Supplemental Data

Doxycycline host-directed therapy in human pulmonary tuberculosis

Supplemental Methods:

RT-qPCR

The expression of selected genes in the 69 RNA samples were validated with quantitative PCR (qPCR). Equal amounts of RNA were converted to cDNA using Maxima First Stand cDNA Synthesis Kit (ThermoFisher) following manufacturer's recommendations. RT-qPCR was performed with the CFX Connect Real-Time PCR system (Bio-Rad) using iTaq Universal Probes Supermix (Bio-Rad) with TaqMan Gene Expression Assay (Life Technologies) for *MMP8* (Hs01029057_m1), *IFIT3* (Hs01922752_s1), *FCGR1B* (Hs02341825_m1), *MRFAP1* (Hs00738144_g1), *HNRNPA2B1* (Hs00242600_m1) or KiCqStart Probe Assays (Sigma-Aldrich) for *FCGR1A* (HSAP_NM_000566_1), *MMP9* (HSAP_NM_004994_1), *APOL1* (HSAP_NM_145343_1), *PLAUR* (HSAP_NM_001005377_1), *MX2* (HSAP_NM_002463_1), *GBP5* (HSAP_NM_001134486_1), *GBP6* (HSAP_NM_198460_1), *TNFAIP6* (HSAP_NM_007115_1), *IRF1* (HSAP_NM_002198_1). The expression levels were determined by absolute quantitation method using pooled library of the 69 RNA samples as the standard curve. Each target gene/sample was run in duplicate, and the average was normalised to the average of the housekeeping genes (*MRFAP1* and *HNRNPA2B1*).

Supplemental Figures:

Supplemental Table 1. Effect of doxycycline and placebo on adverse and serious adverse events in TB patients

	Overall		Placebo		Doxycycline		Effect
	Events/n	Risk	Events/n	Risk	Events/n	Risk	RR (95% CI)
All reasons	21/30	70.0%	10/15	66.7%	11/15	73.3%	1.1 (0.69 – 1.76)
Grade 1 and 2 events	20/30	66.7%	10/15	66.7%	10/15	66.7%	1.0 (0.60 – 1.66)
Nausea and vomiting	8/30	26.7%	2/15	13.3%	6/15	40.0%	3.0 (0.72 – 12.56)
ALT (Grade 1 and 2 events)	4/30	13.3%	2/15	13.3%	2/15	13.3%	1.0 (0.16 – 6.20)
Rash	4/30	13.3%	1/15	6.7%	3/15	20.0%	3.0 (0.35 – 25.69)
Grade 1 and 2 events related to IP	8/30	26.7%	3/15	20.0%	5/15	33.3%	1.7 (0.48 – 5.76)
Grade 3 and 4 events	1/30	3.3%	0/15	0.0%	1/15	6.7%	3.0 (0.13 – 68.26)
Grade 3 and 4 events related to IP	0/30	0.0%	-	0.0%	-	0.0%	-
SAEs	2/30	6.7%	2/15	13.3%	0/15	0.0%	0.2 (0.01 – 3.85)
SAEs related to IP	0/30	0.0%	-	0.0%	-	0.0%	-

ALT, alanine transaminase; IP, investigational product; SAE, serious adverse events; RR, relative risk; CI, confidence interval.

Supplemental Table 2. Effect of doxycycline on adverse events and serious adverse events in healthy volunteers

	Doxycycline	
	Events/n	Risk
All reasons	2/10	20.0%
Grade 1 and 2 events	2/10	20.0%
Nausea and vomiting	2/10	20.0%
Grade 1 and 2 events related to IP	2/10	20.0%
Grade 3 and 4 events	0/10	0.0%
Grade 3 and 4 events related to IP	-	0.0%
SAEs	0/10	0.0%

IP, investigational product; SAE, serious adverse events

Supplemental Table 3. Pathway analysis of the co-expressed network clusters for doxycycline arm.

Cluster	Gene set ID	Gene set name	Source	*p*-value	FDR	Genes from input	Genes in annotation
1	GO:0045047	protein targeting to ER	QuickGO	4.41E-53	3.29E-48	73	120
	GO:0006613	cotranslational protein targeting to membrane	QuickGO	6.11E-52	2.28E-47	69	109
	GO:0072599	establishment of protein localization to endoplasmic reticulum	QuickGO	1.26E-51	3.12E-47	73	124
	GO:0006614	SRP-dependent cotranslational protein targeting to membrane	QuickGO	8.37E-51	1.56E-46	67	105
	GO:0000184	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	QuickGO	1.88E-50	2.80E-46	71	12
2	GSM854306500	Myeloid Cells, GN.Bl, CD11b+ Ly6-G+, Blood, avg-3	Immgen.org, GSE15907	6.59E-68	1.74E-63	75	409
	GSM854312500	Myeloid Cells, GN.UrAc.PC, CD11b+ Ly6-G+, Peritoneal Cavity, avg-3	Immgen.org, GSE15907	1.56E-59	2.06E-55	69	410
	GSM605846500	Myeloid Cells, GN.BM, CD11b+ Ly6-G+, Bone marrow, avg-4	Immgen.org, GSE15907	1.75E-56	1.55E-52	67	415
	GSM854303500	Myeloid Cells, GN.Arth.BM, CD11b+ Ly6-G+, Bone marrow, avg-3	Immgen.org, GSE15907	4.02E-56	2.65E-52	67	420
	GSM854309500	Myeloid Cells, GN.Thio.PC, CD11b+ Ly6-G+, Peritoneal Cavity, avg-3	Immgen.org, GSE15907	1.77E-52	9.34E-49	64	416
	GO:0045321	leukocyte activation	QuickGO	7.04E-35	2.87E-30	83	1386
	GO:0002274	myeloid leukocyte activation	QuickGO	1.23E-34	2.87E-30	61	684
	GO:0001775	cell activation	QuickGO	1.37E-33	2.14E-29	86	1559
	GO:0046903	secretion	QuickGO	3.61E-32	4.24E-28	91	1835
	GO:0002446	neutrophil mediated immunity	QuickGO	2.15E-31	1.71E-27	51	506
3 (T cells)	GSM538409500	alpha beta T cells, T.8Nve.MLN, 4- 8+ 25-62Lhi 44lo, Lymph Node, avg-3	Immgen.org, GSE15907	5.45E-16	8.93E-12	22	356
	GSM538377500	alpha beta T cells, T.4Nve.MLN, 4+ 8- 25-62Lhi 44lo, Lymph Node, avg-3	Immgen.org, GSE15907	3.40E-15	1.88E-11	21	344
	GSM605790500	gamma delta T cells, Tgd.vg2+.Sp.TCRbko, TCRd+ Vg2+ CD44-, Spleen, avg-3	Immgen.org, GSE15907	3.44E-15	1.88E-11	22	389
	lymph node	lymph node	Human Protein Atlas	5.17E-15	2.11E-11	19	268
	GSM605796500	gamma delta T cells, Tgd.vg2-.Sp.TCRbko, TCRd+ Vg2- CD44-, Spleen, avg-3	Immgen.org, GSE15907	7.88E-15	2.58E-11	22	405

