II Simposio Multidisciplinar

Enfermedades Autoinmunes Sistémicas

#multiEAS

Madrid

20-21 enero 2023

NH COLLECTION EUROBUILDING

SEI
Sociedad Española
de Inmunología

AEDV Academia Española de Dermatología y Venereología

SEMI Sociedad Española de Medicina Interna

SEI Sociedad Española de Inmunología

Sociedad Española de Nefrología

Sociedad Española de Neumología y Cirugía Torácica SEPAR

Sociedad Española de Reumatología

SEPD Sociedad Española de Patología Digestiva

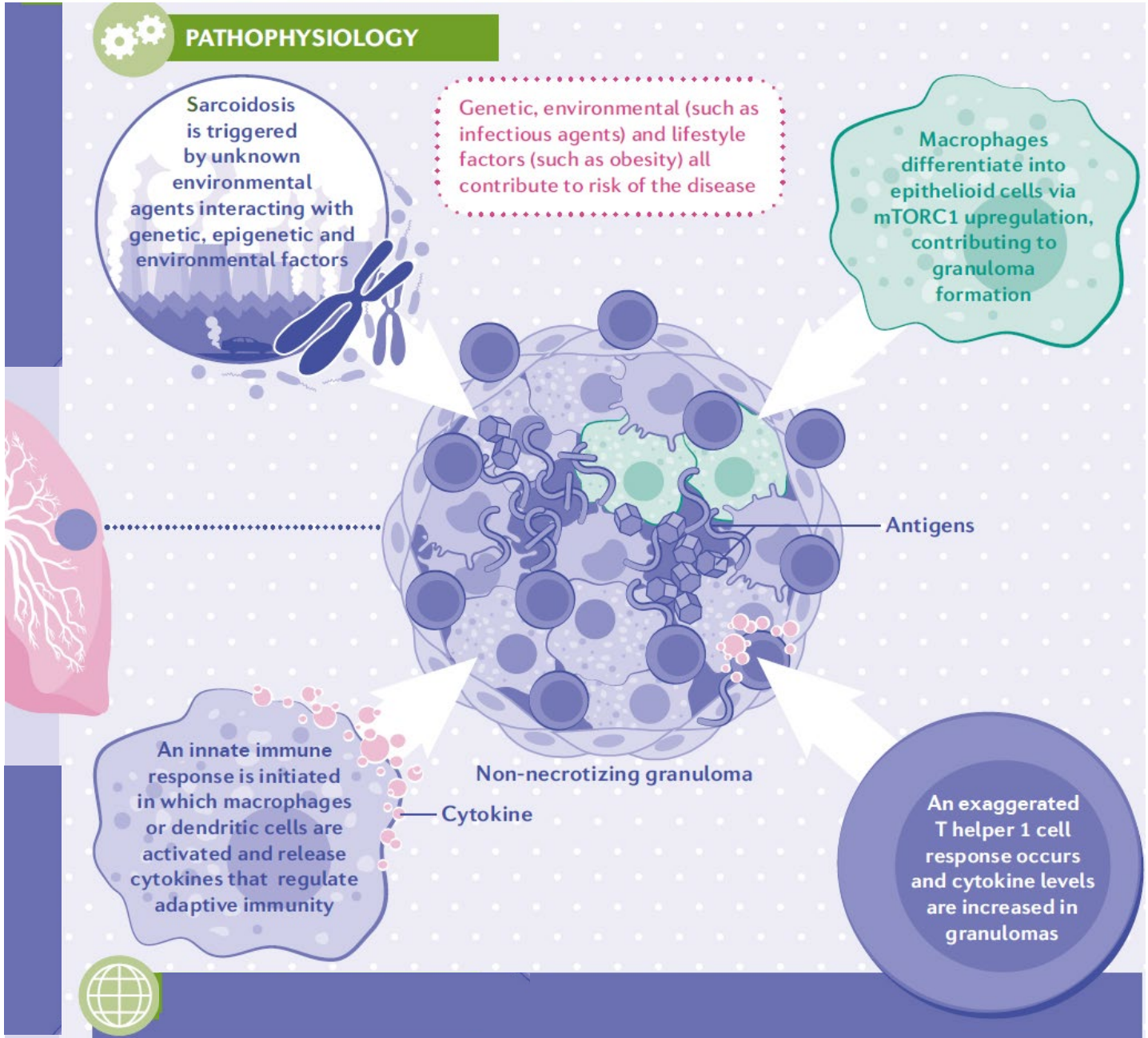
Sarcoidosis e Inmunodeficiencia: ¿Cruce de Caminos?

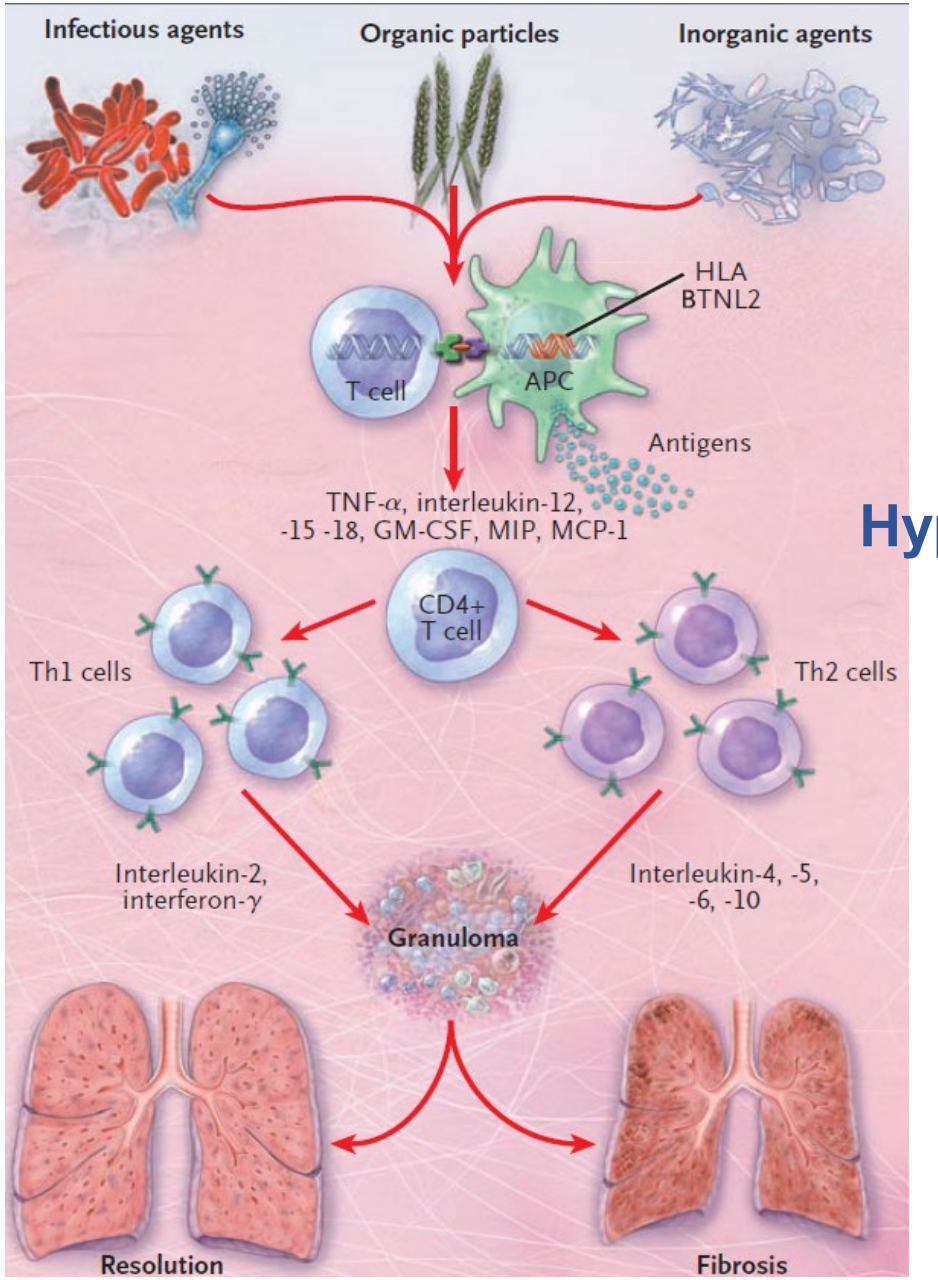
Dr. Oscar de la Calle-Martín

Servei d' Immunología
Hospital de la Santa Creu i Sant Pau, Barcelona
Universitat Autònoma de Barcelona

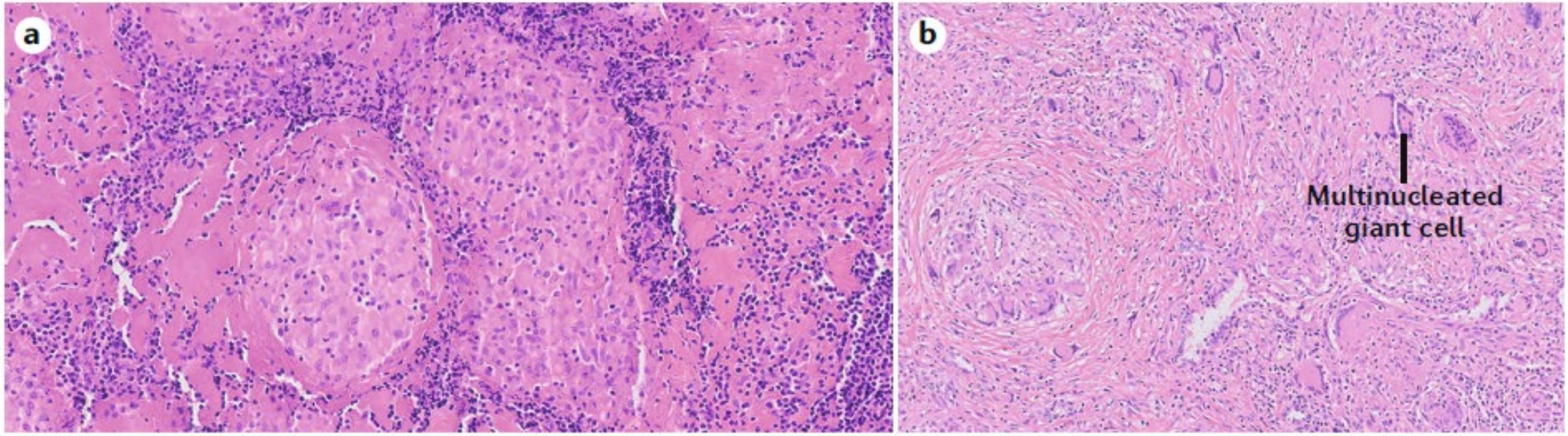
¿Puedo contemplar la desdicha ajena,
Y no sentir pena igualmente?
¿Puedo contemplar la angustia de otro
Y no buscarle alivio bondadoso?

