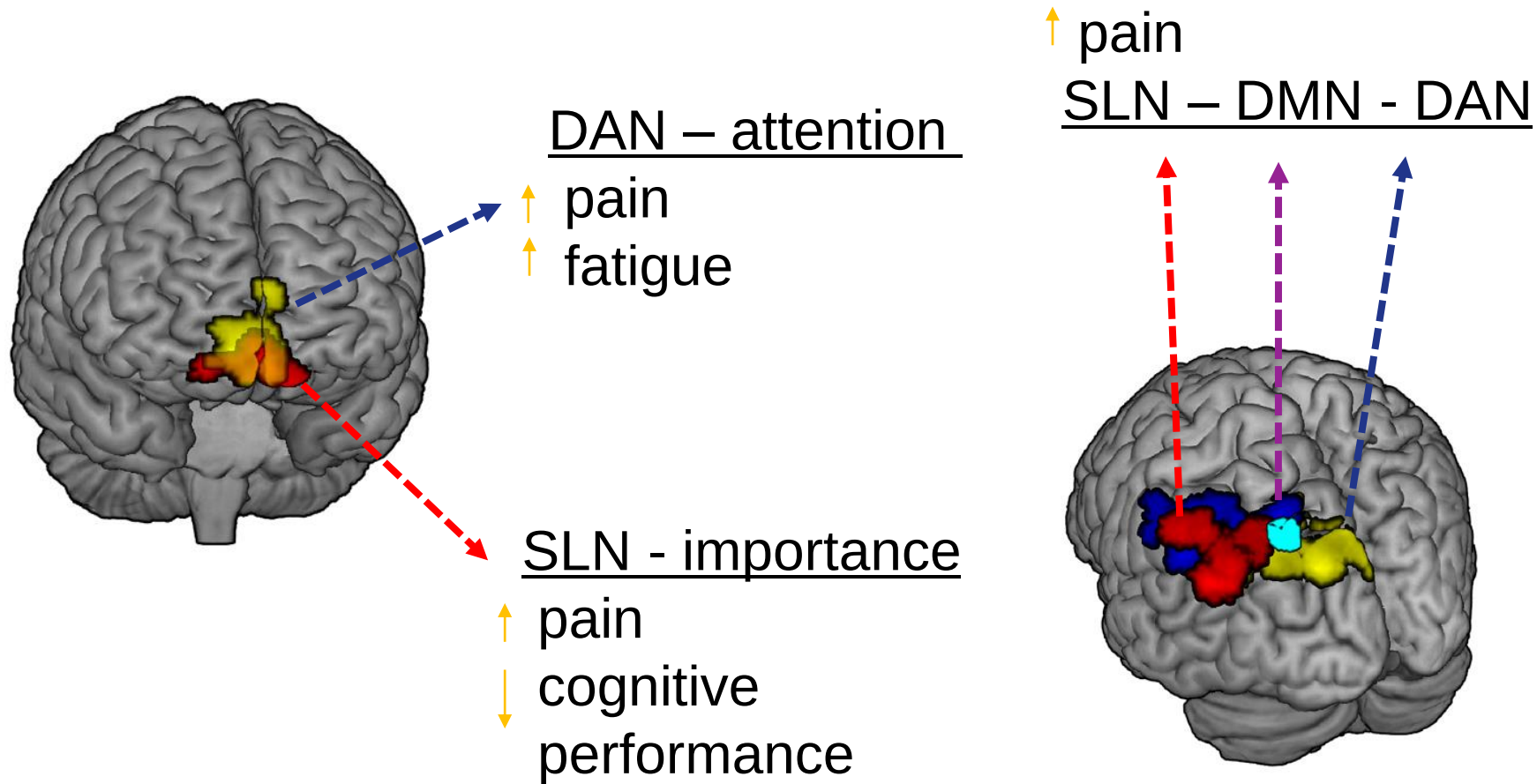
Figure 2: Representative image of changes in brainstem [123I]-β-CIT uptake, used to measure SERT availability, before and after etanercept treatment

Multi-modal MRI study of the central response to inflammation in RA – giving up the brain's secrets?