3 (T cells)	GO:0002250	adaptive immune response	QuickGO	8.31E-10	2.29E-05	23	715
	GO:0030217	T cell differentiation	QuickGO	8.15E-08	1.12E-03	13	280
	GO:0030098	lymphocyte differentiation	QuickGO	8.95E-07	8.21E-03	14	404
	GO:0050852	T cell receptor signaling pathway	QuickGO	2.56E-06	1.76E-02	10	214
	GO:0050851	antigen receptor-mediated signaling pathway	QuickGO	3.22E-06	1.77E-02	12	328
4	GSM476684500	gamma delta T cells, Tgd.vg2-.Sp, TCRd+ Vg2- CD44-, Spleen, avg-3	Immgen.org, GSE15907	1.23E-05	1.44E-01	11	382
5	M3189	Genes up-regulated in comparison of IgD+ peripheral blood B cells versus dark zone germincal center B cells.	MSigDB C7 (v6.0)	4.08E-08	2.03E-03	9	199
	M6238	Genes up-regulated in single positive cells: immature CD4 [GeneID=920] versus CD8 thymocytes.	MSigDB C7 (v6.0)	6.14E-07	1.02E-02	8	200
	M5781	Genes up-regulated in comparison of peripheral blood mononuclear cells (PBMC) from healthy donors versus PBMCs from patients with type 2 diabetes at the time of diagnosis.	MSigDB C7 (v6.0)	6.14E-07	1.02E-02	8	200
	M4736	Genes up-regulated in comparison of dendritic cells (DC) stimulated with R848 at 2 h versus DCs stimulated with LPS (TLR4 agonist) at 8 h.	MSigDB C7 (v6.0)	7.49E-06	7.71E-02	7	199
	M6437	Genes up-regulated in CD8A [GeneID=925] T cells versus B2 B lymphocytes.	M MSigDB C7 (v6.0)	7.74E-06	7.71E-02	7	200
6	M4460	Genes up-regulated in comparison of monocytes cultured for 0 days versus those cultured for 7 days.	MSigDB C7 (v6.0)	6.35E-12	2.64E-07	11	200
	M5530	Genes up-regulated in comparison of neutrophils versus NK cells.	MSigDB C7 (v6.0)	1.60E-10	3.31E-06	10	200
	M5526	Genes up-regulated in comparison of neutrophils versus effector memory CD4 [GeneID=920] T cells.	MSigDB C7 (v6.0)	3.56E-09	4.92E-05	9	200
	M4482	Genes down-regulated in comparison of naive B cells versus unstimulated neutrophils.	MSigDB C7 (v6.0)	6.98E-08	7.24E-04	8	200
	20418243-SuppTable1a	Human Leukemia Chiaretti10 405genes	GeneSigDB	1.83E-07	1.52E-03	9	316