William Blake


PATHOPHYSIOLOGY
Sarcoidosis is triggered by unknown environmental agents interacting with genetic, epigenetic and environmental factors
Genetic, environmental (such as infectious agents) and lifestyle factors (such as obesity) all contribute to risk of the disease
Macrophages differentiate into epithelioid cells via mTORC1 upregulation, contributing to granuloma formation
Antigens
Non-necrotizing granuloma
An innate immune response is initiated in which macrophages or dendritic cells are activated and release cytokines that regulate adaptive immunity
Cytokine
An exaggerated T helper 1 cell response occurs and cytokine levels are increased in granulomas

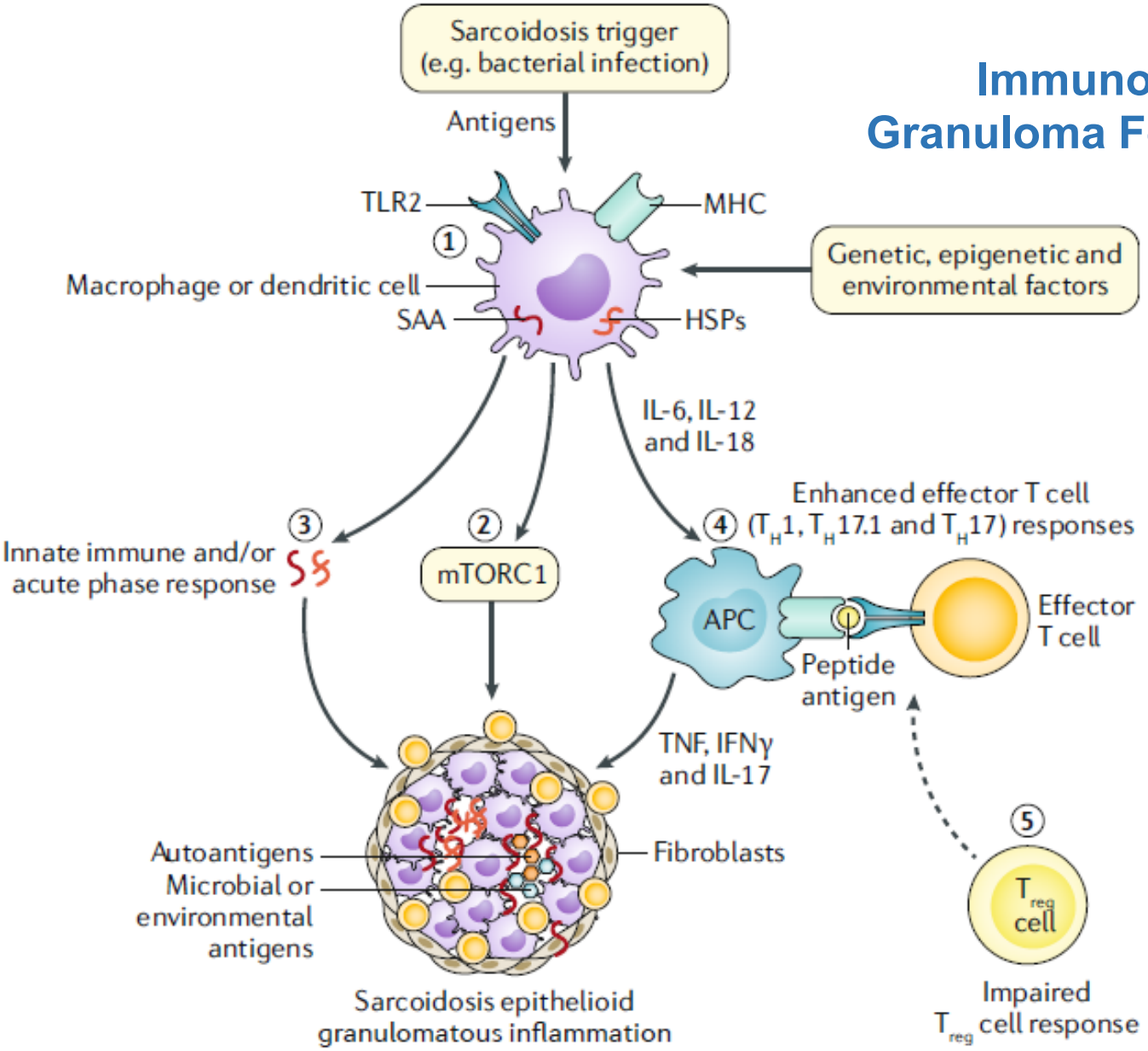


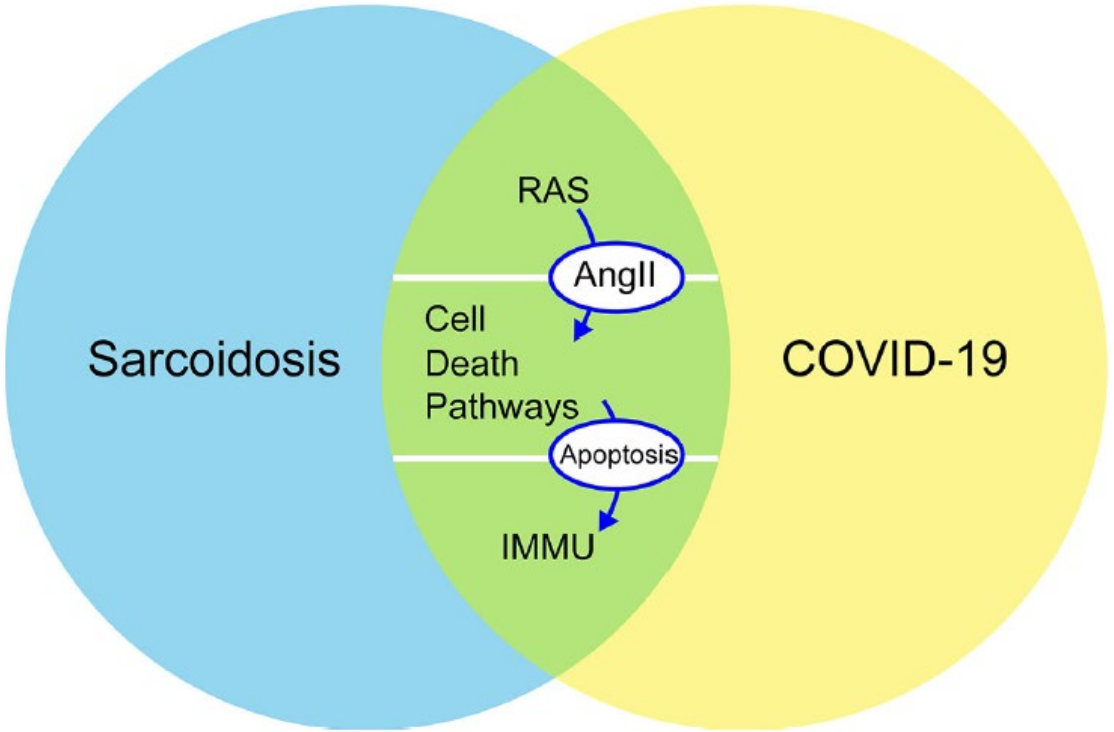
Hypothesized Immunopathogenesis of Sarcoidosis NEJM 2007

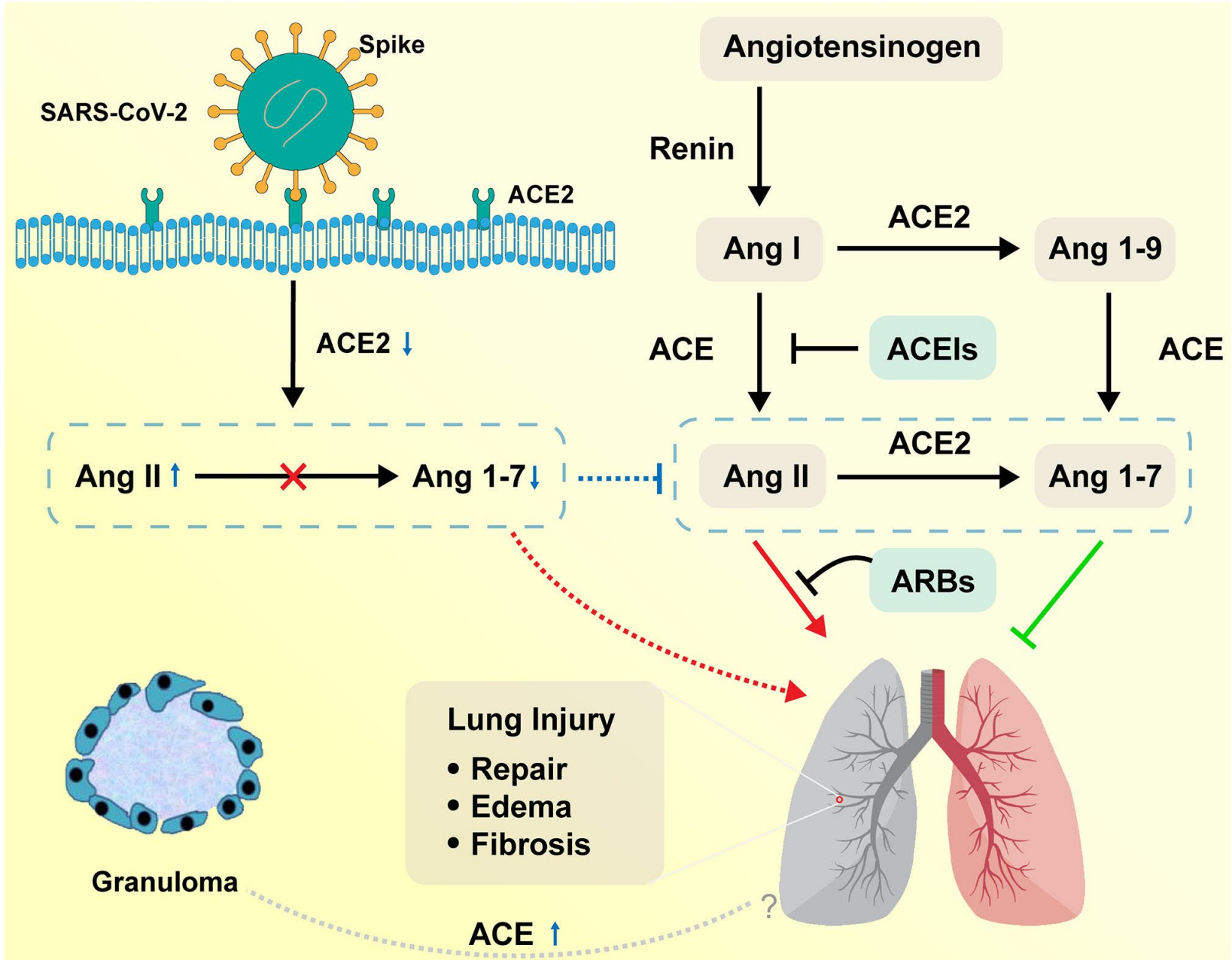


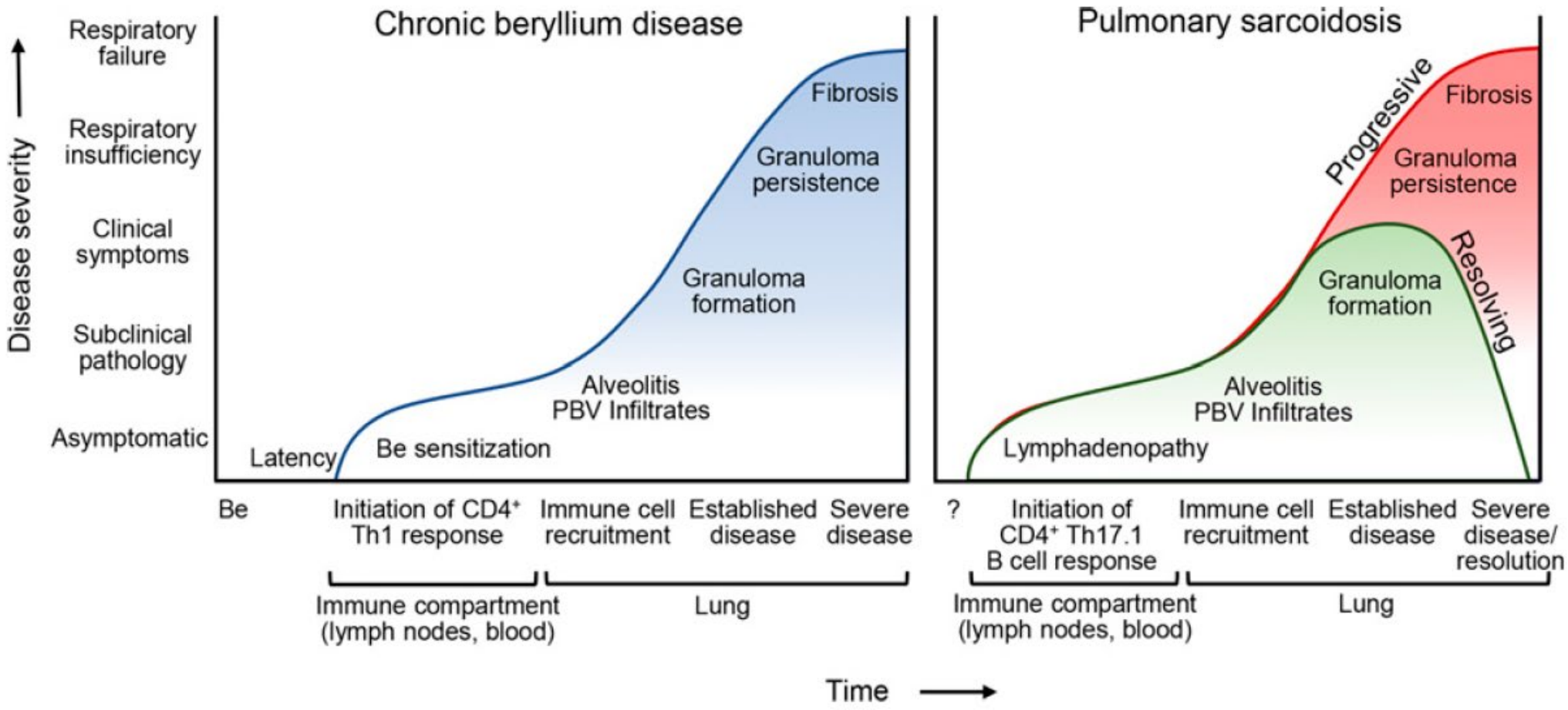
Histology of Lymph Node and Lung Granuloma in Sarcoidosis