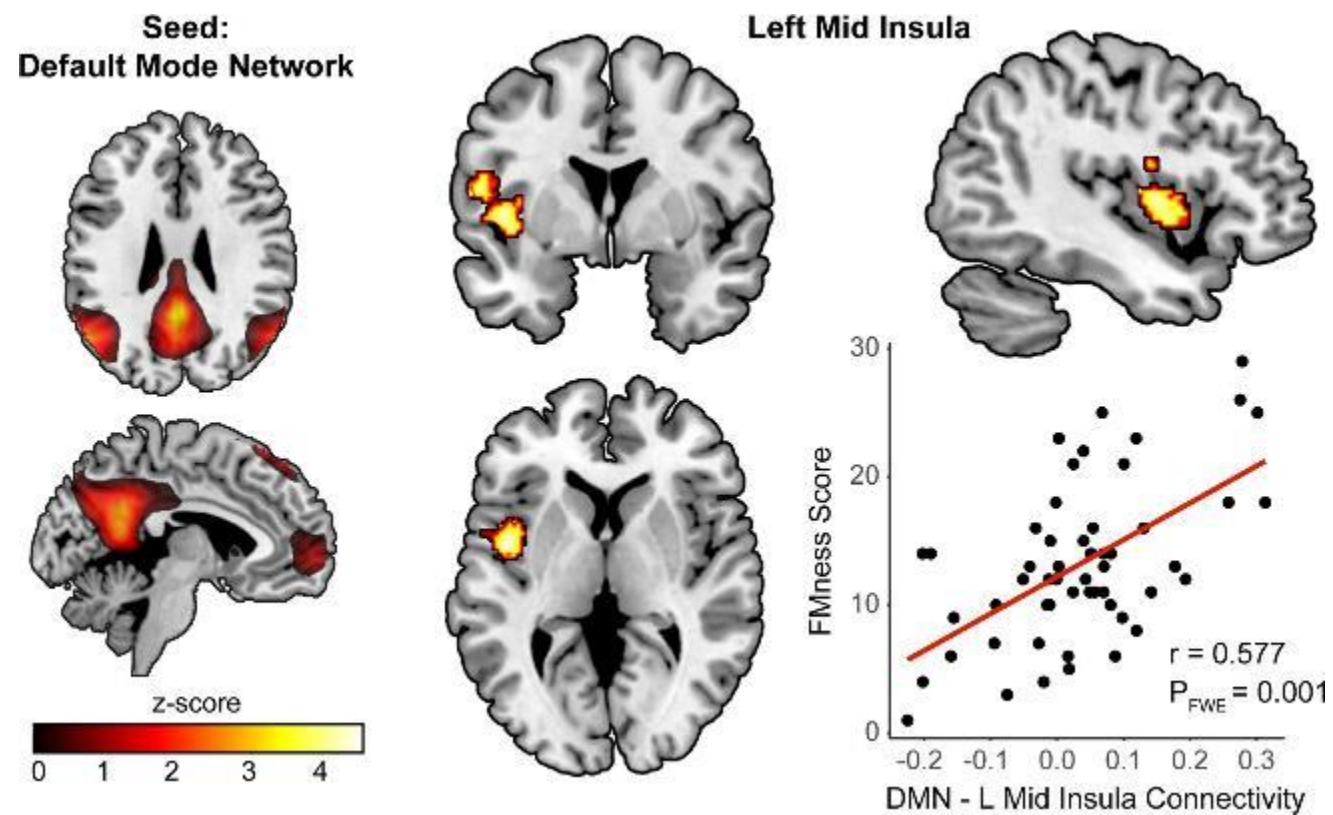


“higher levels of inflammation are associated with more positive connections between the inferior parietal lobule (IPL), medial prefrontal cortex, and multiple brain networks, as well as reduced IPL grey matter, **and that these patterns of connectivity predicted fatigue, pain and cognitive dysfunction**”

