

Supplementary Tables

Supplementary Table 1. Comparison analysis of canonical pathways of sarcoidosis and TB with and without uveitis in IPA®

Canonical pathways	Sarcoidosis vs Dutch HC (Z-score)	TB vs Indonesian HC (Z-score)	Remarks
Antioxidant Action of Vitamin C	-2	N/A	Inhibited
CDX Gastrointestinal Cancer Signaling Pathway	-2.496	-1.667	
MSP-RON Signaling in Macrophages Pathway	-2.449	-1.633	
Adrenergic Receptor Signaling Pathway (Enhanced)	-3.317	-2.828	
Erythropoietin Signaling Pathway	-3.464	-2.333	
PPAR Signaling	-2.646	-2.236	
RAR Activation	-2.84	-2.53	
LXR/RXR Activation	-2.646	-2.449	
Retinoic acid Mediated Apoptosis Signaling	2	N/A	Activated in sarcoidosis only
Reelin Signaling in Neurons	2	N/A	
HGF Signaling	2	N/A	
NF-κB Activation by Viruses	2	N/A	
NAD Signaling Pathway	2	N/A	
Lymphotoxin β Receptor Signaling	2	N/A	
Ribonucleotide Reductase Signaling Pathway	2	N/A	
iNOS Signaling	2.236	N/A	
B Cell Activating Factor Signaling	2.236	N/A	
Sertoli Cell-Sertoli Cell Junction Signaling	2.236	N/A	
IL-1 Signaling	2.236	N/A	
April Mediated Signaling	2.449	N/A	
RANK Signaling in Osteoclasts	2.449	N/A	
Inhibition of ARE-Mediated mRNA Degradation Pathway	2.449	N/A	
Senescence Pathway	2.449	N/A	
IL-8 Signaling	2.449	N/A	
Estrogen Receptor Signaling	1	2.236	Activated in both sarcoidosis and TB
Aryl Hydrocarbon Receptor Signaling	N/A	2	Activated in TB only
Role of IL-17F in Allergic Inflammatory Airway Diseases	N/A	2	
MSP-RON Signaling in Cancer Cells Pathway	N/A	2	
Pathogen Induced Cytokine Storm Signaling Pathway	5.385	4.796	Activated in both sarcoidosis and TB
Cardiac Hypertrophy Signaling (Enhanced)	4.796	3.873	
Wound Healing Signaling Pathway	4.583	3.873	
Cachexia Signaling Pathway	4.583	3.317	
Macrophage Classical Activation Signaling Pathway	4.472	3.207	
Th1 Pathway	4	3.742	
Crosstalk between Dendritic Cells and Natural Killer Cells	3.873	3.464	
Dendritic Cell Maturation	4.123	3.464	
Multiple Sclerosis Signaling Pathway	4	3.464	
NOD1/2 Signaling Pathway	4	3.162	
IL-17 Signaling	3.638	3.207	
Role of Chondrocytes in Rheumatoid Arthritis Signaling Pathway	3.742	3.317	
S100 Family Signaling Pathway	3.638	3.357	
NF-κB Signaling	3.742	2.828	
Regulation of the Epithelial Mesenchymal Transition by Growth Factors Pathway	3.464	2.449	
Type I Diabetes Mellitus Signaling	3.317	2.449	
Role of Osteoblasts in Rheumatoid Arthritis Signaling Pathway	3.357	2.887	