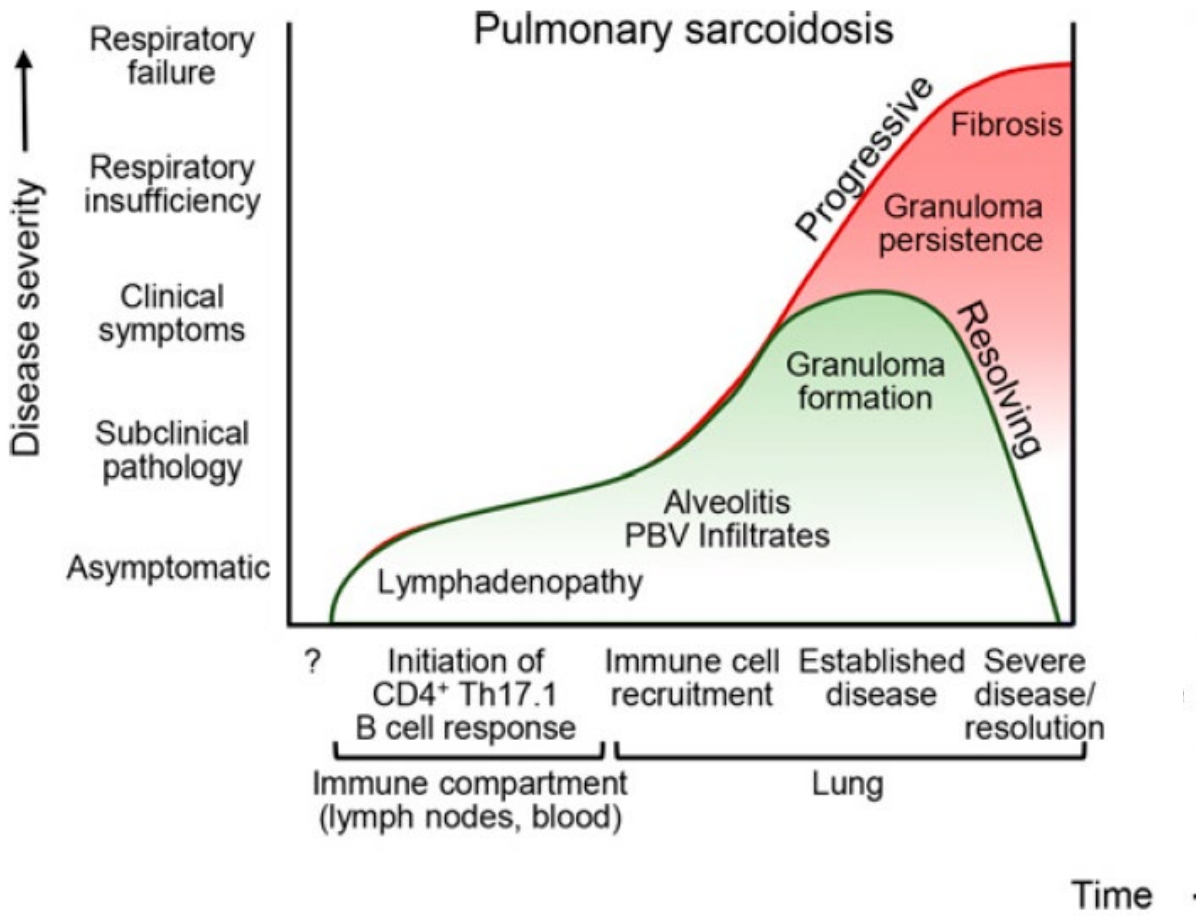
Immunological Features of Granuloma Formation in Sarcoidosis

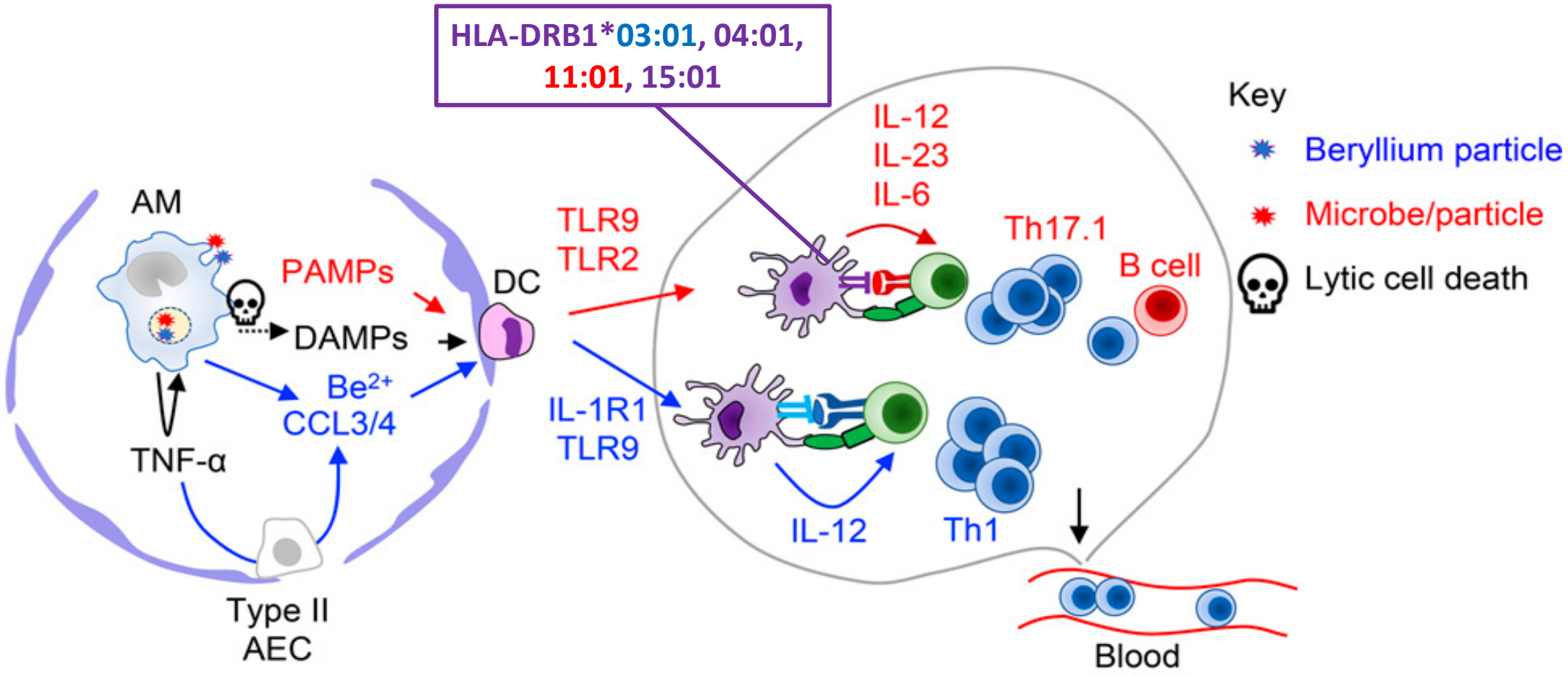



Sarcoidosis
COVID-19
RAS
AngII
Cell
Death
Pathways
Apoptosis
IMMU


Spike
SARS-CoV-2
ACE2
ACE2 ↓
Angiotensinogen
Renin
Ang I
ACE2
Ang 1-9
ACE
ACEIs
ACE
Ang II ↑
Ang 1-7 ↓
Ang II
ACE2
Ang 1-7
ARBs
Lung Injury
• Repair
• Edema
• Fibrosis
Granuloma
?
ACE ↑


Disease severity
Respiratory failure
Respiratory insufficiency
Clinical symptoms
Subclinical pathology
Asymptomatic
Chronic beryllium disease
Fibrosis
Granuloma persistence
Granuloma formation
Alveolitis
PBV Infiltrates
Latency
Be sensitization
Pulmonary sarcoidosis
Progressive
Fibrosis
Granuloma persistence
Resolving
Granuloma formation
Alveolitis
PBV Infiltrates
Lymphadenopathy
Be
Initiation of CD4+ Th1 response
Immune cell recruitment
Established disease
Severe disease
?
Initiation of CD4+ Th17.1 B cell response
Immune cell recruitment
Established disease
Severe disease/ resolution
Immune compartment (lymph nodes, blood)
Lung
Immune compartment (lymph nodes, blood)
Lung
Time


Pulmonary sarcoidosis
Disease severity
Respiratory failure
Respiratory insufficiency
Clinical symptoms
Subclinical pathology
Asymptomatic
Progressive
Fibrosis
Granuloma persistence
Resolving
Granuloma formation
Alveolitis
PBV Infiltrates
Lymphadenopathy
?
Initiation of CD4+ Th17.1 B cell response
Immune cell recruitment
Established disease
Severe disease/ resolution
Immune compartment (lymph nodes, blood)
Lung
Time