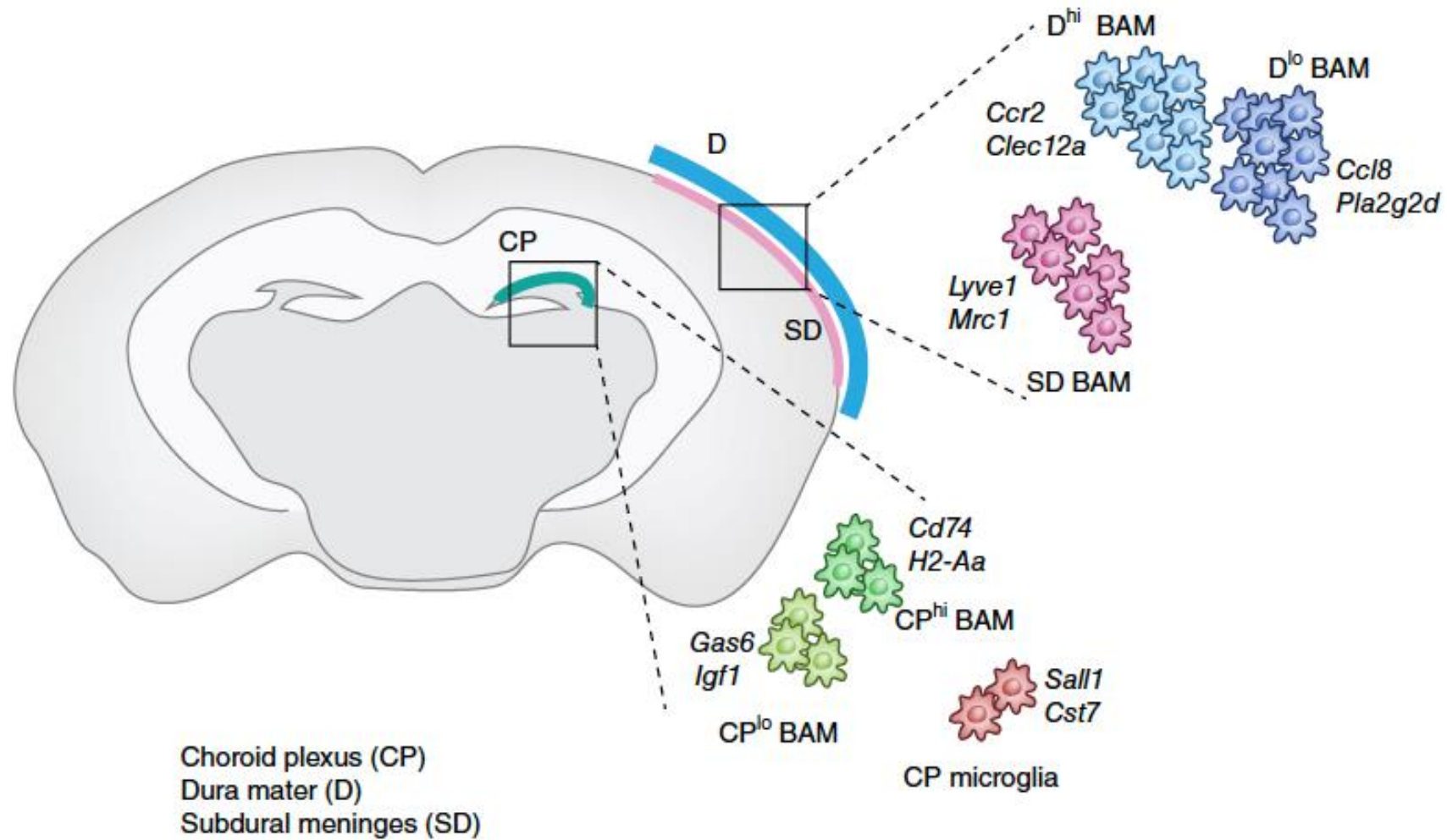
Increased Connectivity is Associated With Symptoms of RA