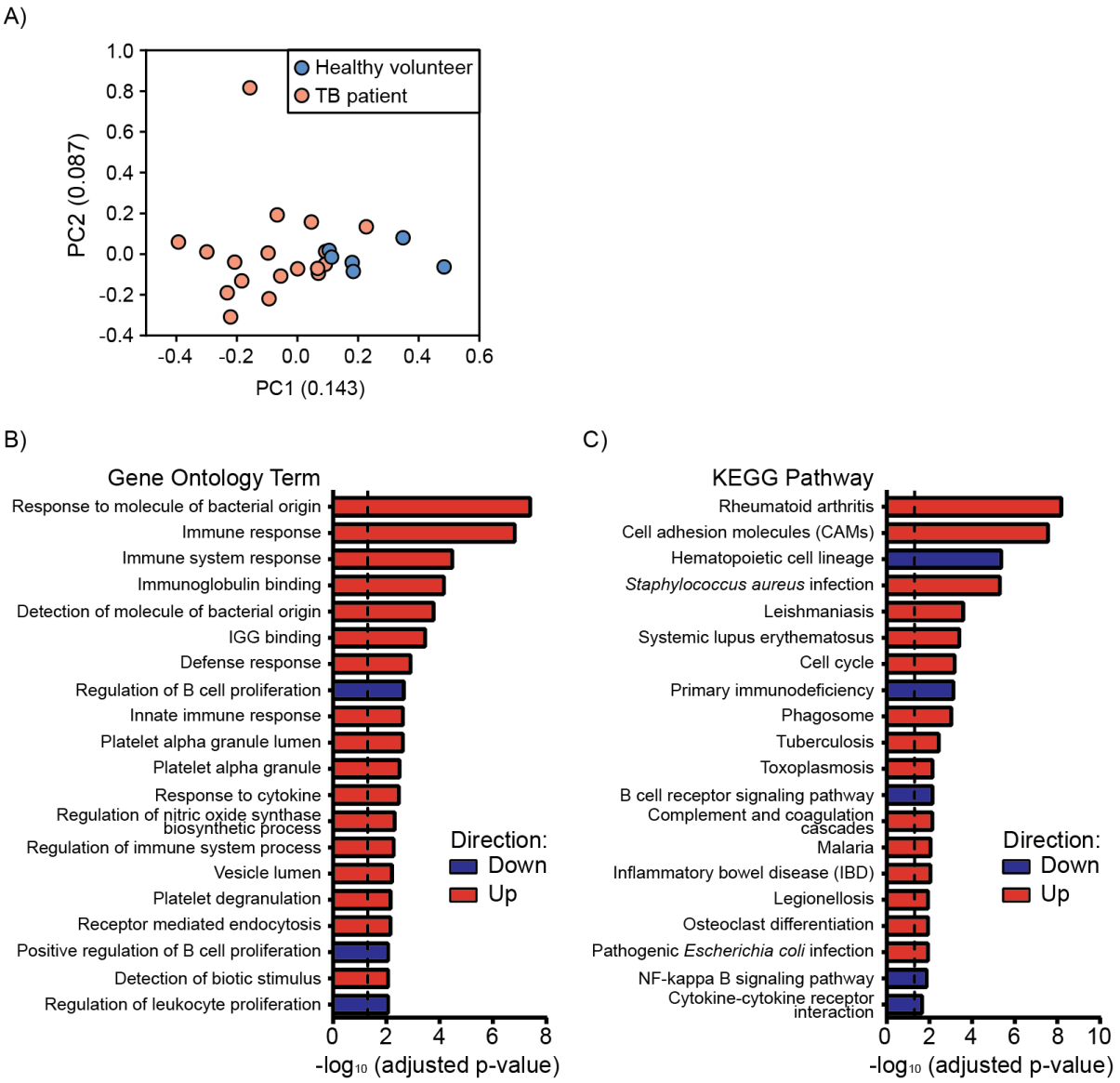
7	M5945	Genes involved in metabolism of heme (a cofactor consisting of iron and porphyrin) and erythroblast differentiation.	MSigDB H (v6.0)	1.09E-17	3.84E-13	14	200
	M5141	Genes up-regulated in comparison of peripheral blood mononuclear cells (PBMC) from infancts with acute RSV infection versus PBMCs from infants with acute influenza infection.	MSigDB C7 (v6.0)	1.49E-14	2.63E-10	12	196
	M5137	Genes down-regulated in comparison of peripheral blood mononuclear cells (PBMC) from healthy donors versus PBMCs from infanct with acute RSV infection.	MSigDB C7 (v6.0)	1.47E-08	1.49E-04	8	200
	M11205	Genes in the expression cluster 'MBC Shared': up-regulated in mature blood cell populations from adult bone marrow and fetal liver.	MSigDB C2 (v6.0)	1.69E-08	1.49E-04	9	293
8	GO:0006958	complement activation, classical pathway	QuickGO	1.27E-53	2.50E-50	27	138
	GO:0002455	humoral immune response mediated by circulating immunoglobulin	QuickGO	2.24E-52	2.21E-49	27	152
	GO:0006956	complement activation	QuickGO	5.16E-50	3.39E-47	27	183
	GO:0072376	protein activation cascade	QuickGO	1.82E-48	8.97E-46	27	207
	GO:0016064	immunoglobulin mediated immune response	QuickGO	3.74E-47	1.47E-44	27	230
9 (Granulocytes)	GSM854306500	Myeloid Cells, GN.Bl, CD11b+ Ly6-G+, Blood, avg-3	Immgen.org, GSE15907	7.09E-07	3.52E-03	8	409
	GSM854312500	Myeloid Cells, GN.UrAc.PC, CD11b+ Ly6-G+, Peritoneal Cavity, avg-3	Immgen.org, GSE15907	7.22E-07	3.52E-03	8	410
	GSM605886500	Myeloid Cells, Mo.6C-IIint.Bl, CD115+ B220- CD43- Ly6C- MHCIIint, Blood, avg-5	Immgen.org, GSE15907	7.91E-06	1.99E-02	7	400
	GSM854332500	Myeloid Cells, Mo.6C-II-.BM, B220neg CD3neg CD115+ Ly-6C/Glo CD43+, Bone marrow, avg-3	Immgen.org, GSE15907	9.14E-06	1.99E-02	7	409
	GSM854309500	Myeloid Cells, GN.Thio.PC, CD11b+ Ly6-G+, Peritoneal Cavity, avg-3	Immgen.org, GSE15907	1.02E-05	1.99E-02	7	416
	GO:0030851	granulocyte differentiation	QuickGO	1.16E-06	1.98E-02	4	40
	GO:0009887	animal organ morphogenesis	QuickGO	3.15E-06	2.70E-02	12	1241
	GO:0002573	myeloid leukocyte differentiation	QuickGO	7.17E-06	4.09E-02	6	239

10	M5945	Genes involved in metabolism of heme (a cofactor consisting of iron and porphyrin) and erythroblast differentiation.	MSigDB H (v6.0)	2.64E-20	6.95E-16	14	200
	M5141	Genes up-regulated in comparison of peripheral blood mononuclear cells (PBMC) from infancts with acute RSV infection versus PBMCs from infants with acute influenza infection.	MSigDB C7 (v6.0)	1.51E-18	1.99E-14	13	196
	M6241	Top 40 genes from cluster 8 of aculte myeloid leukemia (AML) expression profile; 69% of the samples are FAB M2 subtype.	MSigDB C2 (v6.0)	7.64E-15	6.72E-11	7	26
	M5137	Genes down-regulated in comparison of peripheral blood mononuclear cells (PBMC) from healthy donors versus PBMCs from infanct with acute RSV infection.	MSigDB C7 (v6.0)	3.88E-13	2.56E-09	10	200
	17312329-SuppTable2	Human Leukemia Juric07 617genes	GeneSigDB	2.03E-12	1.07E-08	12	449
11	19841744-TableS5	Human Liver Tzur09 1908genes	GeneSigDB	2.62E-11	6.24E-07	17	1499
	M2228	Genes down-regulated in erythroid progenitor cells from fetal livers of E13.5 embryos with KLF1 [GeneID=10661] knockout compared to those from the wild type embryos.	MSigDB C2 (v6.0)	1.91E-10	1.85E-06	18	1972
	17676974-TableS1	Mouse StemCell Chambers07 1667genes	GeneSigDB	2.33E-10	1.85E-06	15	1236
	M1410	Cluster 4: genes down-regulated in B493-6 cells (B lymphocytes) upon serum stimulation but not affected by MYC [GeneID=4609].	MSigDB C2 (v6.0)	6.02E-10	3.18E-06	12	712
	M4023	Genes up-regulated in kidney biopsies from patients with well functioning kidneys more than 1-year post transplant compared to the biopsies from normal living kidney donors.	MSigDB C2 (v6.0)	6.66E-10	3.18E-06	11	555
	GO:0038096	Fc-gamma receptor signaling pathway involved in phagocytosis	QuickGO	1.59E-07	5.95E-04	6	139
	GO:0002433	immune response-regulating cell surface receptor signaling pathway involved in phagocytosis	QuickGO	1.59E-07	5.95E-04	6	139