IL-6 Signaling	3.162	2.828	
Natural Killer Cell Signaling	3	2.714	
HMGB1 Signaling	3.317	3.162	
Hepatic Fibrosis Signaling Pathway	3.153	3.162	
Role of Hypercytokinemia/hyperchemokine in the Pathogenesis of Influenza	3	3	
Systemic Lupus Erythematosus in B Cell Signaling Pathway	2.985	3.051	
Tumor Microenvironment Pathway	2.53	3	
Immunogenic Cell Death Signaling Pathway	2.828	2.646	
TREM1 Signaling	2.828	2.828	
Role of Tissue Factor in Cancer	2.828	2.828	
Role of MAPK Signaling in Inhibiting the Pathogenesis of Influenza	2.646	2.828	
Acute Phase Response Signaling	2.53	2.646	
IL-17A Signaling in Fibroblasts	2.646	2.646	
Phagosome Formation	2.646	2.646	
Pulmonary Fibrosis Idiopathic Signaling Pathway	1.633	2.449	
HIF1 α Signaling	1.667	2.449	
Role of PKR in Interferon Induction and Antiviral Response	2.333	2.646	
Colorectal Cancer Metastasis Signaling	2.121	2.828	
T Cell Receptor Signaling	2.121	2.646	
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	2	2.449	
Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F	2	2.449	
STAT3 Pathway	2.121	2.449	
ILK Signaling	2.236	2.449	
IL-33 Signaling Pathway	2.887	2.449	
NFKBIE Signaling Pathway	3	2	
p38 MAPK Signaling	3	2.236	
Activin Inhibin Signaling Pathway	2.887	2.121	
Cholecystokinin/Gastrin-mediated Signaling	2.236	2.236	
FAT10 Cancer Signaling Pathway	2.236	2	
IL-15 Production	2.236	2	
Neuroinflammation Signaling Pathway	2.065	2.138	
Pyroptosis Signaling Pathway	2	2	
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	2	2	
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	2.646	2.236	
Activation of IRF by Cytosolic Pattern Recognition Receptors	2.646	2	
IL-12 Signaling and Production in Macrophages	2.496	1.941	
T Cell Exhaustion Signaling Pathway	2.53	1.897	
Necroptosis Signaling Pathway	2.449	2	
Adrenomedullin signaling pathway	2.449	2	
LPS/IL-1 Mediated Inhibition of RXR Function	2.449	2	
Toll-like Receptor Signaling	2.449	2	

Supplementary Table 2. Top 10 activated inhibited upstream regulators in sarcoidosis and active pulmonary TB

No	Sarcoidosis			Active pulmonary TB		
	Upstream regulators	z-score	P-value (B-H corrected)	Upstream regulators	z-score	P-value (B-H corrected)
<u>Activated</u>						
1	lipopolysaccharide	6.774	2.81E-36	TNF	5.724	8.76E-28
2	TNF	6.478	7.19E-32	tetradecanoylphorbol acetate	5.076	9.86E-17
3	tetradecanoylphorbol acetate	5.869	4.8E-17	poly rI:rC-RNA	4.989	9.41E-24
4	IFNG	5.655	2.15E-29	lipopolysaccharide	4.809	2.71E-28
5	poly rI:rC-RNA	5.455	1.91E-21	IL2	4.592	3.09E-19
6	IL2	4.754	5.06E-21	NFkB (complex)	4.563	6.99E-19
7	NFkB (complex)	4.667	4.41E-16	IFNG	4.346	2.28E-29
8	Interferon alpha	4.635	2.57E-26	CD40LG	4.314	2.94E-20
9	CD40LG	4.571	6.27E-19	IL1B	4.17	2.23E-24
10	IL1B	4.361	2.83E-24	CSF2	4.037	4.09E-14
<u>Inhibited</u>						
1	SB203580	-3.551	5.05E-11	SP600125	-3.951	4.97E-15
2	SP600125	-3.449	2.45E-09	SB203580	-3.373	1.21E-14
3	N-acetyl-L-cysteine	-3.437	2.07E-13	U0126	-3.268	2.50E-10
4	ETV6-RUNX1	-3.401	3.09E-09	Sb202190	-3.243	1.22E-11
5	U0126	-3.094	3.42E-08	resveratrol	-3.203	7.72E-09
6	APOE	-3.083	1.38E-09	APOE	-3.084	2.37E-14
7	(S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid, methyl ester	-2.976	1.58E-11	RNF5	-3	2.05E-10
8	HIVEP1	-2.967	3.33E-10	HBB	-3	7.21E-15
9	etanercept	-2.96	1.58E-11	ETV6-RUNX1	-2.982	5.51E-06
10	Sb202190	-2.936	1.40E-06	(S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid, methyl ester	-2.976	4.74E-14

Supplementary Table 3. Two RNA-seq datasets sourced from *in vitro* studies through analysis match feature in IPA® with more than 50% overall similarities with the current sarcoidosis and TB proteomic datasets