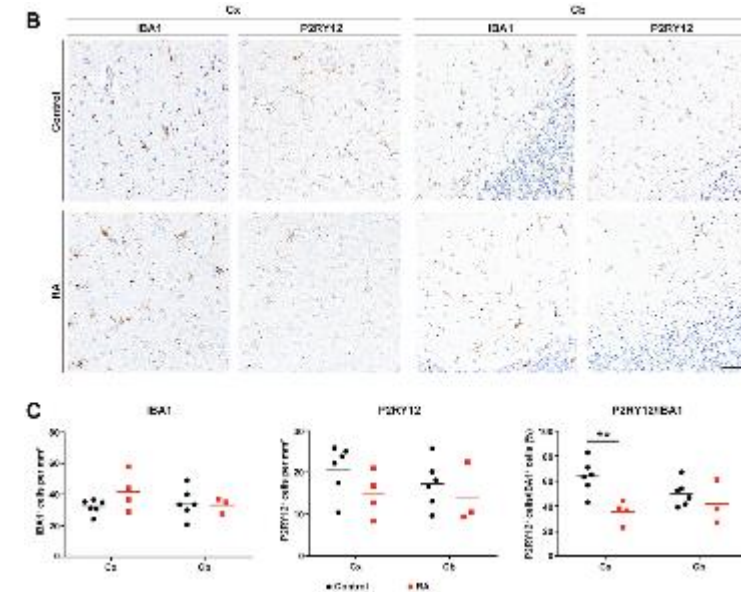
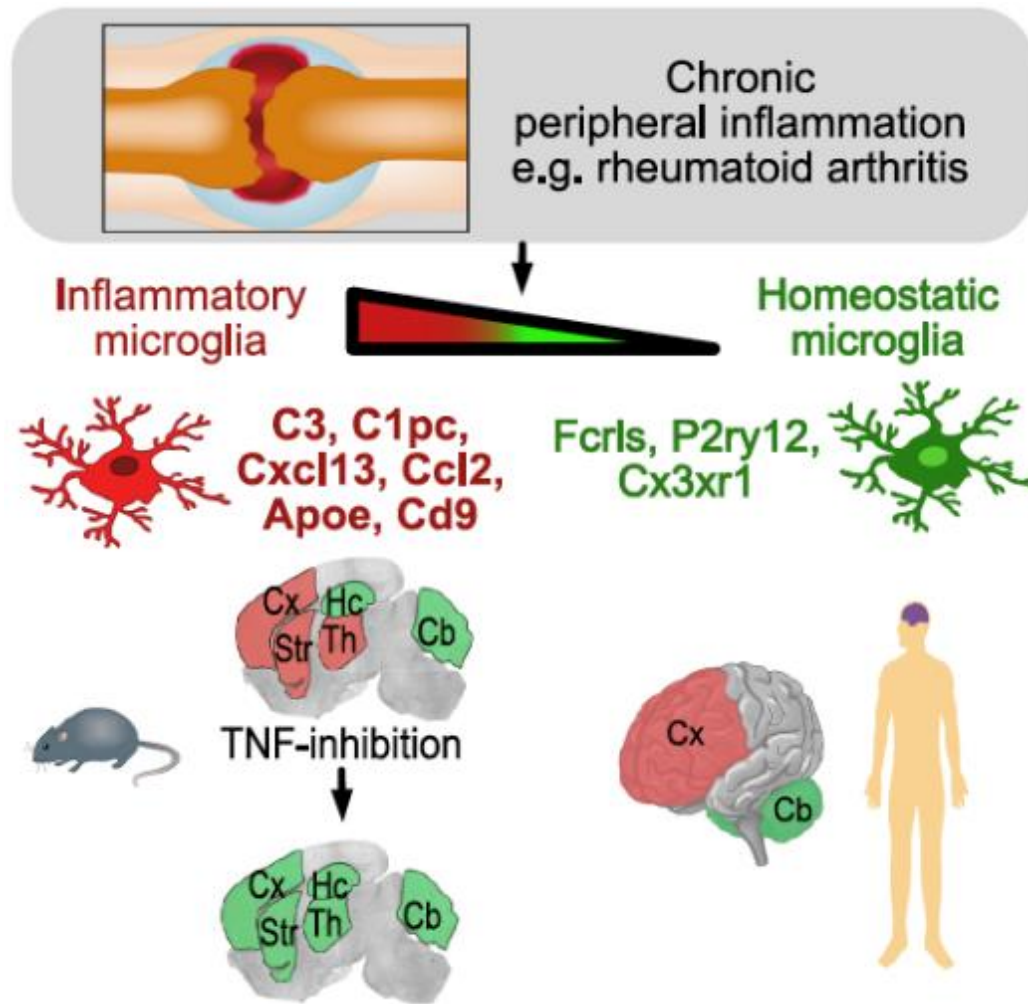
DMN-Insula Connectivity Correlates With FMness Among RA Patients



Critical role for myeloid lineage cells in the brain?



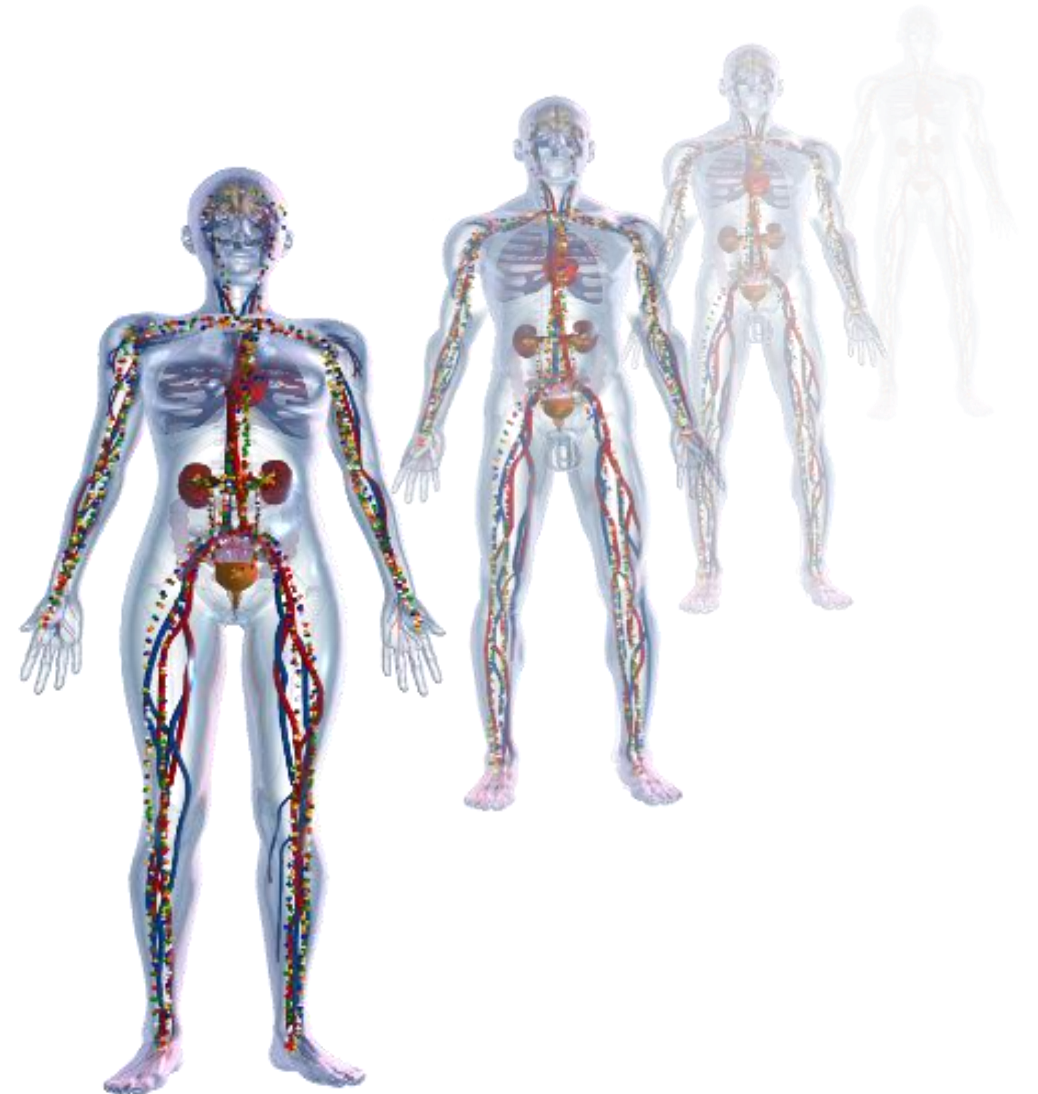
Critical role for myeloid lineage cells in the brain?