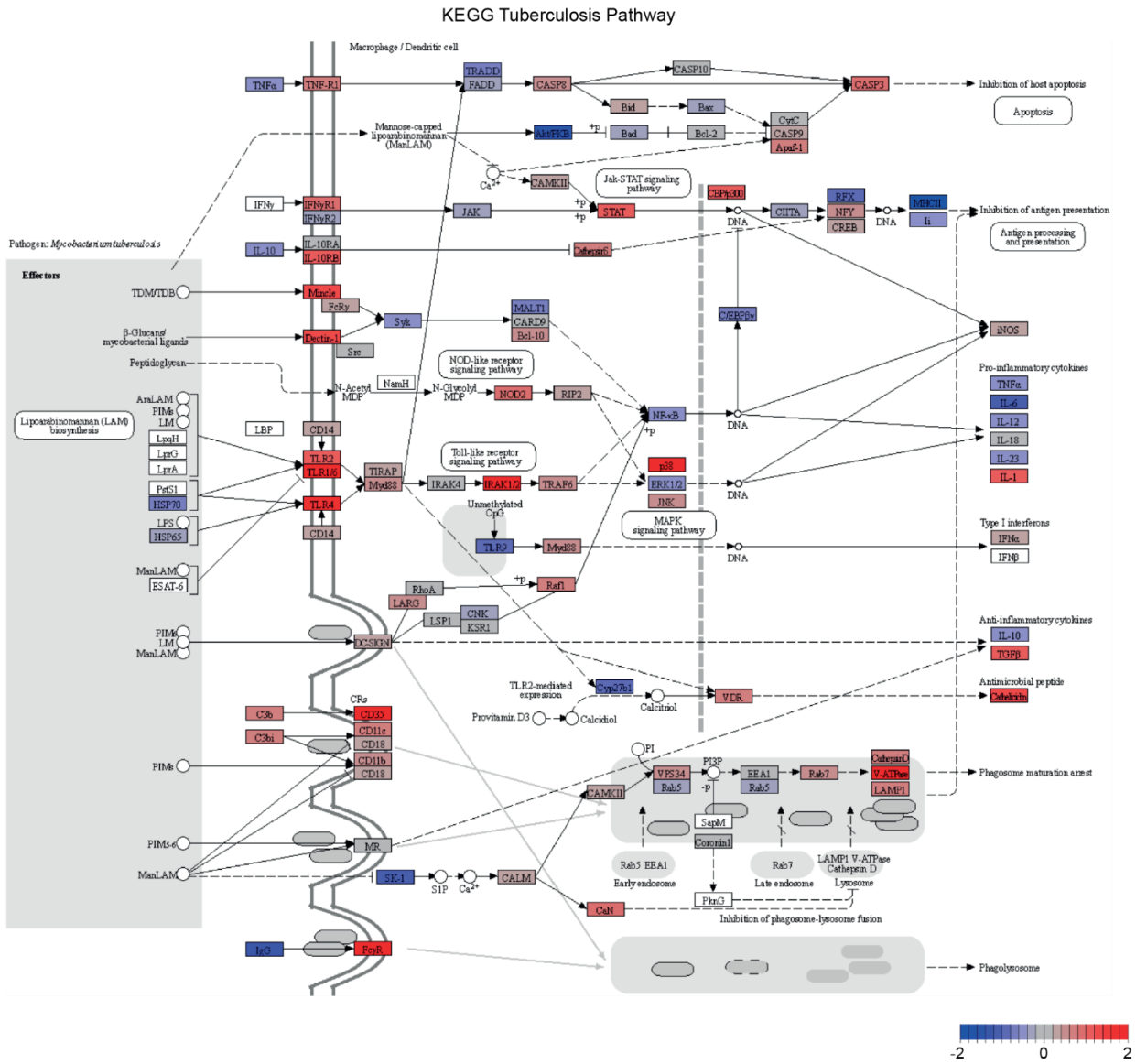
11	GO:0038094	Fc-gamma receptor signaling pathway	QuickGO	1.88E-07	5.95E-04	6	143
	GO:0002431	Fc receptor mediated stimulatory signaling pathway	QuickGO	2.04E-07	5.95E-04	6	145
	GO:0038093	Fc receptor signaling pathway	QuickGO	4.07E-06	9.47E-03	6	242
12	M2200	Genes enriched at every T lymphocyte differentiation stage compared to the early passage fetal thymic stromal cultures (TSC).	MSigDB C2 (v6.0)	1.78E-08	5.40E-04	7	200
	M535	Genes up-regulated in CD34+ [GeneID=947] cells isolated from bone marrow of CML (chronic myelogenous leukemia) patients, compared to those from normal donors.	MSigDB C2 (v6.0)	4.99E-08	7.57E-04	13	1382
	M2125	Genes up-regulated in senescent IMR90 cells (fibroblast) after knockdown of RB1 [GeneID=5925] by RNAi.	MSigDB C2 (v6.0)	1.23E-07	1.03E-03	9	569
	17676974-TableS1	Mouse StemCell Chambers07 1667genes	GeneSigDB	1.36E-07	1.03E-03	12	1236
	19096012-TableS2	Human Viral Chetaille09 501genes	GeneSigDB	2.37E-07	1.19E-03	8	439
13	M5945	Genes involved in metabolism of heme (a cofactor consisting of iron and porphyrin) and erythroblast differentiation.	MSigDB H (v6.0)	1.35E-10	2.99E-06	8	200
	14522937-Table1	Human Kidney Twine03 132genes	GeneSigDB	8.75E-09	9.70E-05	6	119
	M10914	Genes down-regulated in prefrontal cortex (PFC) of mice carrying a hemizygotic microdeletion in the 22q11.2 region.	MSigDB C2 (v6.0)	3.48E-06	2.57E-02	7	517
14 (Type II Interferon)	M9306	Genes up-regulated in CD4: FOXP3+ [GeneID=50943] T reg versus FOXP3 [GeneID=50943] knockout T reg precursor.	MSigDB C7 (v6.0)	3.11E-24	8.80E-20	15	195
	M4292	Genes down-regulated in comparison of control conventional dendritic cells (cDC) at 6 h versus cDCs infected with Newcastle disease virus (NDV) at 6 h.	MSigDB C7 (v6.0)	4.92E-22	5.35E-18	14	198
	M8967	Genes down-regulated in CD4 [GeneID=920] over-expressing: FOXP3 [GeneID=50943] and PPARg1 form of PPARG [GeneID=5468] versus FOXP3 [GeneID=50943].	MSigDB C7 (v6.0)	5.68E-22	5.35E-18	14	200