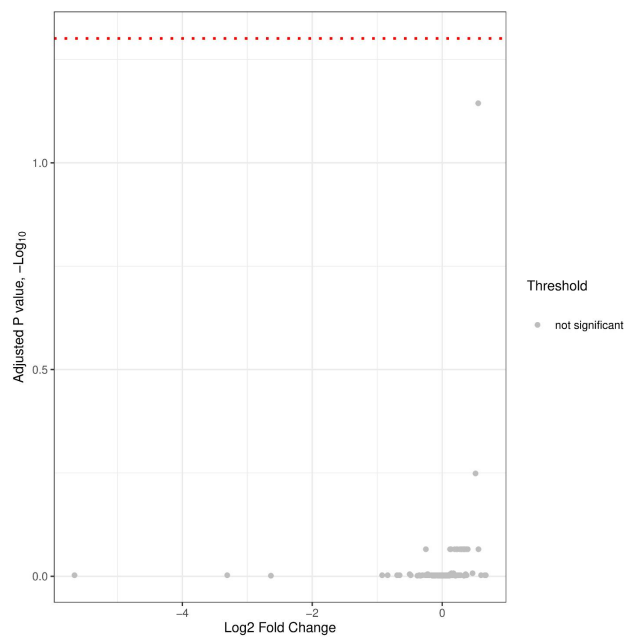
Online datasets	Group	Our dataset	Canonical pathways z-score	Upstream regulators z-score	Causal networks z-score	Diseases & functions z-scores	Overall-z score
<u>GSE67427</u> (RNA-seq of monocyte-derived macrophages isolated from 6 healthy European males at 4-, 18-, and 48-hours post-infection with the following 8 bacteria: Mycobacterium tuberculosis (<i>Mtb</i>) H37Rv, <i>Mtb</i> GC1237, <i>Mtb</i> GC1237, bacillus Calmette-Guérin (BCG), Mycobacterium smegmatis, Yersinia pseudotuberculosis, Salmonella typhimurium, and Staphylococcus epidermidis.)	<i>Mtb</i> GC1237 vs uninfected	All TB vs Indonesian controls	63.25%	70.00%	59.16%	62.13%	63.63%
		All sarcoidosis vs Dutch controls	66.67%	67.82%	55.68%	58.55%	62.18%
	<i>Mtb</i> H37Rv vs uninfected	All TB vs Indonesian controls	77.46%	73.48%	37.42%	56.20%	61.143%
		All sarcoidosis vs Dutch controls	74.54%	67.08%	53.85%	46.29%	60.44%
<u>GSE143731</u> (mRNA sequencing of human monocytes-derived macrophages treated with selected drugs. The cells were either infected with <i>Mtb</i> resistant to the drug, or were uninfected)	<i>Mtb</i> -infected, treated with isoniazid vs uninfected	All TB vs Indonesian controls	77.46%	72.11%	50.00%	62.13%	65.42%
		All sarcoidosis vs Dutch controls	78.17%	67.08%	47.96%	54.77%	62.00%
	<i>Mtb</i> -infected, treated with amikacin vs uninfected	All TB vs Indonesian controls	68.31%	72.80%	44.72%	52.98%	59.70%
		All sarcoidosis vs Dutch controls	70.71%	67.08%	45.83%	52.10%	58.93%

Supplementary Table 4. Effect sizes of selected proteins from serum proteomics after age and sex correction and down sampling of sarcoidosis cohort

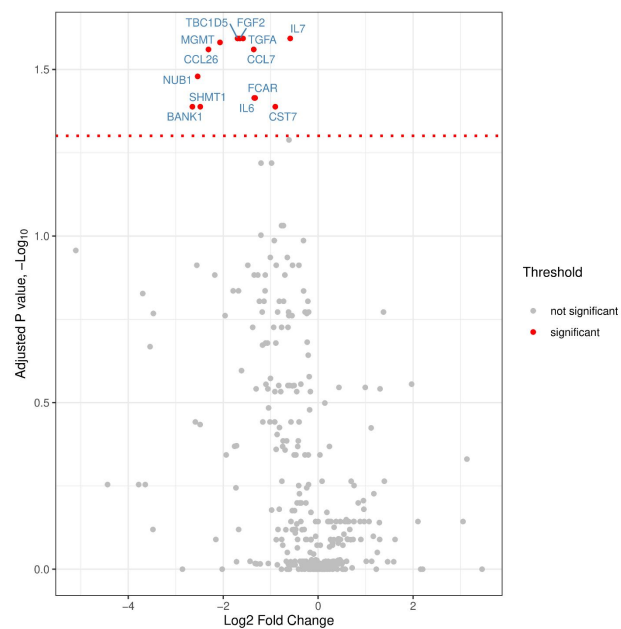
Proteins	Sarcoidosis, all patients (n=90)				Sarcoidosis, age & sex-corrected (down sampled patients, n= 20)		
	Fold change	Uncorrected, p-values	Age and sex- corrected p-values	Cohen's d	Fold change	p-values	Cohen's d
BAFF signaling associated proteins							
TNFRSF13B/TACI	1.650318869	7.37269E-05	0.000594	0.86	1.32786034	0.042222967	0.57
TRAF2	1.262665918	3.45338E-07	9.6E-08	0.87	1.235655779	0.000144719	0.87
IKBKG	1.212411998	9.82379E-08	5.53E-11	1.13	1.200638376	8.35081E-05	1.10
MAPK9	1.406243732	3.69993E-08	1.47E-08	1.02	1.253027489	0.000245604	0.59
NFATC1	1.260849265	3.4988E-07	3.99E-10	0.96	1.270229265	0.000883993	1.04
SLAMF7	1.185568857	0.001121896	0.006885	0.43	1.060233047	0.061878457	0.12
Other selected proteins							
IL-16	1.285615469	1.30999E-07	2.99E-10	1.08	1.26745926	3.61744E-05	0.92
TRAIL/TNFSF10	1.298236503	5.31922E-05	4.89E-05	0.73	1.419336733	0.015703251	1.39
CCL11	1.37836958	0.001112532	0.001737	0.66	1.189917077	0.146275558	0.31
FGF2	1.305279937	0.001206873	0.007317	0.42	0.95264376	0.112700551	0.08
Fas Ligand	1.227140002	0.012398214	0.014355	0.29	0.990433946	0.026034131	0.01
GZMB	0.9188832	0.021661972	0.062019	0.09	1.116744368	0.227749744	0.10
IL-17C	2.003705191	0.002463424	0.006386	0.74	1.605911703	0.019280718	0.70