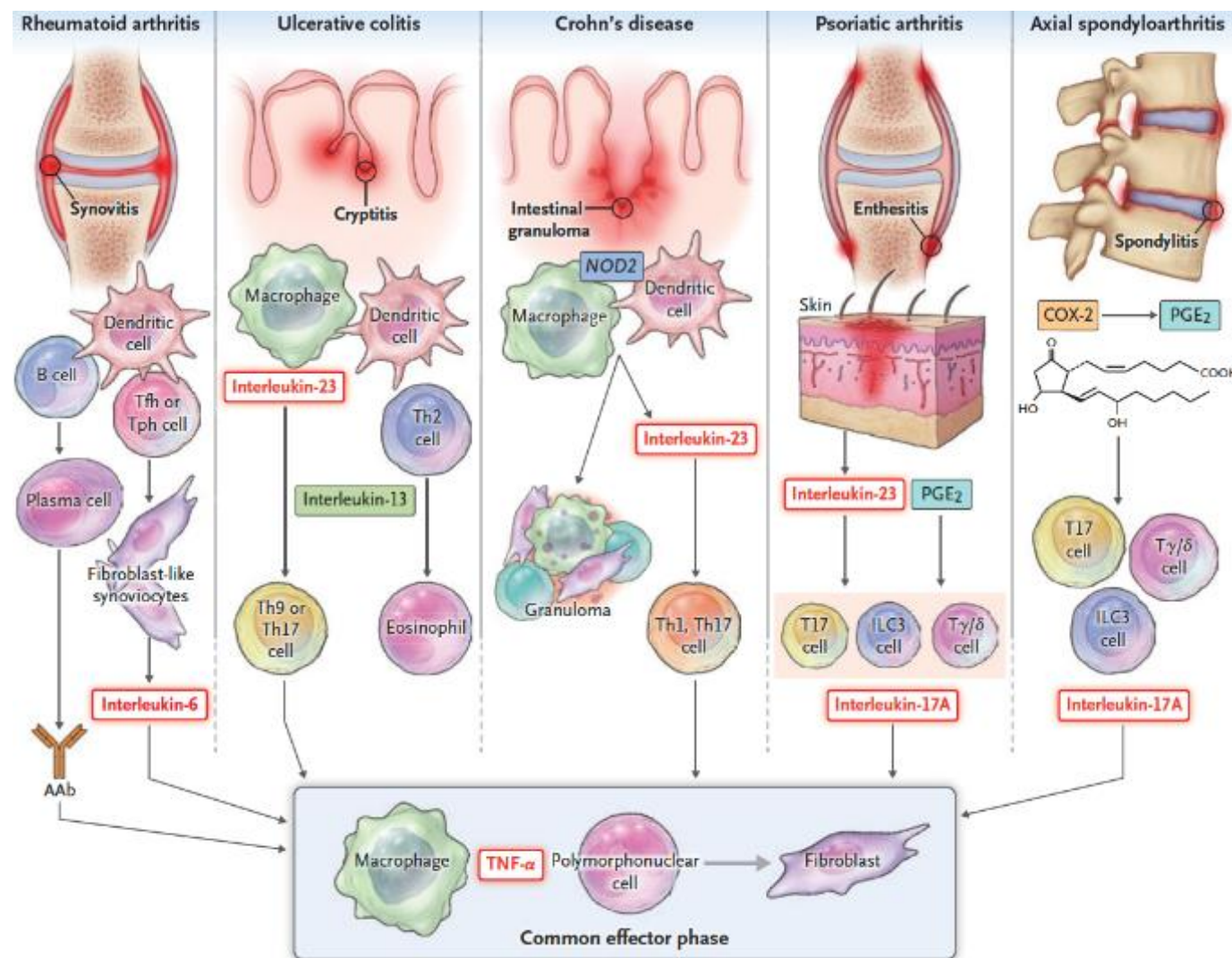
- TNF Tg mice: inflammatory myeloid subpopulations in cortex, striatum, and thalamus
- Human RA post mortem brain slices – macrophages dysregulated