14 (Type II Interferon)	M9576	Genes down-regulated in T reg: peripheral lymph nodes versus thymic CD24 int [GeneID=100133941].	MSigDB C7 (v6.0)	6.10E-20	2.16E-16	13	200
	M8971	Genes down-regulated in CD4 [GeneID=920] T cells treated with pioglitazone [PubChem=4829] and over-expressing: FOXP3 [GeneID=50943] and PPARg1 isoform of PPARG [GeneID=5468] versus FOXP3 [GeneID=50943] and PPARg2 form of PPARG [GeneID=5468].	MSigDB C7 (v6.0)	6.10E-20	2.16E-16	13	200
	GO:0071346	cellular response to interferon-gamma	QuickGO	5.02E-18	5.05E-14	12	189
	GO:0034341	response to interferon-gamma	QuickGO	1.62E-17	8.14E-14	12	208
	GO:0045087	innate immune response	QuickGO	6.48E-16	2.17E-12	17	1045
	GO:0098542	defense response to other organism	QuickGO	1.26E-14	3.16E-11	17	1250
	GO:0006952	defense response	QuickGO	1.96E-14	3.95E-11	19	1850
15 (Type I Interferon)	GO:0071357	cellular response to type I interferon	QuickGO	1.52E-22	5.20E-19	12	95
	GO:0060337	type I interferon signaling pathway	QuickGO	1.52E-22	5.20E-19	12	95
	GO:0034340	response to type I interferon	QuickGO	2.56E-22	5.85E-19	12	99
	GO:0009615	response to virus	QuickGO	2.95E-19	5.06E-16	14	350
	GO:0051607	defense response to virus	QuickGO	4.72E-19	6.47E-16	13	261

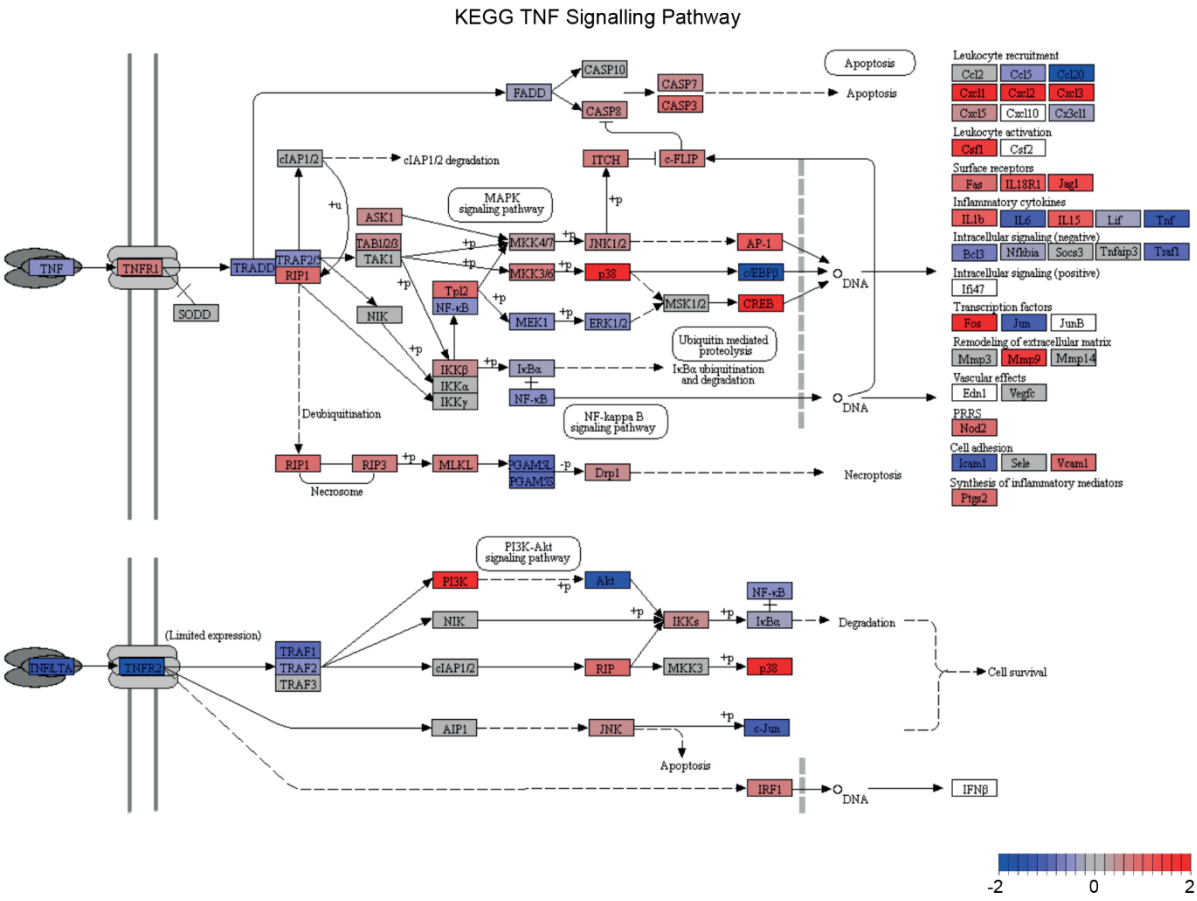
FDR was calculated using the Benjamini & Yekutieli method.