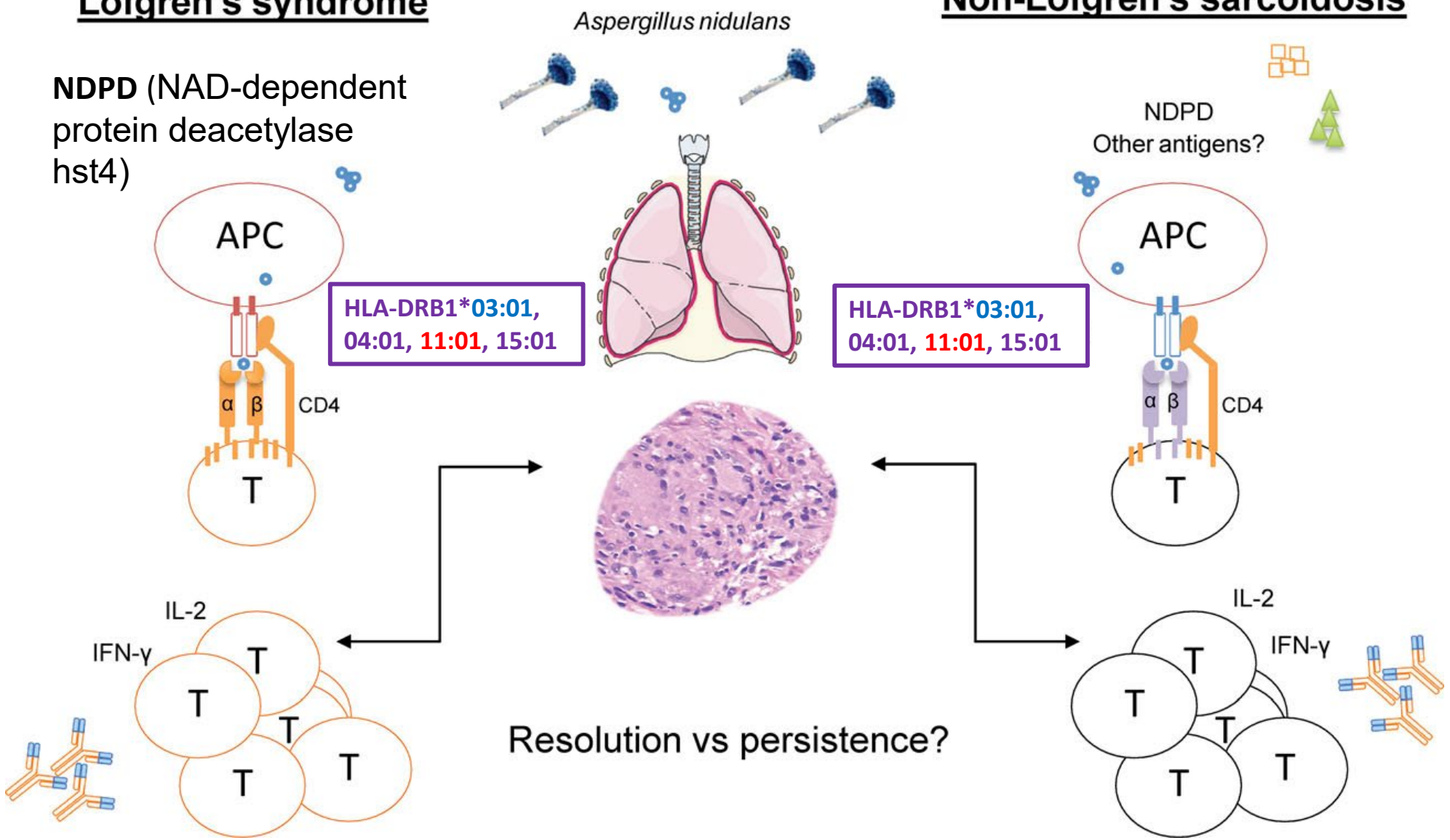

HLA-DRB1*03:01, 04:01, 11:01, 15:01
AM
PAMPs
DAMPs
DC
TLR9
TLR2
IL-12
IL-23
IL-6
Th17.1
B cell
Key
Beryllium particle
Microbe/particle
Lytic cell death
Be2+
CCL3/4
TNF-α
IL-1R1
TLR9
IL-12
Th1
Type II
AEC
Blood

. 2021 Oct 4;218(10):e20211572.

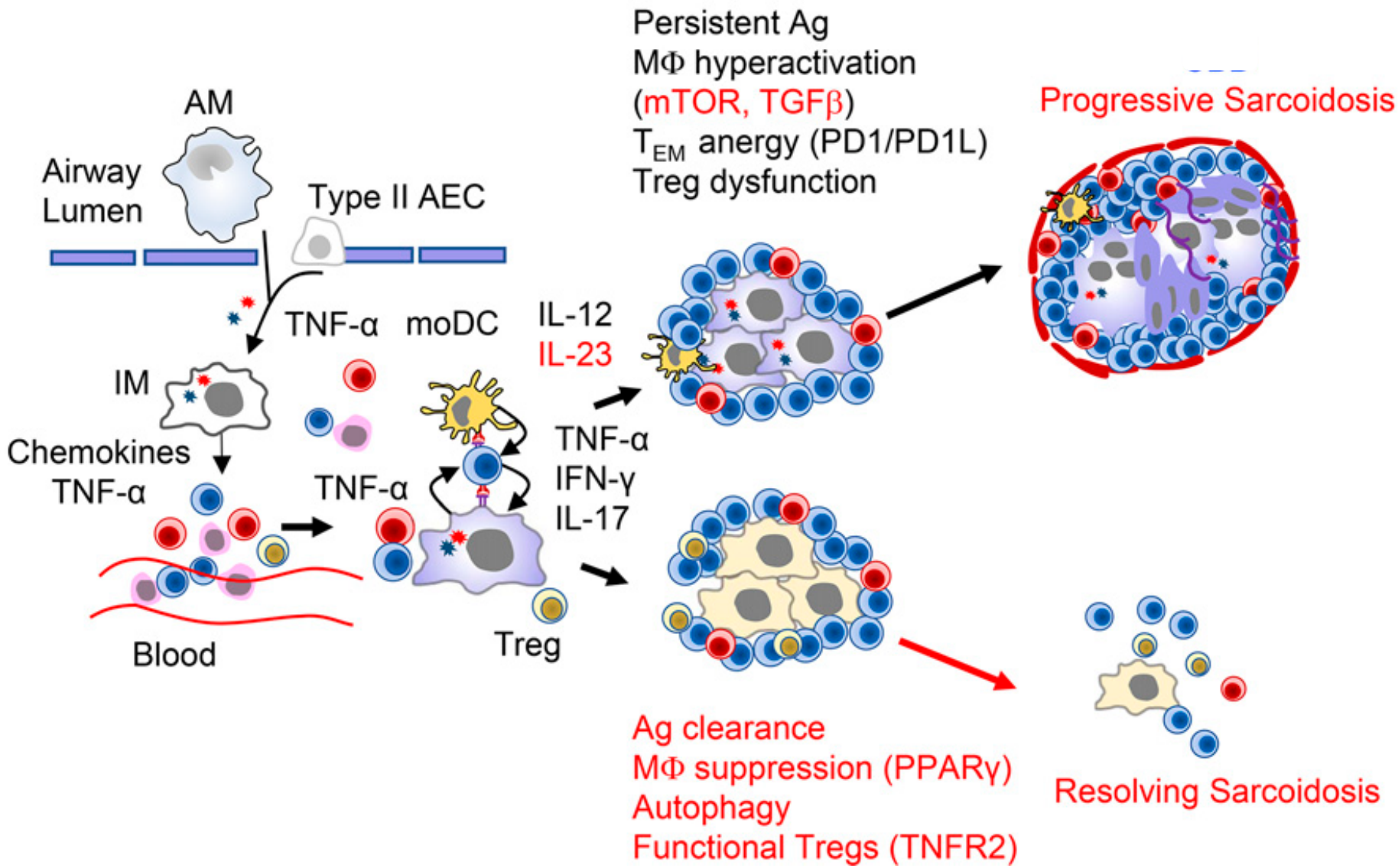
Löfgren's syndrome

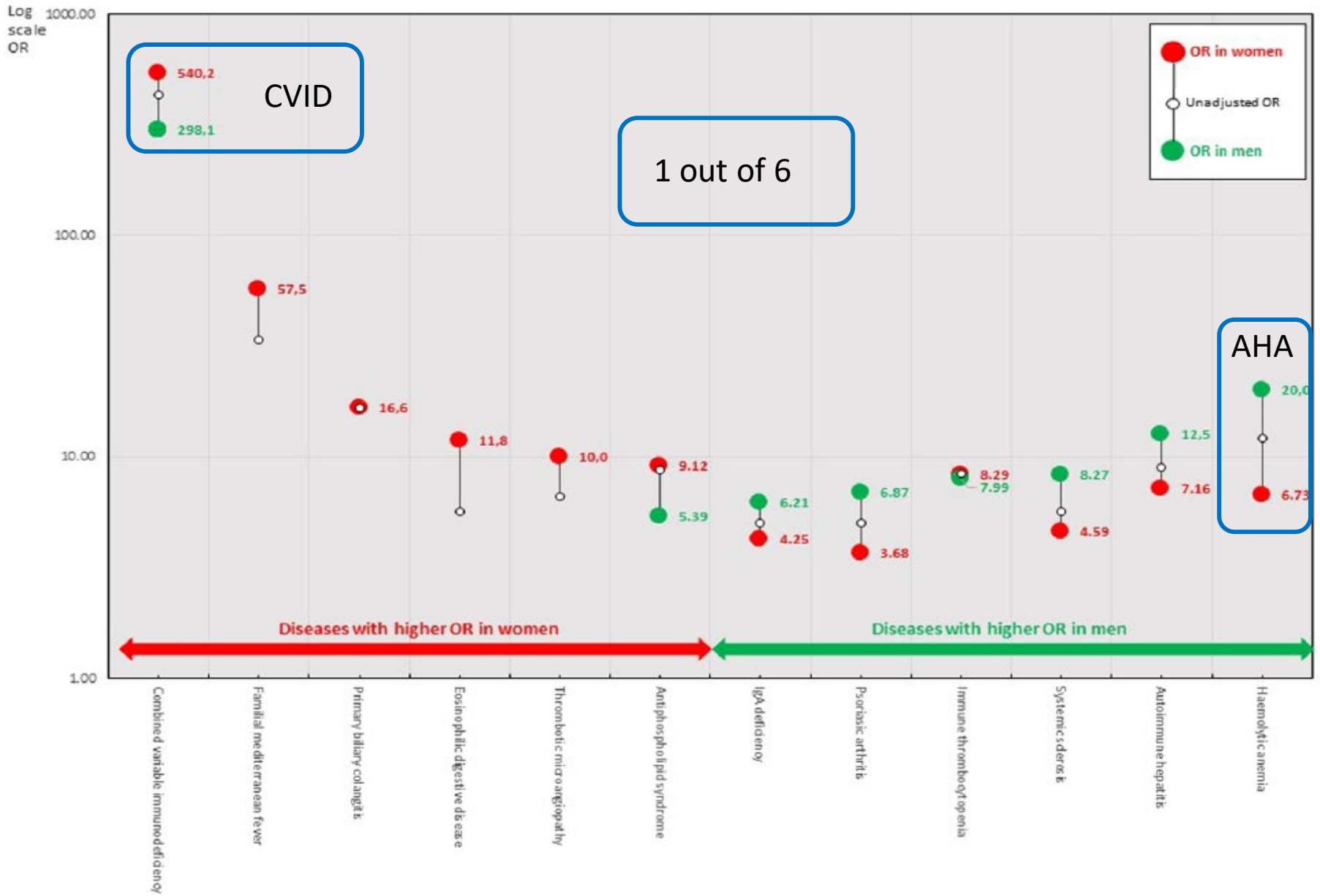
Non-Löfgren's sarcoidosis

NDPD (NAD-dependent protein deacetylase hst4)



A fungal antigenic driver for Löfgren's syndrome sarcoidosis. J Exp Med . 2021 Oct 4;218(10):e20210785.


AM
Airway Lumen
Type II AEC
TNF-α
moDC
IM
Chemokines
TNF-α
TNF-α
Blood
Treg
IL-12
IL-23
TNF-α
IFN-γ
IL-17
Persistent Ag
MΦ hyperactivation
(mTOR, TGFβ)
T_{EM} anergy (PD1/PD1L)
Treg dysfunction
Progressive Sarcoidosis
Ag clearance
MΦ suppression (PPARγ)
Autophagy
Functional Tregs (TNFR2)
Resolving Sarcoidosis



Coexistence of Immune-Mediated Diseases in Sarcoidosis. Frequency and Clinical Significance in 1737 patients. P. Brito-Zerón, et al. 2021

Distinguishing Radiographic features of GLILD in High Resolution Computer Tomography

Feature	CVID	Sarcoidosis
Parenchymal disease	Lower lung zones	Upper lung zones
Hilar adenopathy	+	+++
Nodules	Prominent, large, most randomly distributed	Micronodular, perilymphatic
Bronchiectasis	+++	+

Abbreviations: CVID, common variable immunodeficiency; GLILD, granulomatous and lymphocytic interstitial lung disease