Harnessing cytokine signatures?

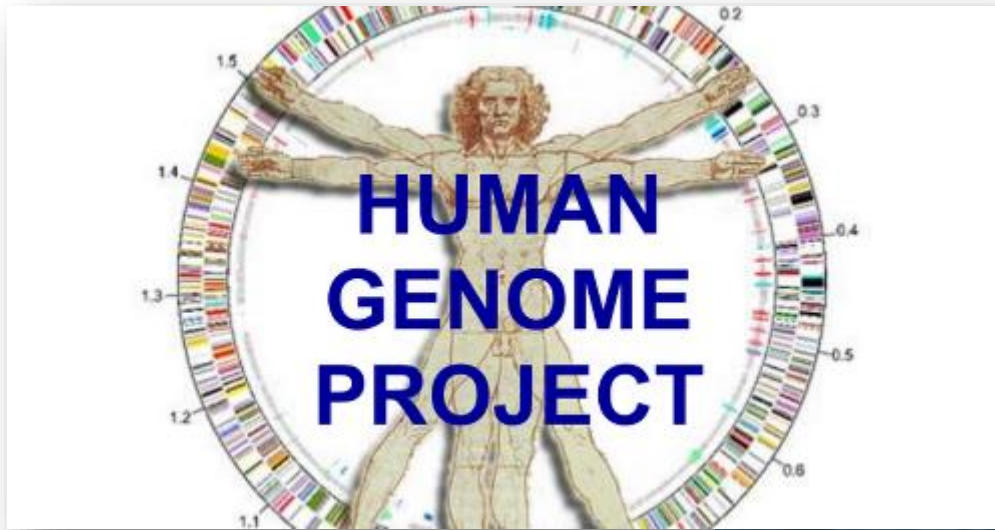
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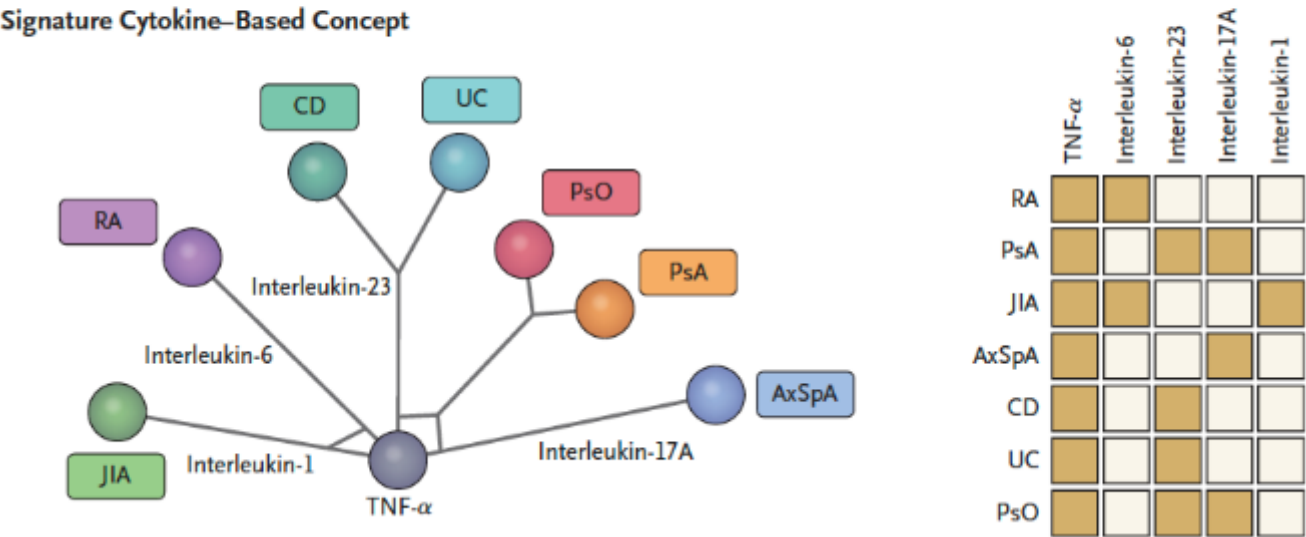
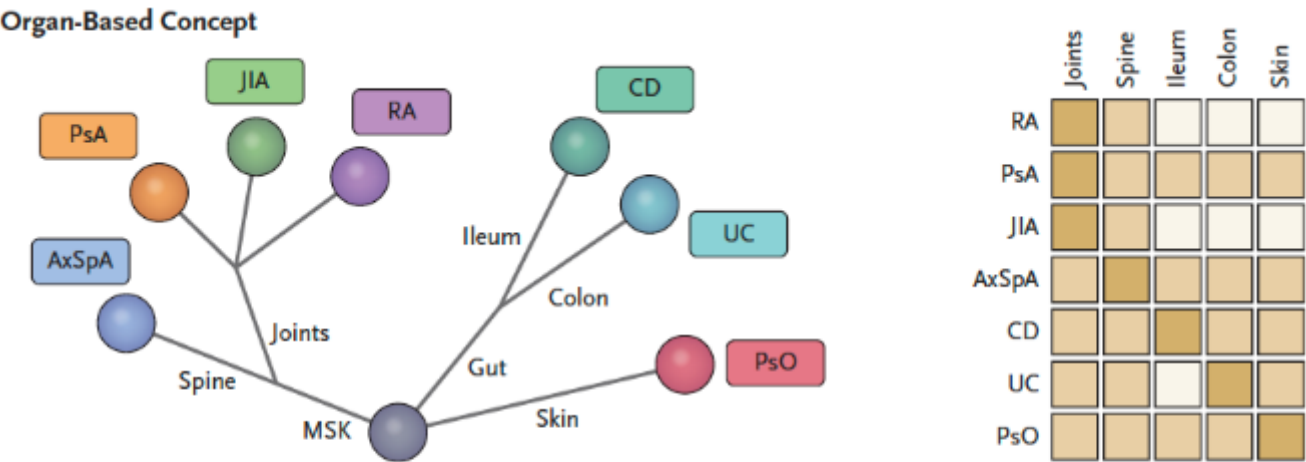
Reflecting on the tissue pathogenesis across IMIDs – organ based therapeutics