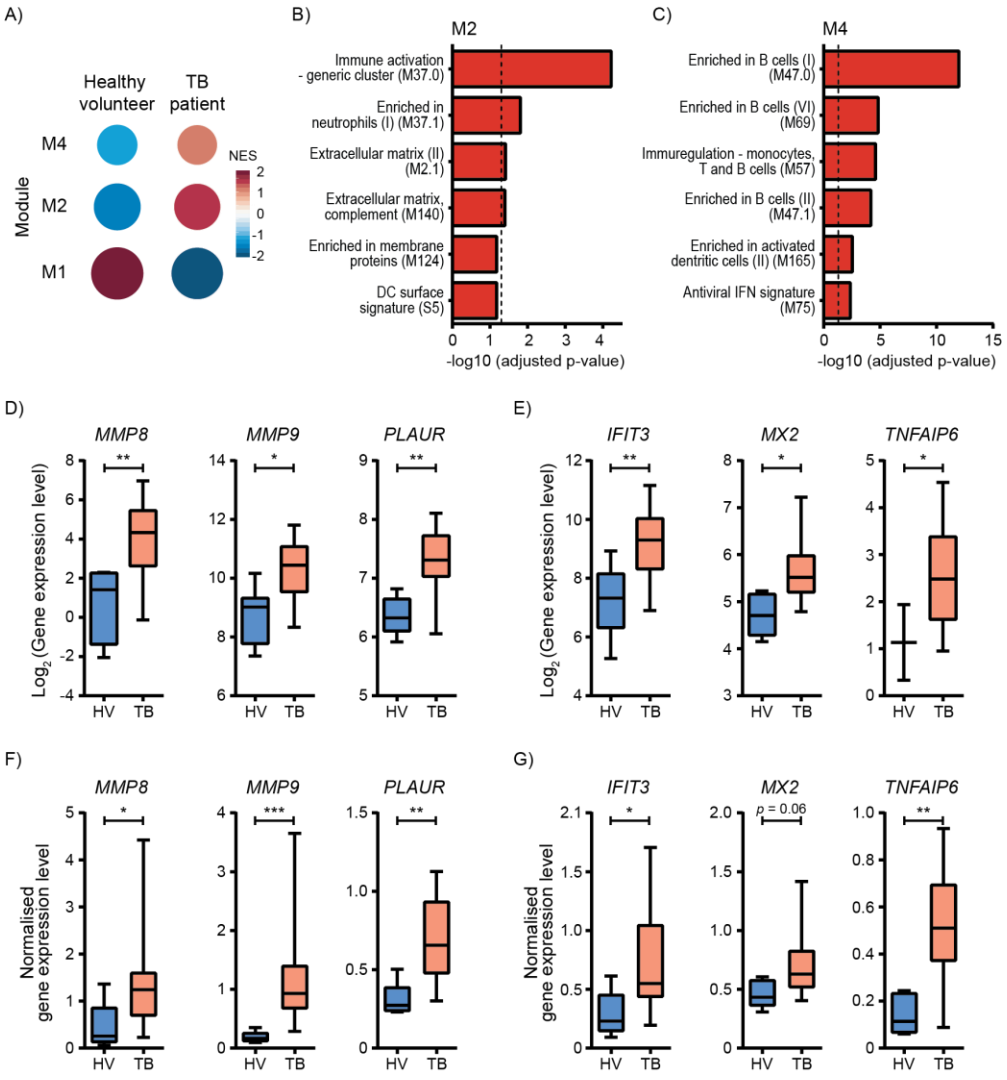
Supplemental Figure 1. Multiple immuno-regulatory pathways are differentially regulated in TB. (A) Principal component analysis (PCA) of whole blood transcriptomes in healthy volunteers (n = 6, blue) and TB patients (n = 18, orange) at baseline. Counts were normalized and filtered using the TMM method. The first two components of PCA are shown and their variances are shown in parenthesis. **(B-C)** Gene set enrichment analysis of 1657 differentially regulated genes between TB patients and healthy volunteers (TB vs. HV) using Gene Ontology gene sets **(B),** and KEGG pathways **(C).** The top 20 enriched gene sets of each category are shown. Dotted line marks adjusted *p*-value = 0.05. Red represents up-regulation and blue represents down-regulation of gene sets.



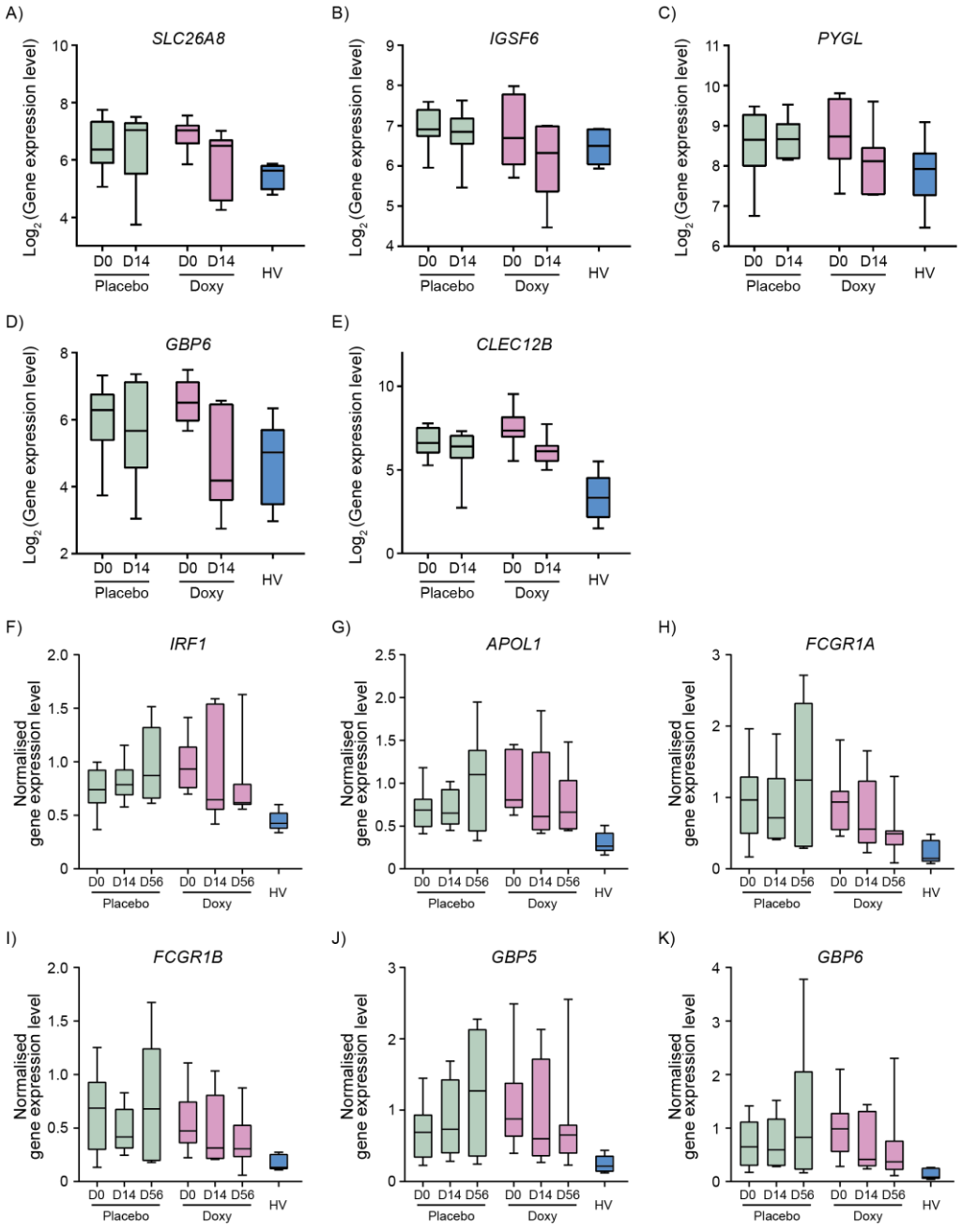
Supplemental Figure 2. TB modulates multiple genes in circulating cells in the KEGG Tuberculosis pathway relative to healthy volunteers. Projection of differentially regulated genes (TB patients vs. Healthy volunteers) onto the KEGG Tuberculosis pathway (map05152) (47-49). Red represents up-regulation and blue represents down-regulation of gene expression.