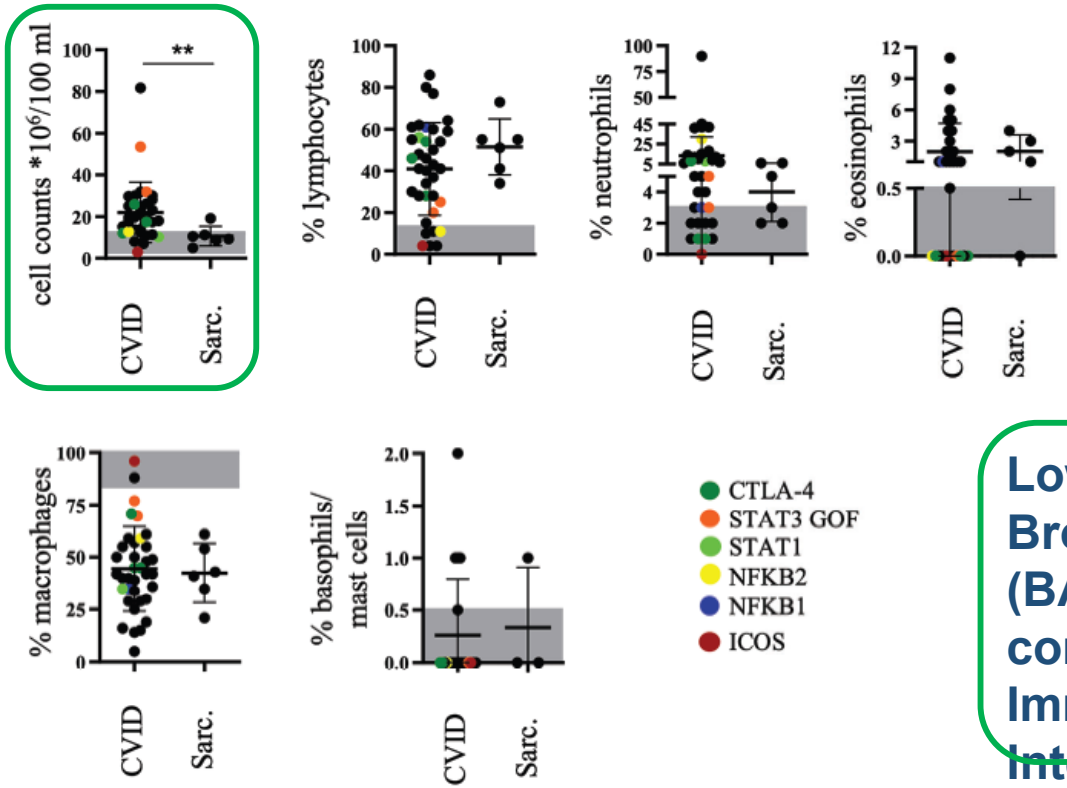
Source: Adapted from Boursiquot et al[7] and Rybicki et al.[10]

Sarcoidosis and Common Variable Immunodeficiency: Similarities and Differences. JW. Verbsky, and JM. Routes, Seminars in Respiratory and Critical Care Medicine Vol. 35 No. 3/2014

Distinguishing Clinical and Laboratory Features of Sarcoidosis versus GLILD

Feature	CVID	Sarcoidosis
Recurrent infections	++ + +	+/−
Autoimmunity	+++	+
Splenomegaly	+++	+/−
Hepatomegaly	++	+/−
Low serum IgG	++ + +	−
Granuloma	++ + +	++ + +
Lymphocytic interstitial pneumonia	++ + +	++
Follicular bronchiolitis	++ + +	++
BAL increased CD4:CD8 ratio	+	+++
Spontaneous disease remission	+/−	+++

Sarcoidosis and Common Variable Immunodeficiency: Similarities and Differences. JW. Verbsky, and JM. Routes, Seminars in Respiratory and Critical Care Medicine Vol. 35 No. 3/2014



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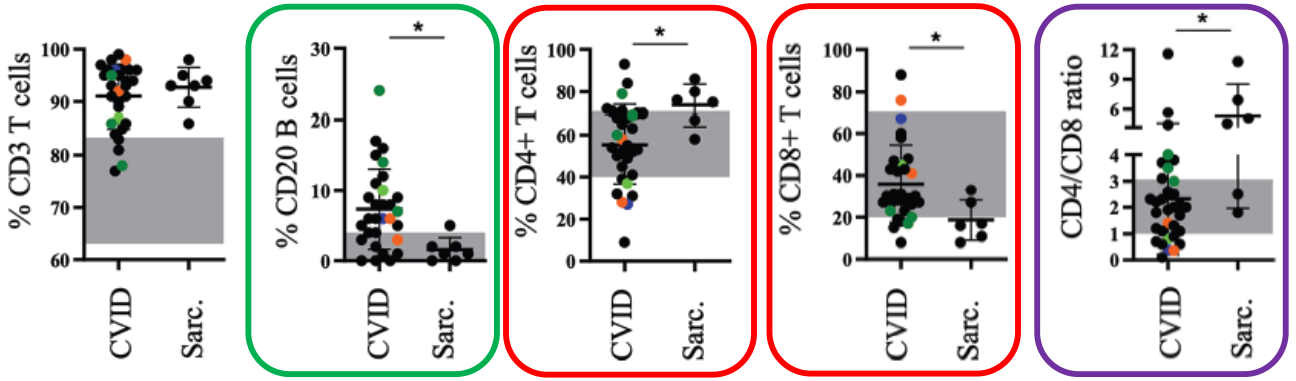
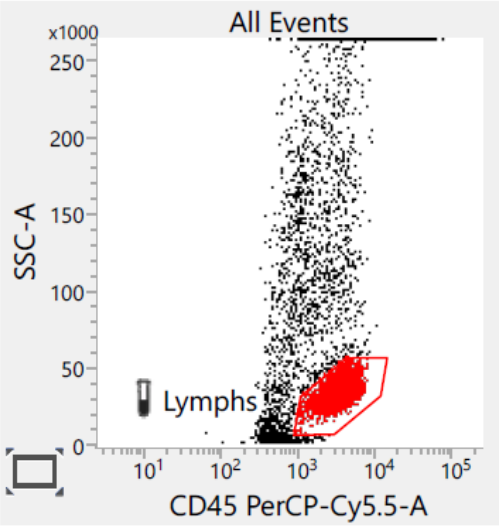
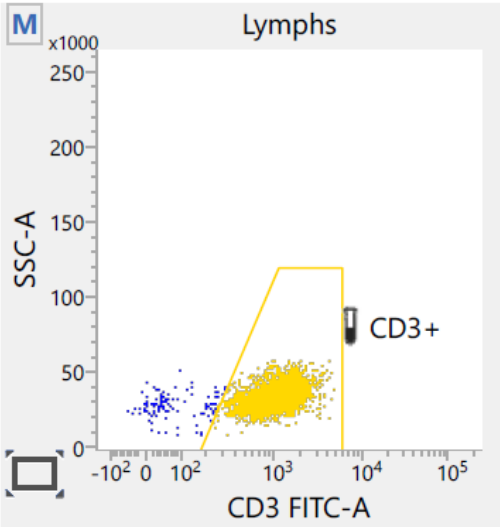
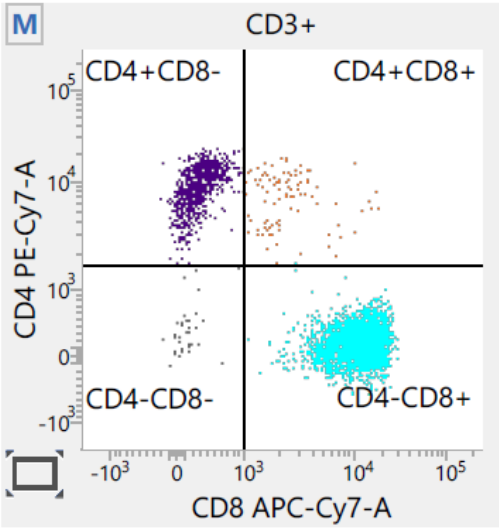
Lower percentage of B cells in Bronchoalveolar Lavage Fluid (BALF) of Sarcoidosis (Sarc) compared to Common Variable Immunodeficiency (CVID) - Interstitial Lung Disease (ILD)

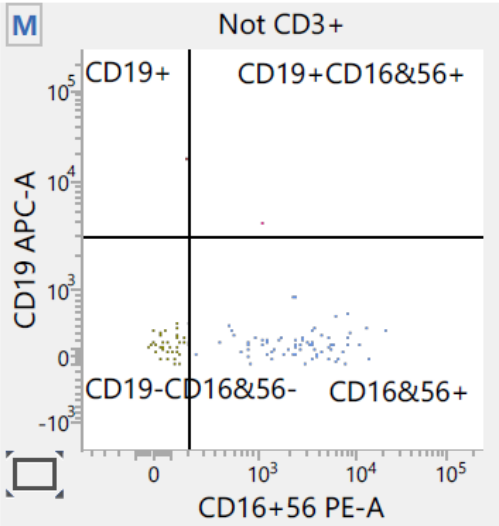


Increased CD4/CD8 Ratio in BALF of Sarcoidosis compared to CVID-ILD



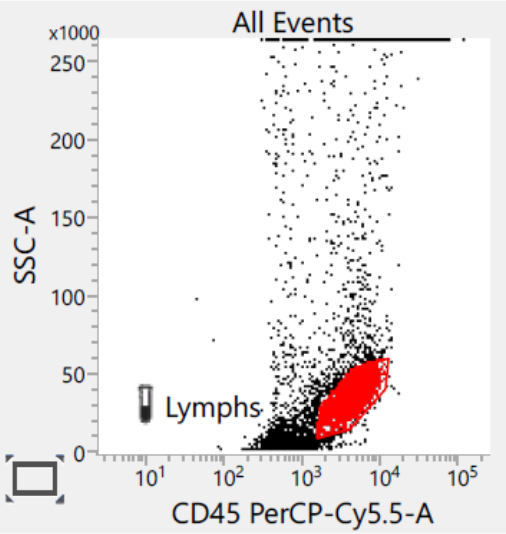


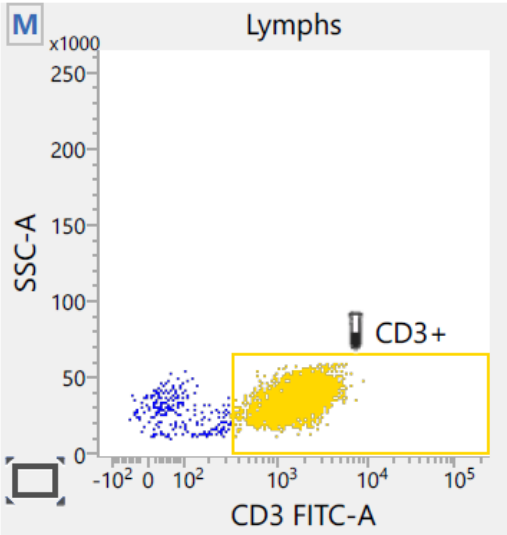


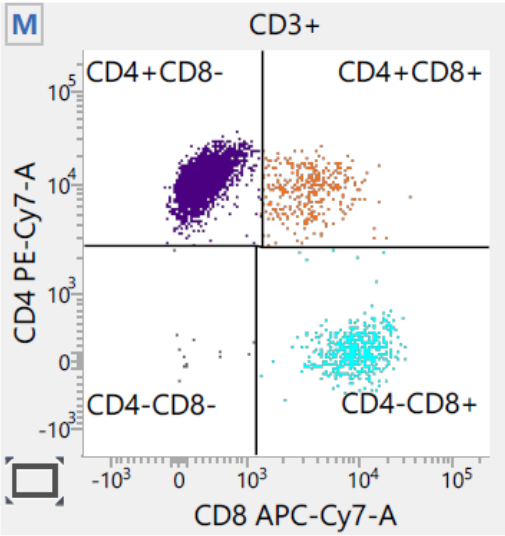


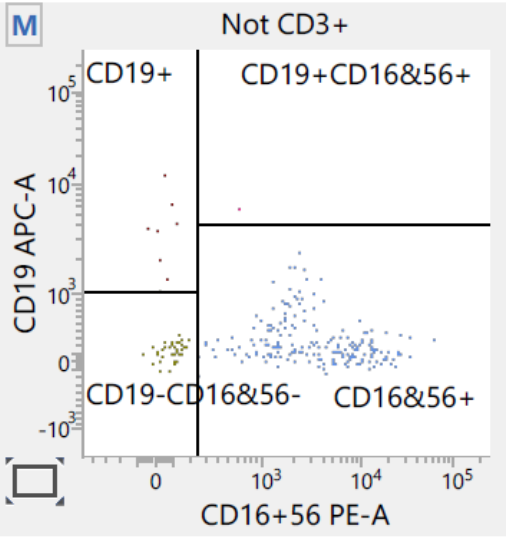
4/8 Ratio	0.34
CD3+	97.23
CD3+CD4+	24.99
CD3+CD4+ (excl. dual pos.)	22.52
CD3+CD8+	73.84
CD3+CD8+ (excl. dual pos.)	71.37
CD3+CD4+CD8+	2.47
CD3+CD4-CD8-	0.87
CD19+	0.03
CD3-CD16+CD56+	1.86