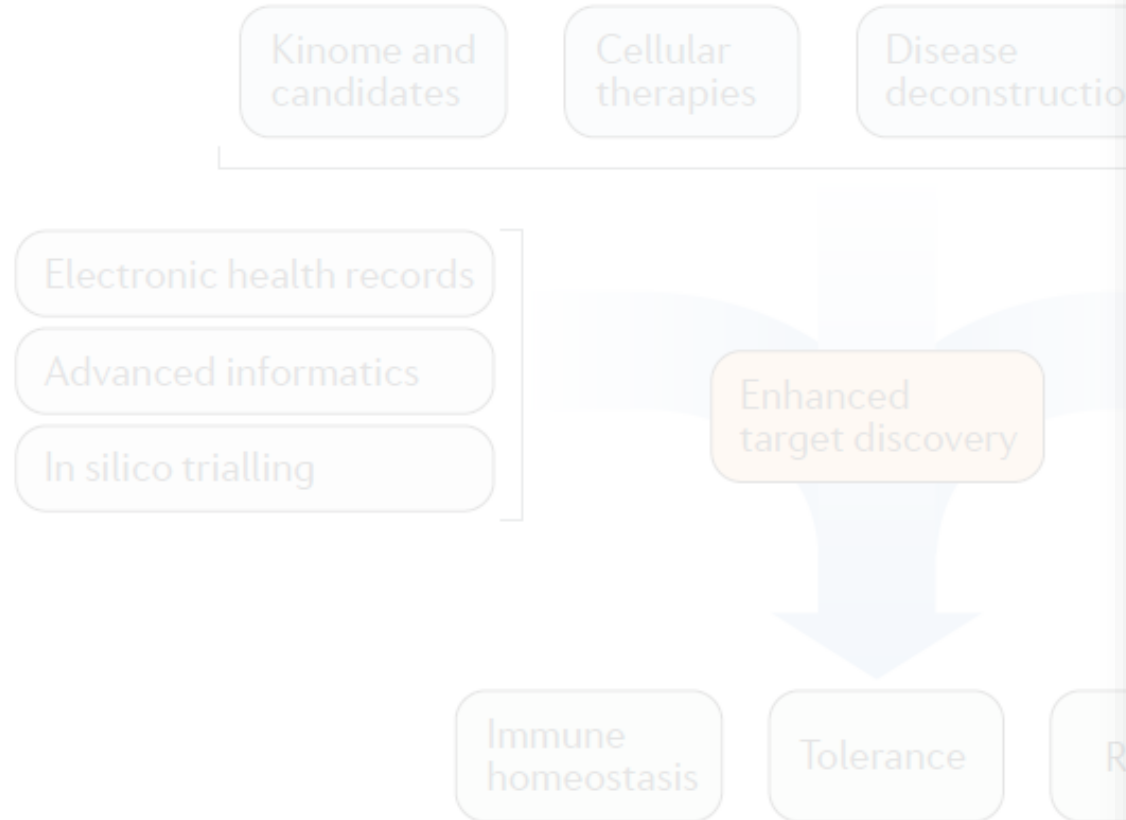
From organ pathology to accepting and resolving molecular complexity?



Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs?



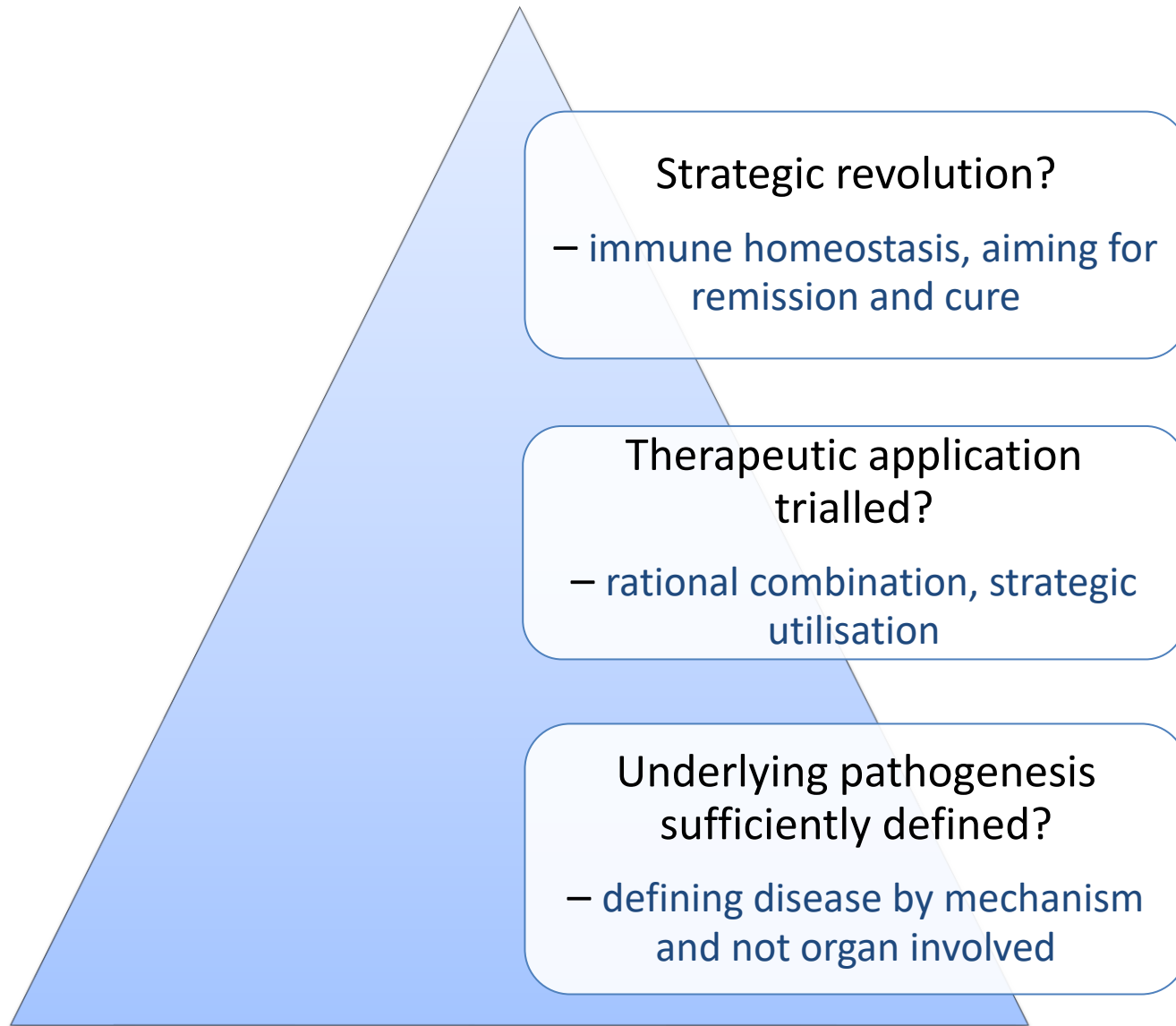
Cytokine therapeutics – what will future drug discovery look like?



“Scottish Water Kelpies”

How do we break through the therapeutic ceiling...

cytokine signatures *per* tissue level?





Thanks to some amazing people...