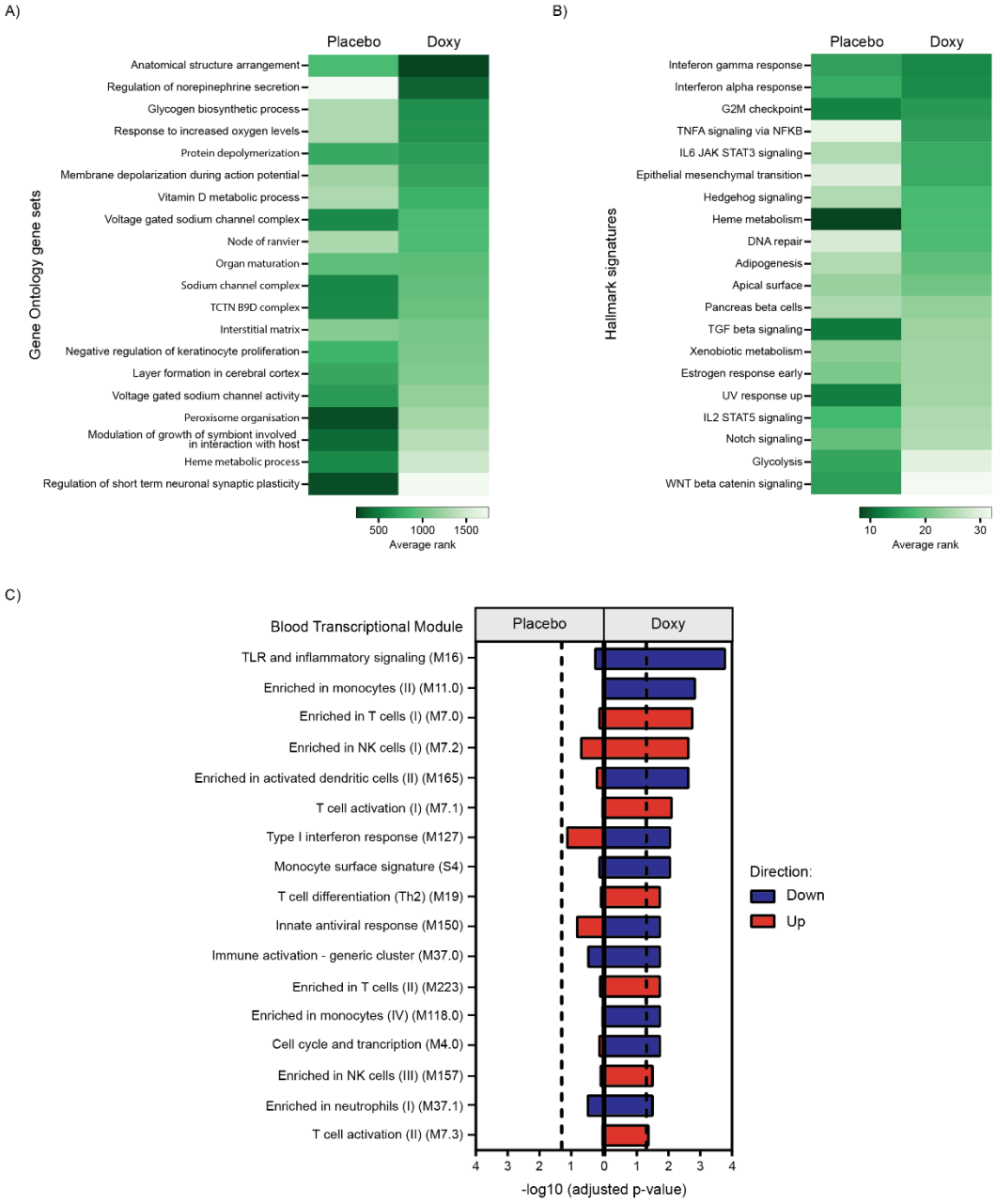
Supplemental Figure 3. TB modulates multiple genes in circulating cells in the KEGG TNF Signalling pathway relative to healthy volunteers. Projection of differentially regulated genes (TB patients vs. Healthy volunteers) onto the KEGG TNF Signalling pathway (map04668) (47-49). Red represents up-regulation and blue represents down-regulation of gene expression.