Interstitial pneumopathy



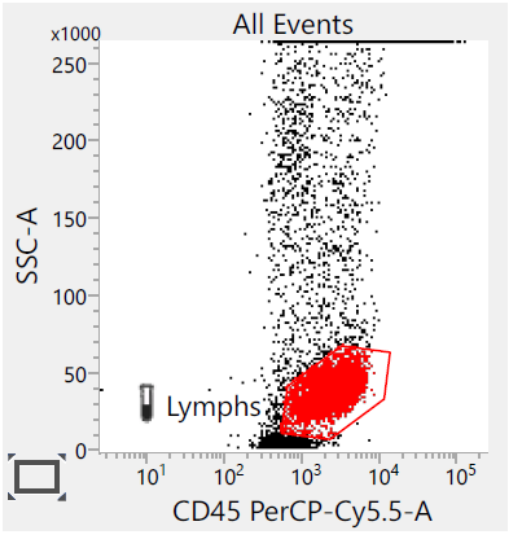


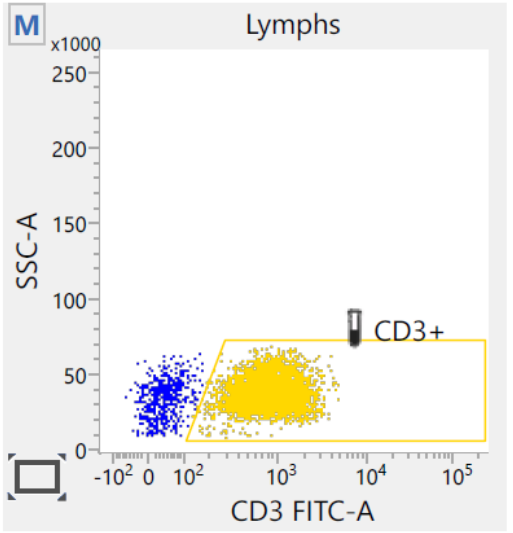


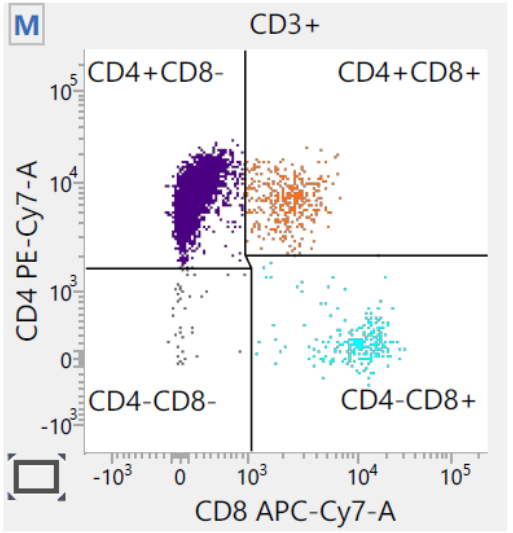


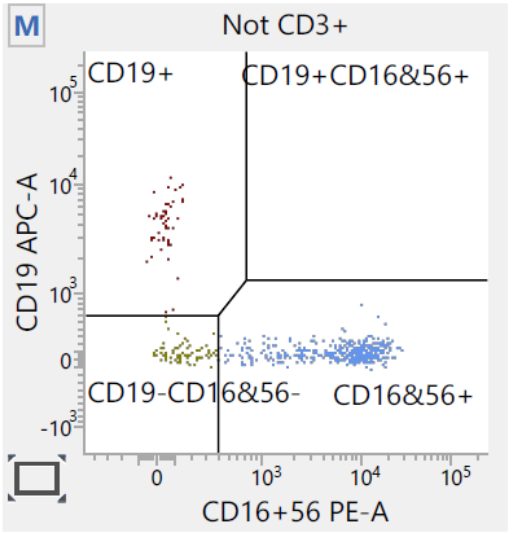
4/8 Ratio	4.34
CD3+	94.84
CD3+CD4+	83.01
CD3+CD4+ (excl. dual pos.)	75.39
CD3+CD8+	19.12
CD3+CD8+ (excl. dual pos.)	11.51
CD3+CD4+CD8+	7.61
CD3+CD4-CD8-	0.32
CD19+	0.15
CD3-CD16+CD56+	4.22

Sarcoidosis 22-934







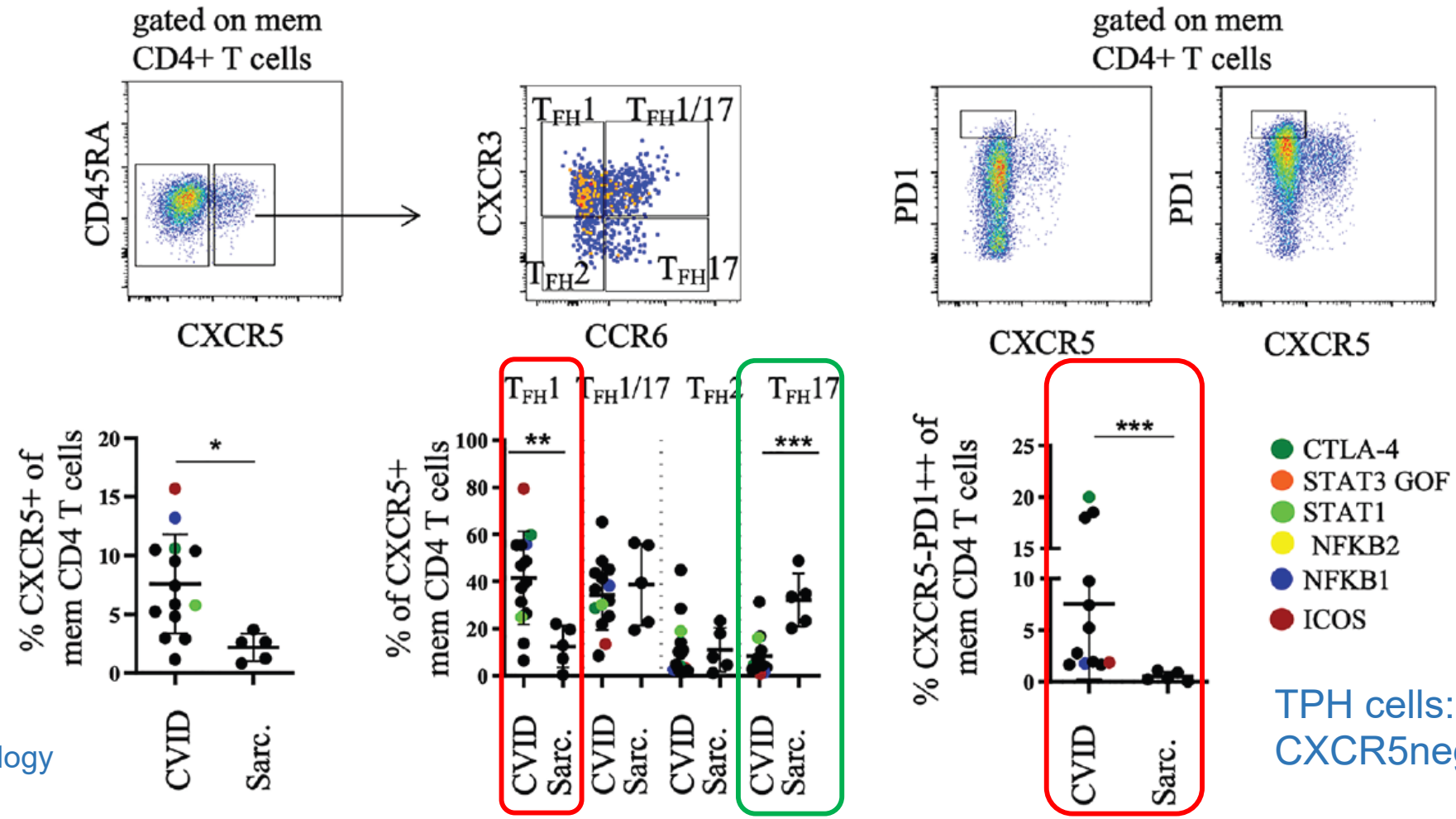


4/8 Ratio	7.92
CD3+	90.51
CD3+CD4+	85.63
CD3+CD4+ (excl. dual pos.)	78.99
CD3+CD8+	10.82
CD3+CD8+ (excl. dual pos.)	4.18
CD3+CD4+CD8+	6.64
CD3+CD4-CD8-	0.70
CD19+	0.97
CD3-CD16+CD56+	7.20

CD4/CD8 ratio >3 plus
CD103+CD4+/CD4+ <0,2

Sarcoidosis 22-315

Increased percentage of TFH17-like and decreased percentage TPH cells in Bronchoalveolar Lavage Fluid (BALF) of Sarcoidosis compared to CVID-ILD



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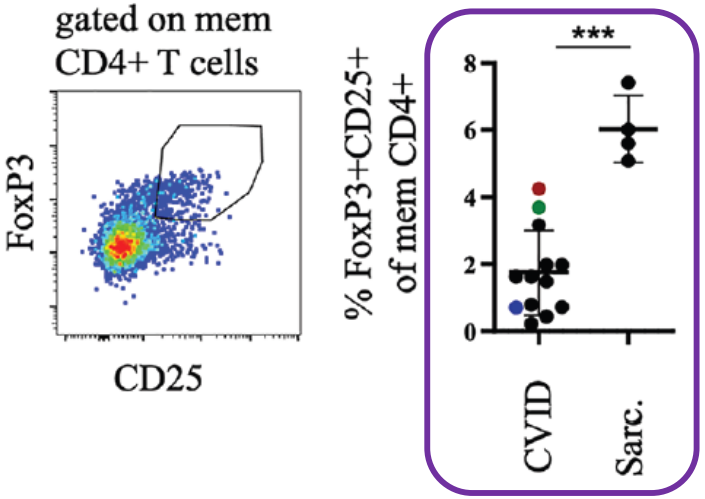
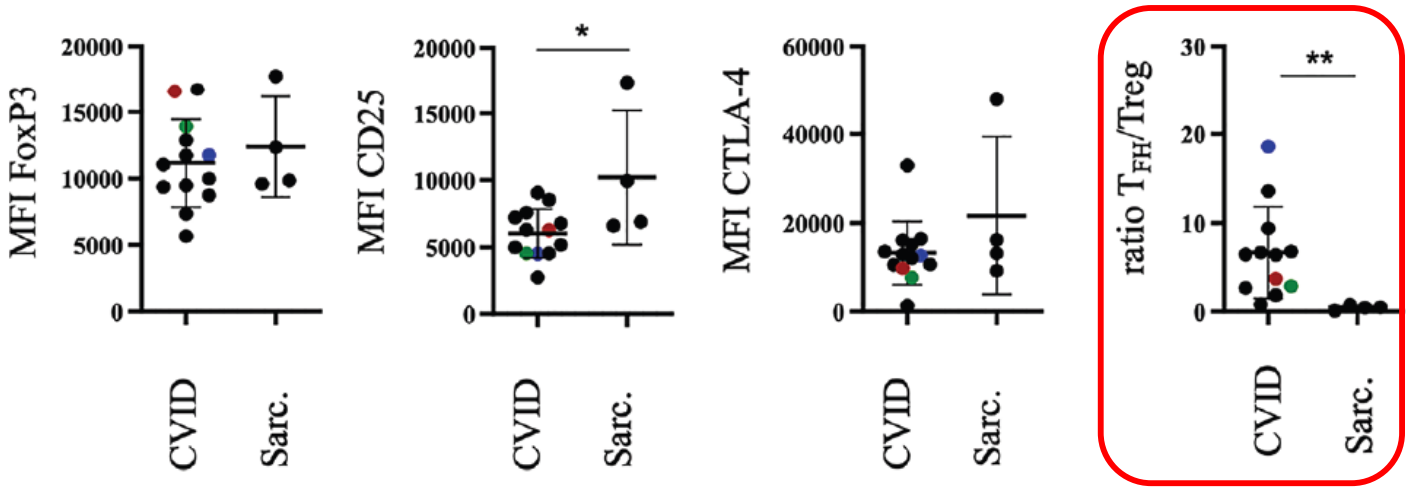
TPH cells: Memory CD4 T cells CXCR5negPD1high