Supplementary Table 5. Effect sizes of selected proteins from serum proteomics after age and sex correction active pulmonary TB cohort

Proteins	Active pulmonary TB, all patients (n=22)			
	Fold change	Uncorrected, p-values	Age and sex-corrected p-values	Cohen's d
BAFF signaling associated proteins				
TNFRSF13B/TACI	1.694772	0.135361	0.226319	0.68
TRAF2	1.329804	0.419745	0.295548	0.37
IKBKG	1.313403	0.31136	0.467203	0.36
MAPK9	0.927153	0.778233	0.812734	0.15
NFATC1	1.1388	0.65352	0.681143	0.16
SLAMF7	1.207088	0.381385	0.226511	0.39
Other selected proteins				
IL-16	1.974892	0.078796	0.481867	0.66
TRAIL/TNFSF10	7.400254	0.061468	0.346249	0.50
CCL11	3.207371	0.102668	0.388918	0.62
FGF2	1.303161	0.61479	0.419608	0.30
Fas Ligand	1.134849	0.972931	0.869449	0.06
GZMB	2.474377	0.463198	0.939401	0.19
IL-17C	0.967668	0.778233	0.803057	0.01

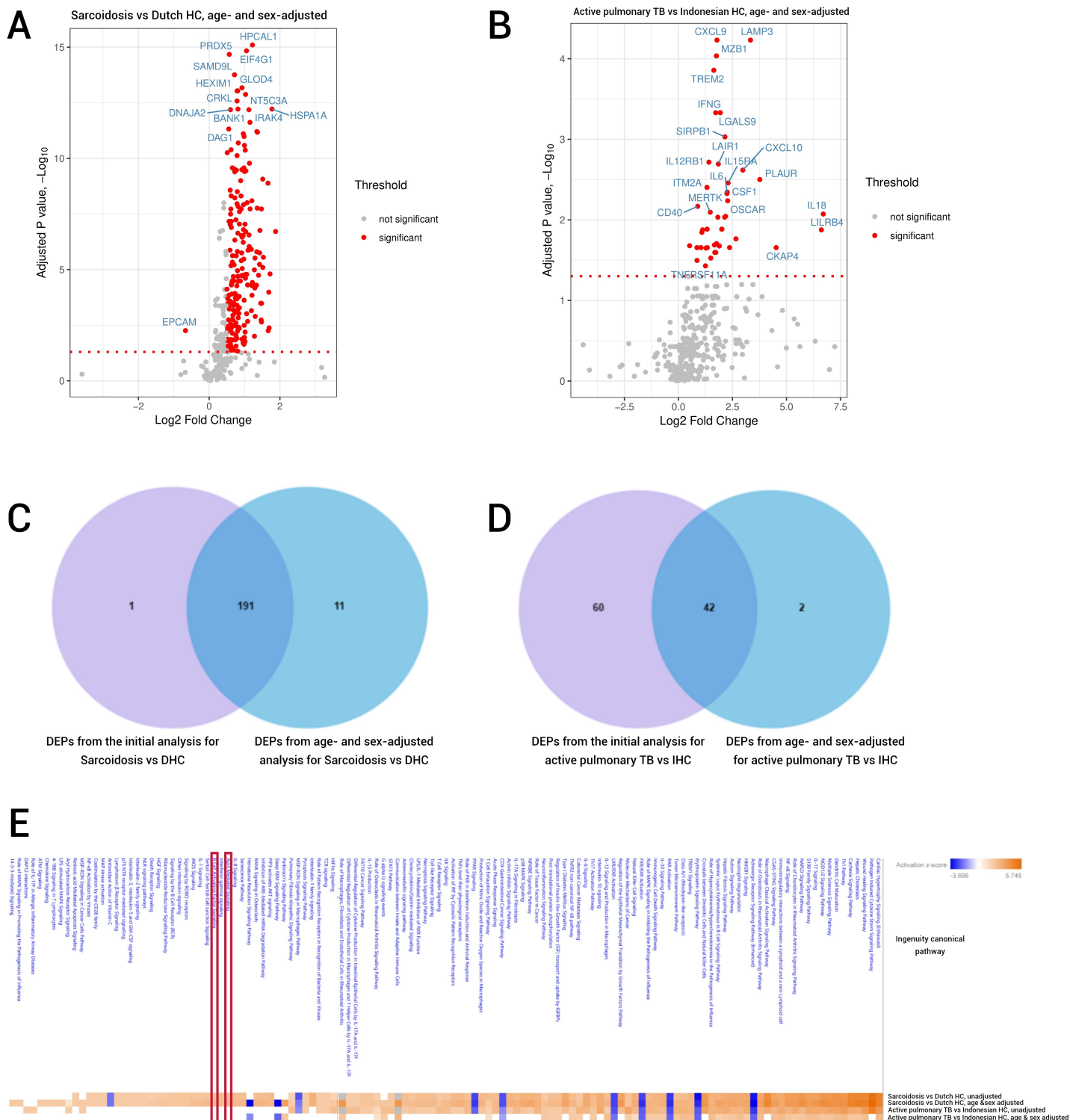
A

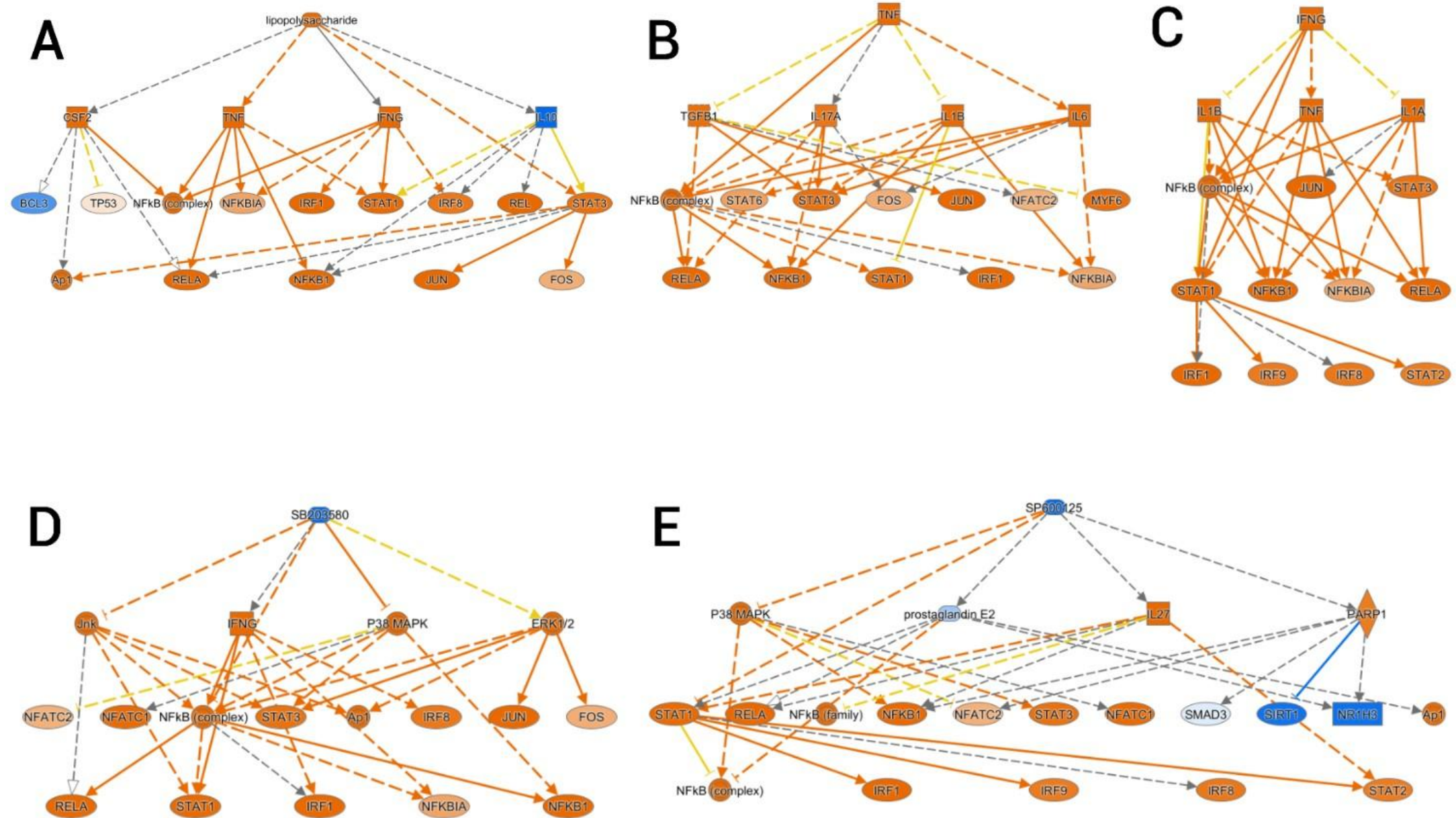
Sarcoidosis with uveitis (S+OS) vs sarcoidosis without uveitis (SS)

B

Pulmonary TB with uveitis (P+OTB) vs pulmonary TB without uveitis (PTB)

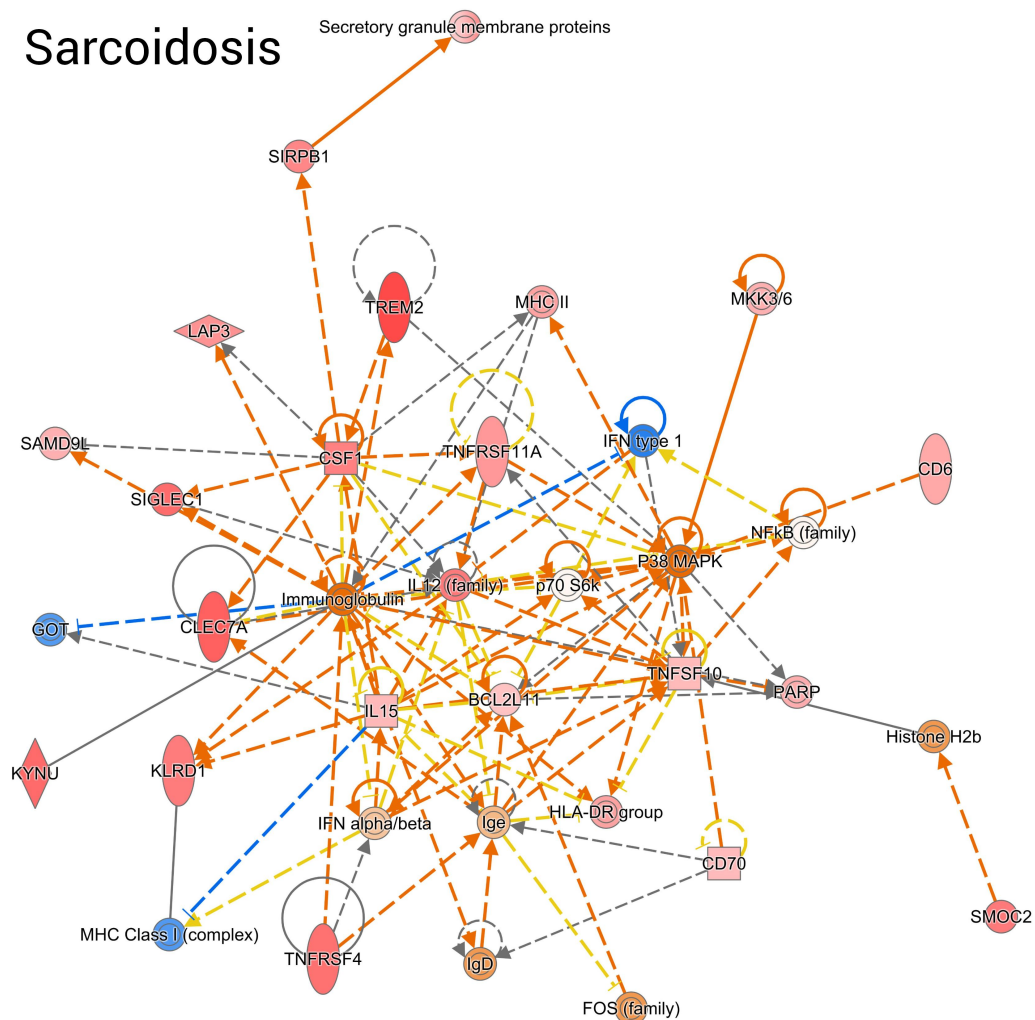
Supplementary Figure 2. Volcano plots with vs without uveitis. **A.** Sarcoidosis with uveitis (S+OS) vs sarcoidosis without uveitis (SS). **B.** Active pulmonary TB with uveitis (P+OTB) vs active pulmonary TB without uveitis (PTB)