Increased percentage of FoxP3+CD25+ Tregs and decrease Tfh/Treg Ratio in BALF of Sarcoidosis compared to CVID-ILD)GLILD)



Increased percentage FoxP3+CD25+Tregs in BALF of Sarcoidosis compared to CVID-ILD



Decreased Tfh/Treg Ratio in BALF of Sarcoidosis compared to CVID-ILD

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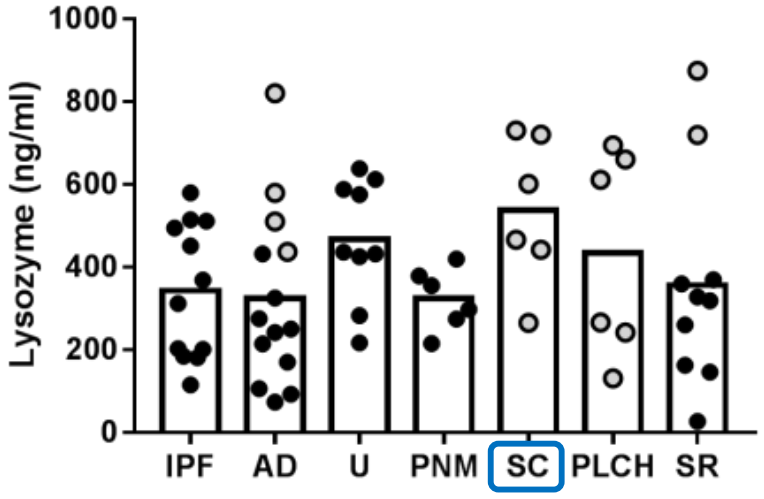
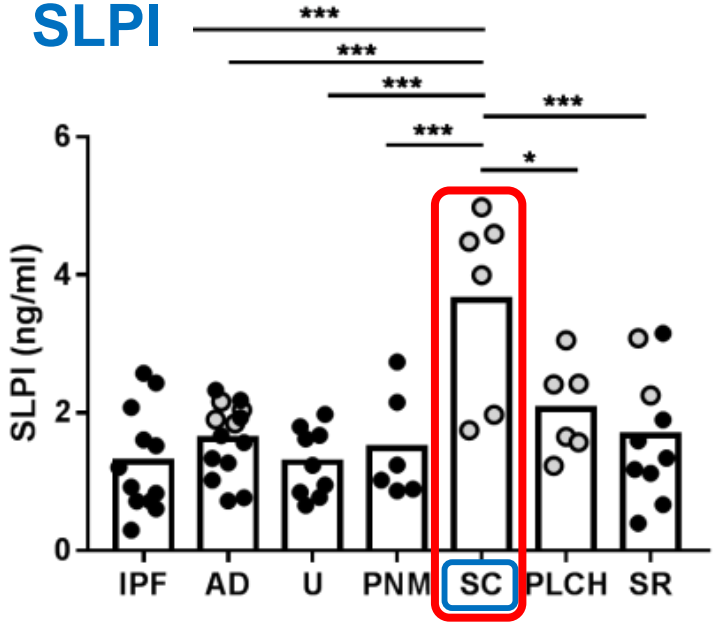
Comparison of Lysozyme and SLPI levels by aetiology: Sarcoidosis versus other Lung Disesases

LYSOZYME



SLPI



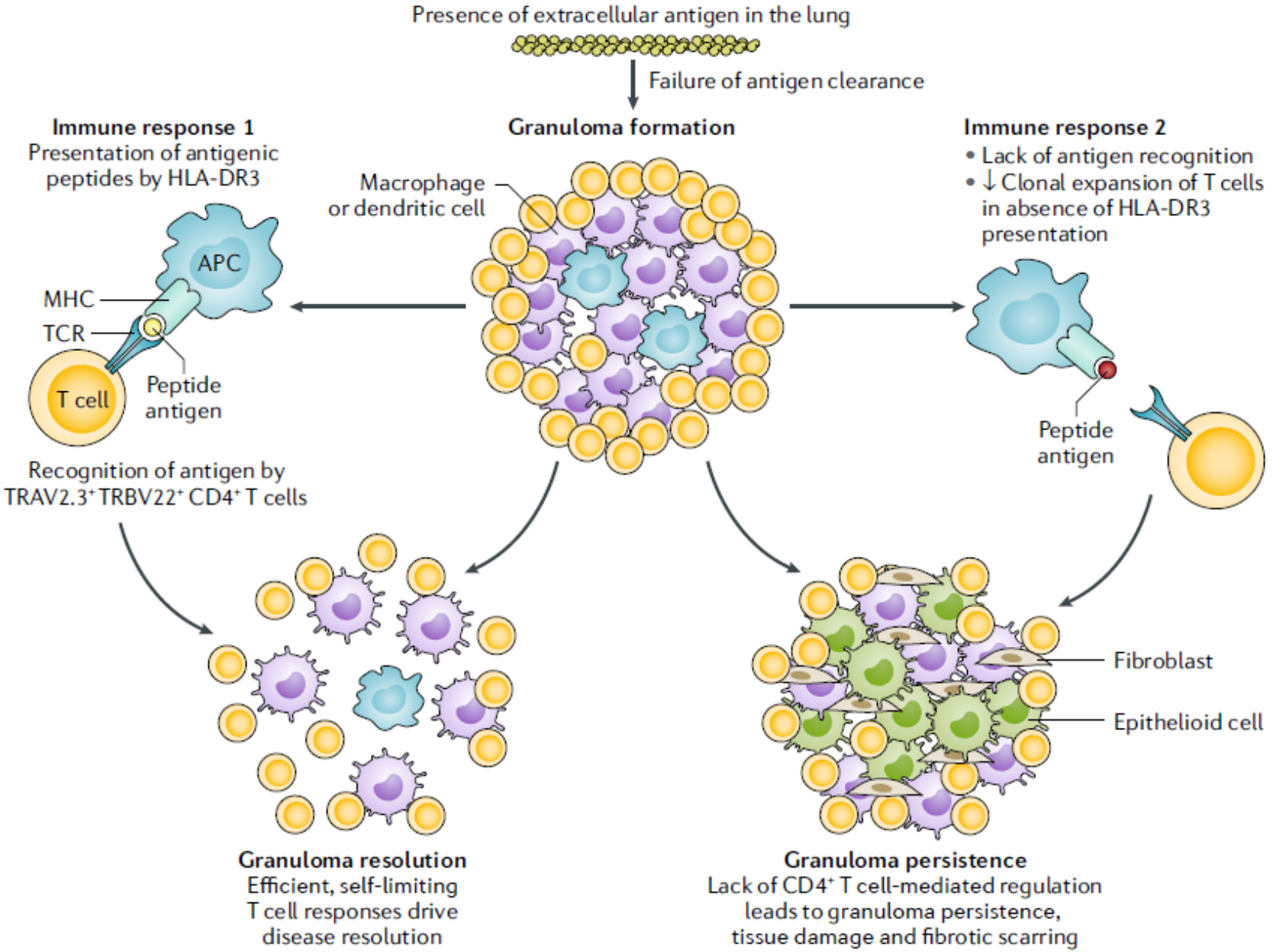
SC: Sarcoidosis

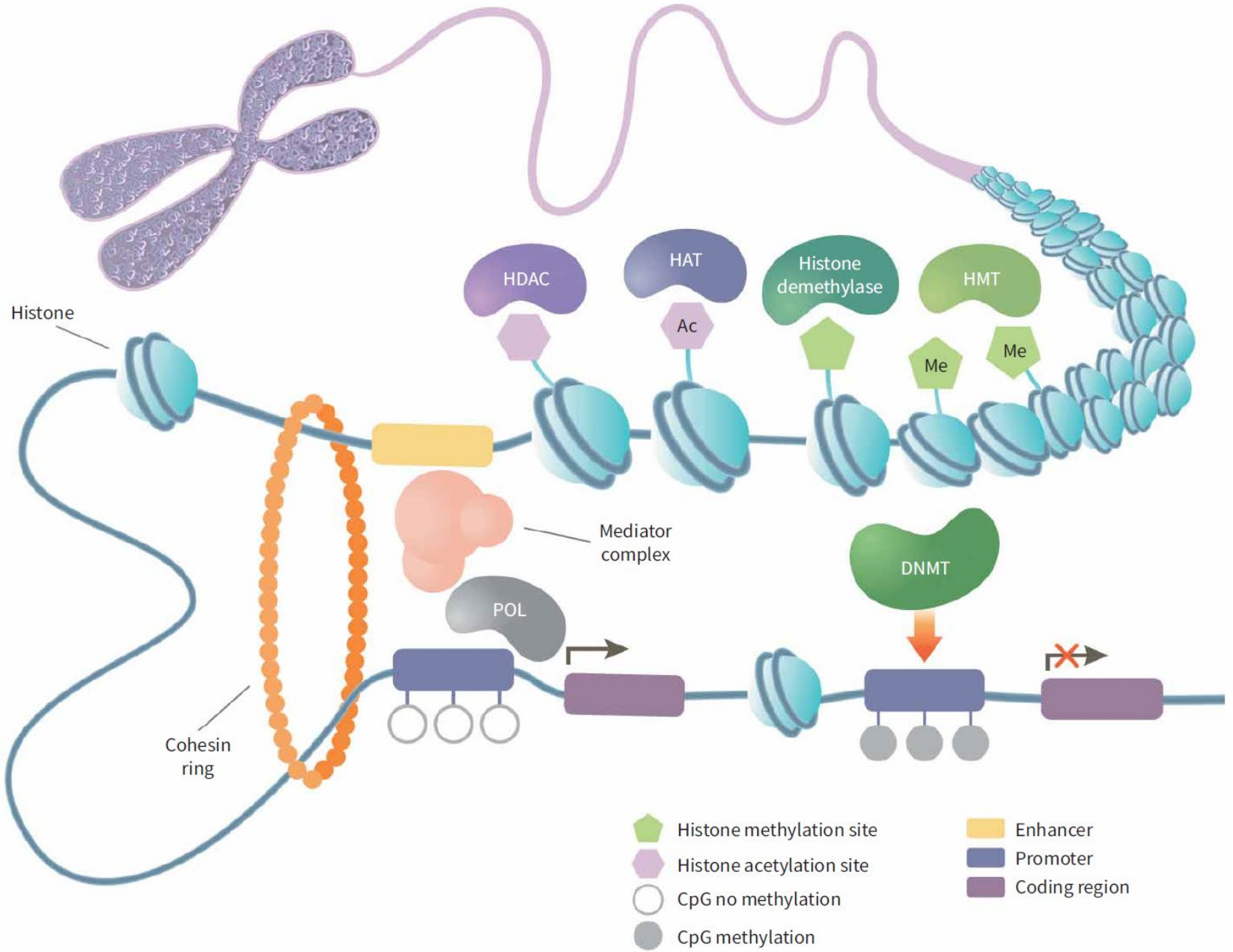
IPF, AD, U, PNM, PLCH: Other Immune-Mediated Lung Diseases