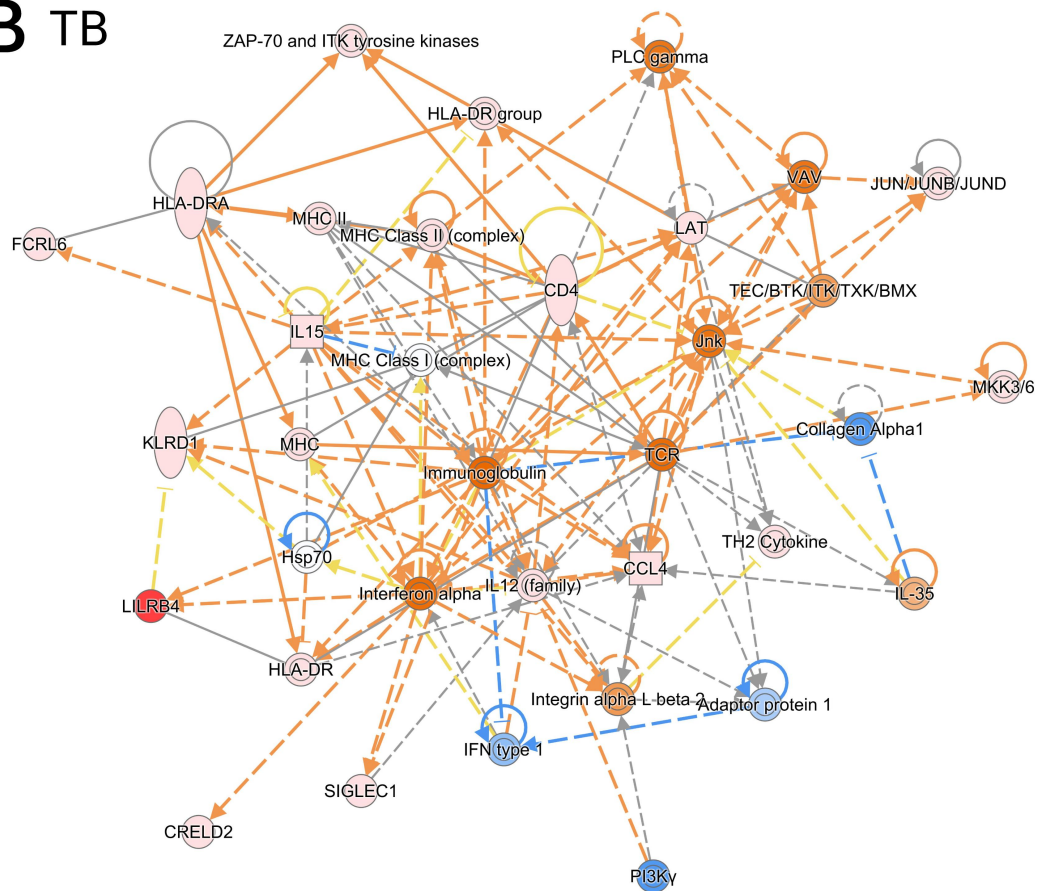


Supplementary Figure 4. Mechanistic networks of selected upstream regulators in sarcoidosis and TB: A. lipopolysaccharide, B. TNF, C. IFNG, D. SB203580, and E. SP600125. Symbols depict the upstream regulators and the colouring indicates the following: orange upstream regulators predicted to be activated, and blue upstream regulators predicted to be inhibited. Line colouring indicates the following: orange line indicates activating effect, blue line indicates inhibitory effect, yellow line indicates inconsistent with what was actually measured for the respective upstream regulators, and grey line indicates an unpredicted effect. Line types indicate the following: solid line indicates a direct relationship and dashed line indicates indirect relationship.

A Sarcoidosis



B TB

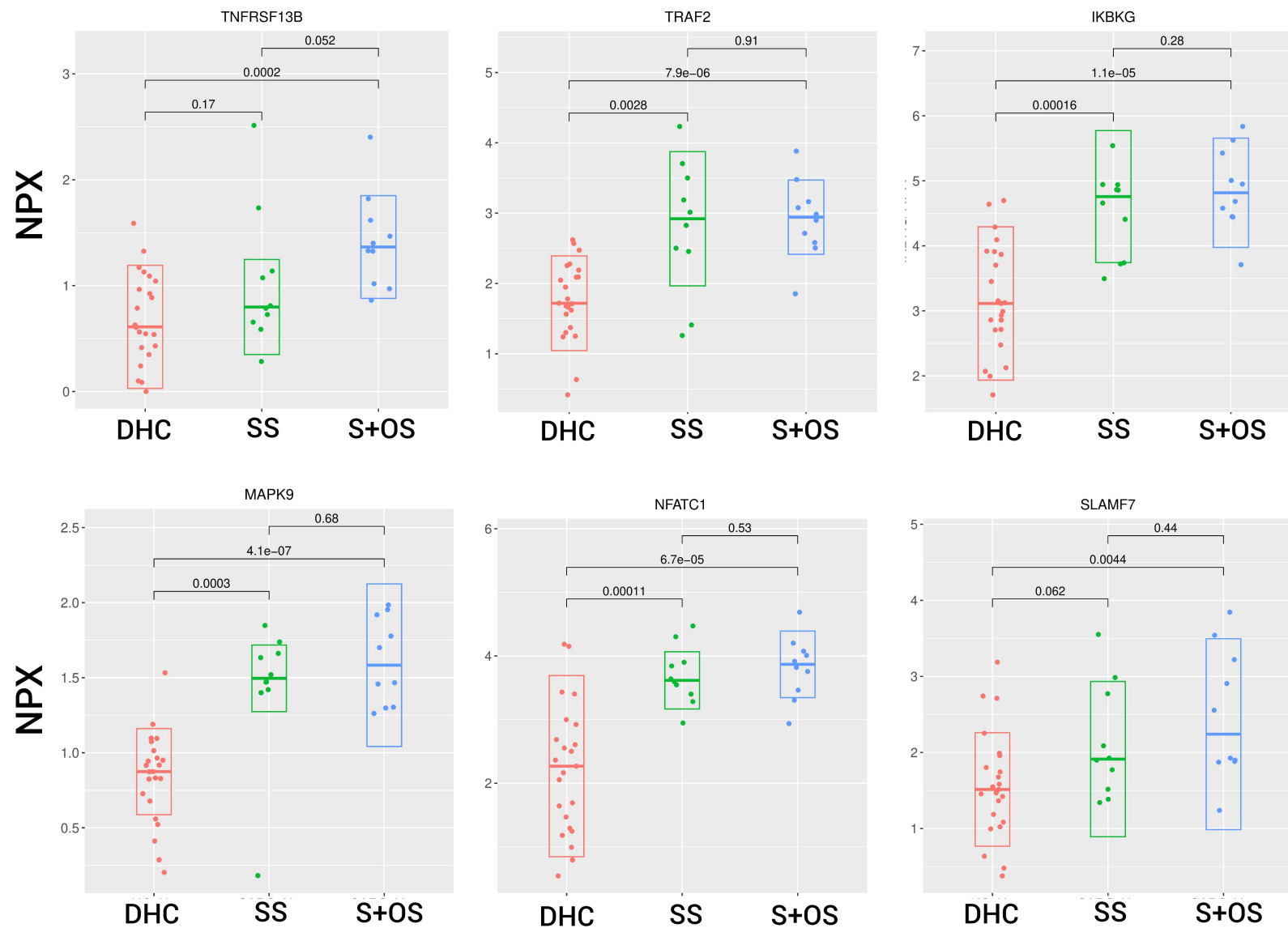


Supplementary Figure 5. Network analysis based on serum DEPs generated from IPA®. **A.** Sarcoidosis vs Dutch HC. **B.** TB vs Indonesian HC.

Symbols depict the proteins and the colouring indicates the following: Red proteins measured at increased level, green proteins measured at decreased level, orange proteins predicted to be activated, and blue proteins predicted to be inhibited. Line colouring indicates the following: orange line indicates activating effect, blue line indicates inhibitory effect, yellow line indicates inconsistent with what was actually measured for the respective protein, and grey line indicates an unpredicted effect. A solid line represents a direct protein-protein interaction while a dashed line indicates an indirect relationship.



Supplementary Figure 6. Comparative analysis of RNA-seq dataset from *Mtb*-infected RPE cells and current proteomic analysis (sarcoidosis and TB). **A.** Canonical pathways comparison. **B.** Upstream regulators comparison



Supplementary Figure 7. NPX values of selected six proteins associated with B cell signaling pathways in sarcoidosis versus Dutch healthy controls following downsampling (10 samples each for sarcoidosis with (S+OS) and without uveitis (SS)) and age and sex adjustments