SR-ILD: Smoking-related interstitial lung disease

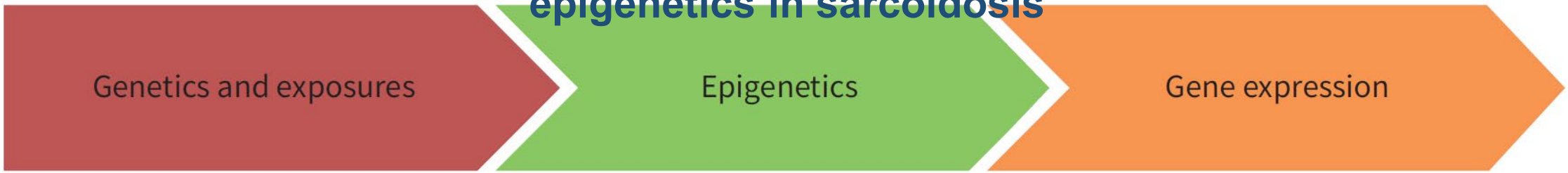
Unpublished Results

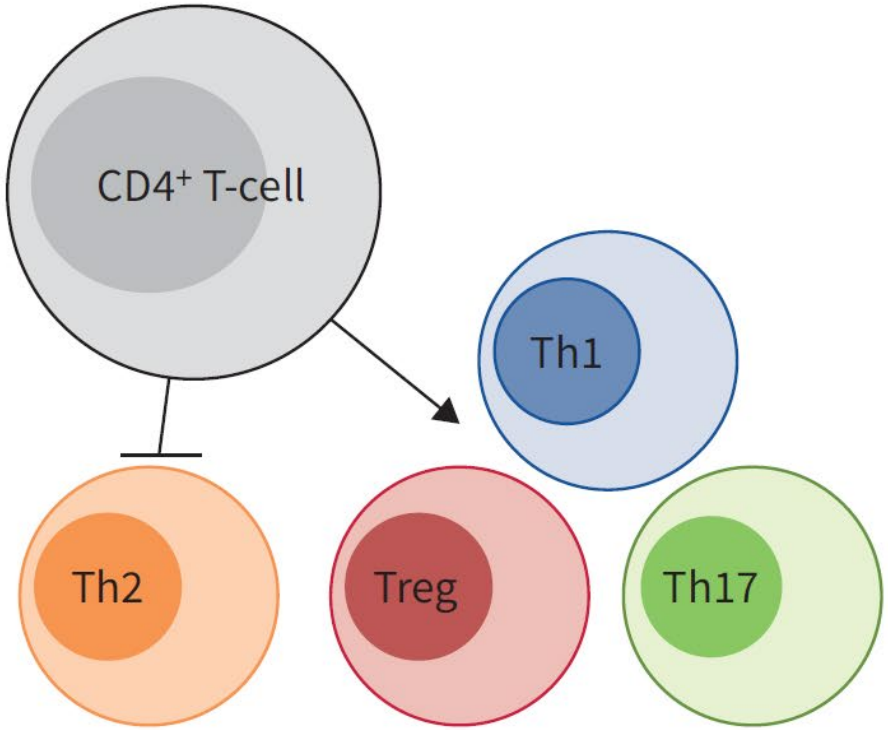
SLPI: Secretory Leukocyte Protease Inhibitor


Presence of extracellular antigen in the lung
Failure of antigen clearance
Granuloma formation
Immune response 1
Presentation of antigenic peptides by HLA-DR3
APC
MHC
TCR
T cell
Peptide antigen
Recognition of antigen by TRAV2.3+ TRBV22+ CD4+ T cells
Macrophage or dendritic cell
Immune response 2
• Lack of antigen recognition
• ↓ Clonal expansion of T cells in absence of HLA-DR3 presentation
Peptide antigen
Fibroblast
Epithelioid cell
Granuloma resolution
Efficient, self-limiting T cell responses drive disease resolution
Granuloma persistence
Lack of CD4+ T cell-mediated regulation leads to granuloma persistence, tissue damage and fibrotic scarring


HDAC
HAT
Histone demethylase
HMT
Histone
Ac
Me
Me
Mediator complex
DNMT
POL
Cohesin ring
Histone methylation site
Histone acetylation site
CpG no methylation
CpG methylation
Enhancer
Promoter
Coding region

Features common to sarcoidosis aetiology that can be mediated through epigenetic modifications, providing the rationale for the study of epigenetics in sarcoidosis

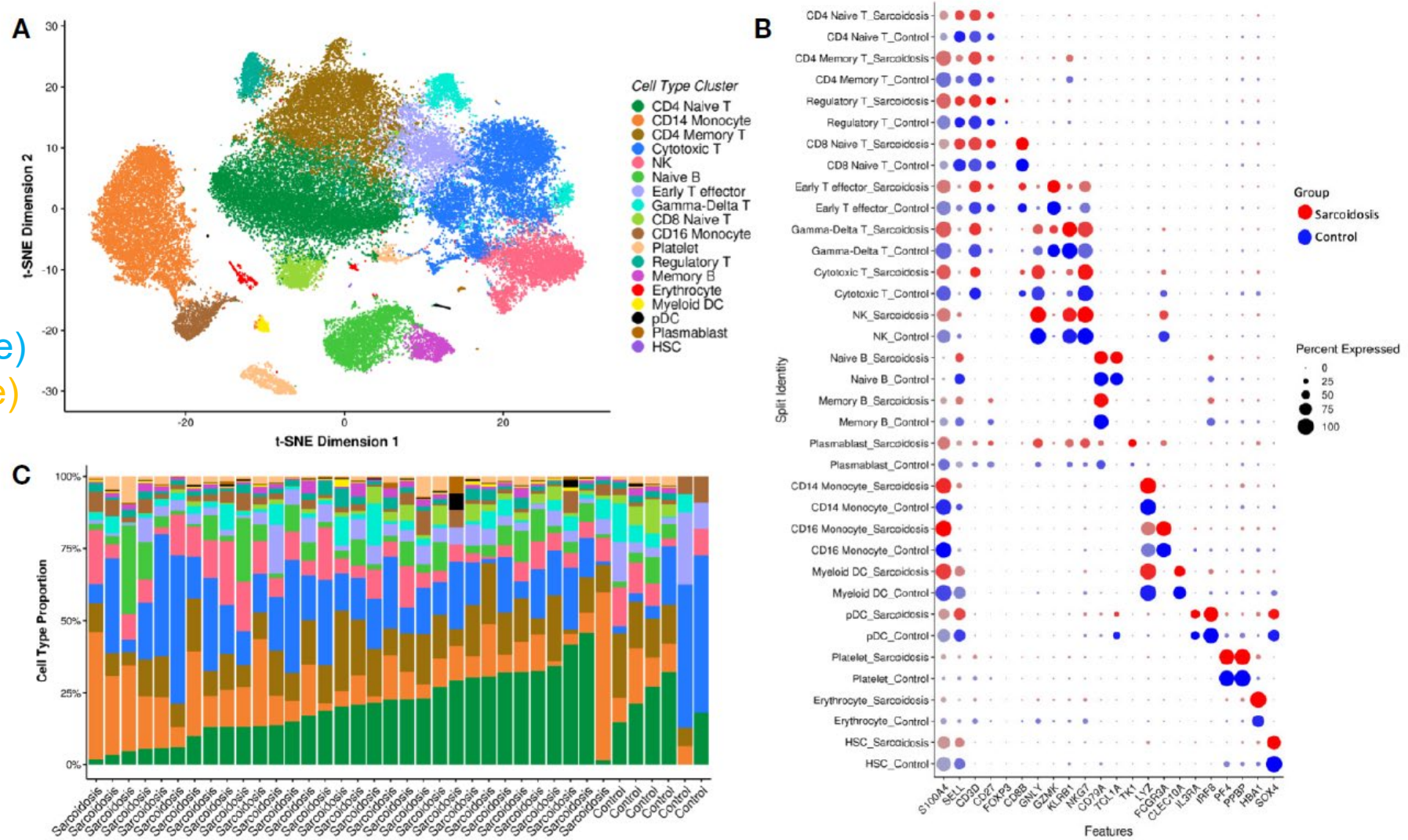




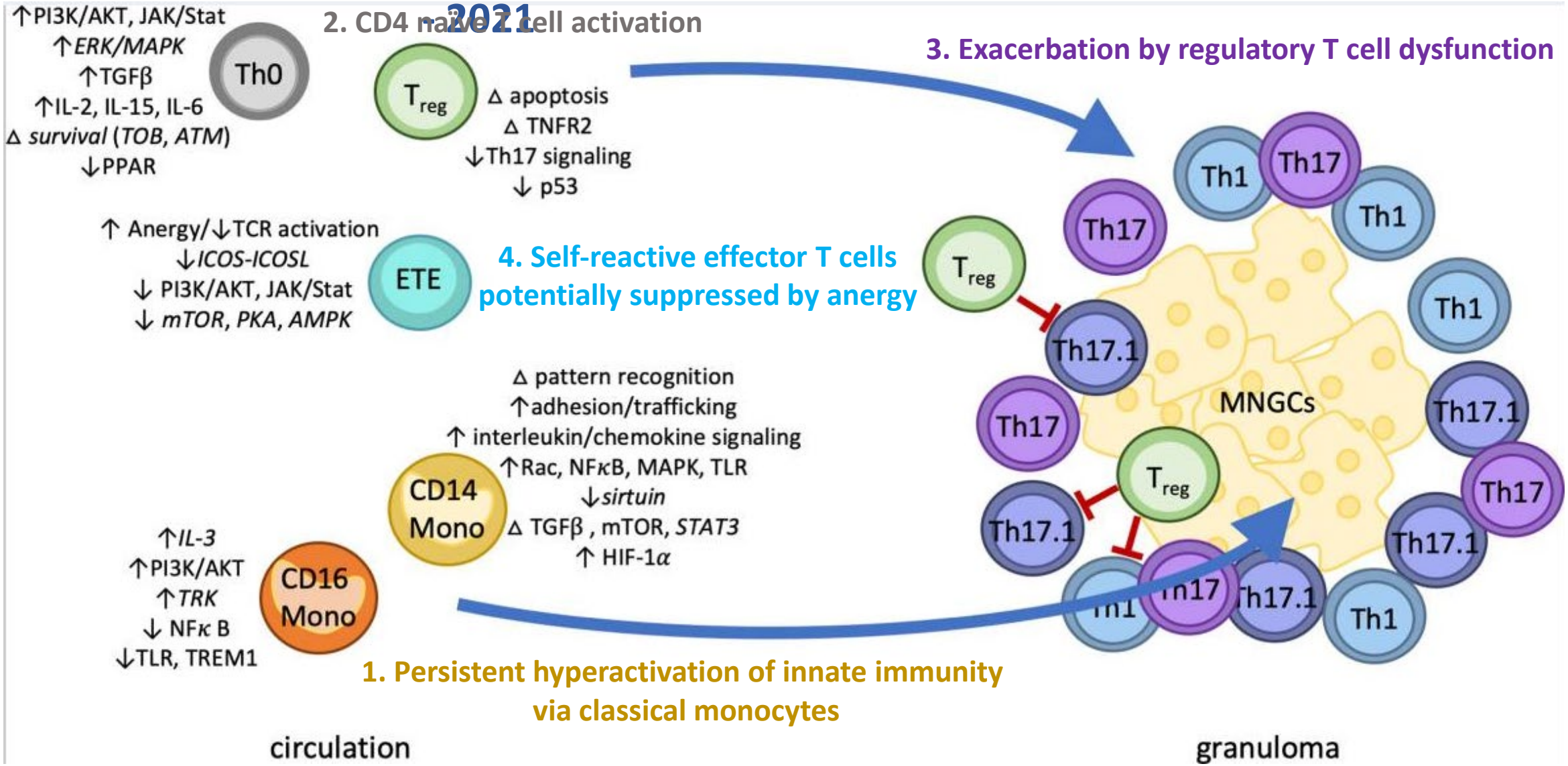
Pulmonary sarcoidosis
- Disease severity
- Disease biology
- Biomarkers
- Therapeutic targets

Single Cell Transcriptomics Implicate Novel Monocyte and T Cell Immune Dysregulation in Sarcoidosis

CD4 T (dark green and brown)
Cytotoxic T (medium blue)
CD14 monocytes (orange)
NK cells (pink)



The Four Pillars of Sarcoidosis Model 2021



Concluding Remarks

- Sarcoidosis is an Immune-mediated inflammatory disease characterized by the presence of non-necrotizing granulomas.
- Sarcoidosis is frequently associated with other Immune-mediated diseases, either Autoimmune or not, as Primary Immunodeficiencies (CVID).
- Sarcoidosis is a disorder of Immune Dysregulation rather than an Autoimmune or an Immunodeficiency disease. The immunomoduladory treatment further support this concept.
- The main antigen underlying Sarcoidosis could be an autoantigen, an infectious agent or different environmental factors, interacting with genetically susceptible individuals (Immunogenetics, Epigenetics).

Muchas Gracias