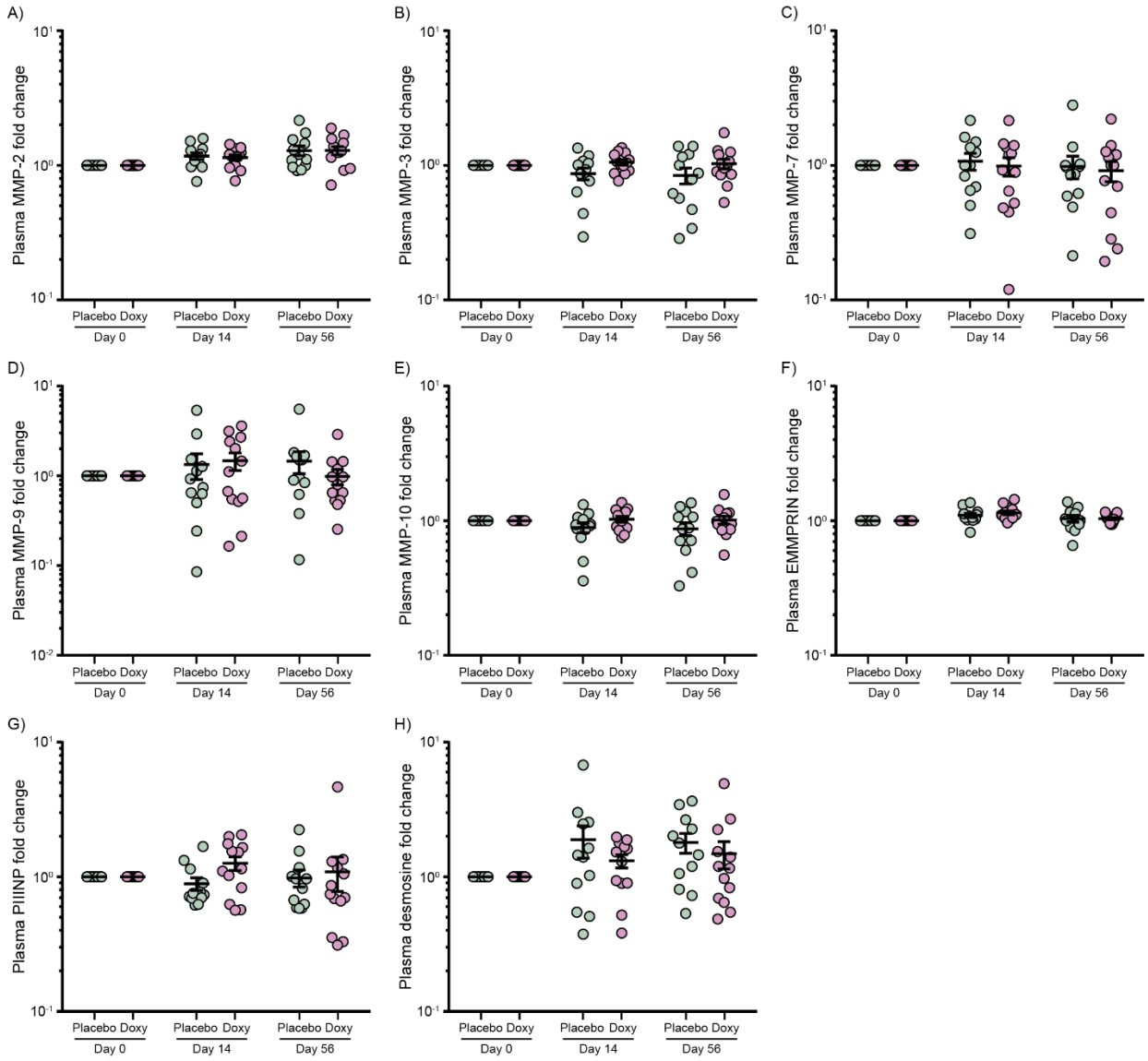
Supplemental Figure 4. TB dysregulates diverse pathways in whole blood relative to healthy volunteers. **(A)** Transcript to transcript correlation analysis on all genes using CEMITool (50) identified 5 modules of co-expressed genes in healthy volunteers and TB patients. Significantly enriched modules are shown (adjusted *p*-value < 0.05). The size and intensity of the circles correspond to the Normalized Enrichment Score (NES, red: positive NES, blue: negative NES) of the modules. **(B-C)** Gene set enrichment analysis of gene co-expression modules, M2 **(B)** and M4 **(C)**, which were highly expressed in TB patients. Blood transcriptional modules (54) were used as gene sets. The top 6 enriched gene sets are plotted for each module. Dotted line marks adjusted *p*-value = 0.05. **(D-E)** Baseline gene expression levels of selected genes from M2 **(D)** and M4 **(E)** in healthy volunteers (HV, n = 6, blue) and TB patients (TB, n = 18, orange). TMM normalized counts are shown. *Adjusted *p*-value < 0.05, **adjusted *p*-value < 0.01. **(F-G)** Quantitative PCR (qPCR) validation of the RNA-sequencing results from M2 **(F)** and M4 **(G)** in healthy volunteers (HV, n = 6, blue) and TB patients (TB, n = 18, orange). Gene expression level were normalised to housekeeping genes (*HNRNPA2B1* and *MRFAP1*). Analysis by Mann-Whitney *U*-test. **p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001. Box represents 25th and 75th percentile, line is median, with whiskers denoting extremes.



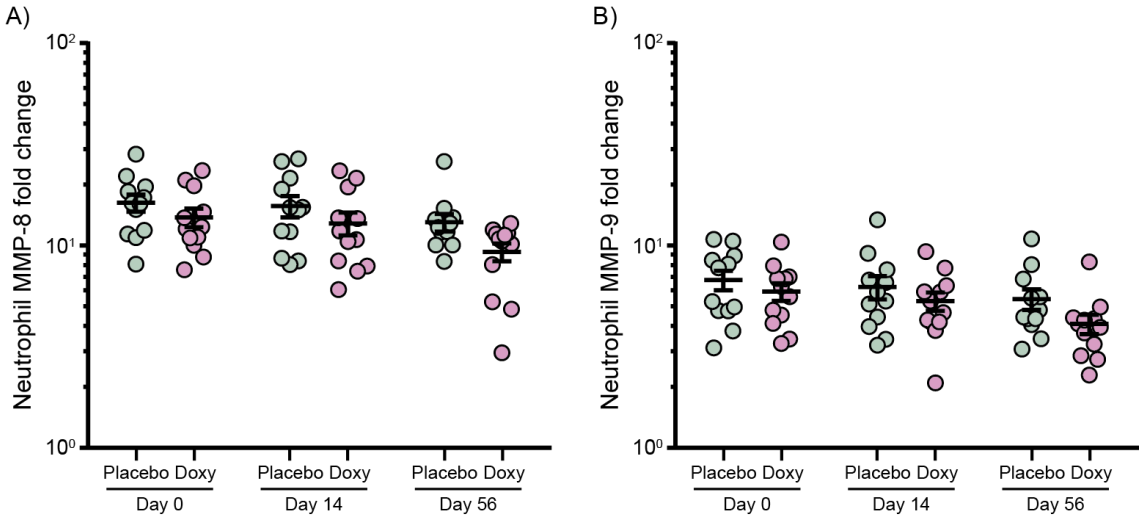
Supplemental Figure 5. Doxycycline results in faster normalization of immune response genes relative to placebo. (A-E) Longitudinal analysis of selected immune response genes, *SLC26A8* **(A)**, *ISF6* **(B)**, *PYGL* **(C)**, *GBP6* **(D)**, and *CLEC12B* **(E)** that were differentially expressed over the course of doxycycline treatment (Day 14 vs. Day 0). TMM normalized gene expression at Day 0 and 14 of TB patients in placebo (green) and doxycycline (Doxy, purple) arms, and baseline expression of healthy volunteers (HV, blue) are plotted. **(F-K)** qPCR validation of the RNA-sequencing results for *IRF1* **(F)**, *APOL1* **(G)**, *FCGR1A* **(H)**, *FCGR1B* **(I)**, *GBP5* **(J),** and *GBP6* **(K)**. Gene expression level were normalised to housekeeping genes (*HNRNPA2B1* and *MRFAP1*). Box represents 25th and 75th percentile, line is median, with whiskers denoting extremes. n = 8 placebo, n = 7 doxycycline and n = 6 healthy volunteers.



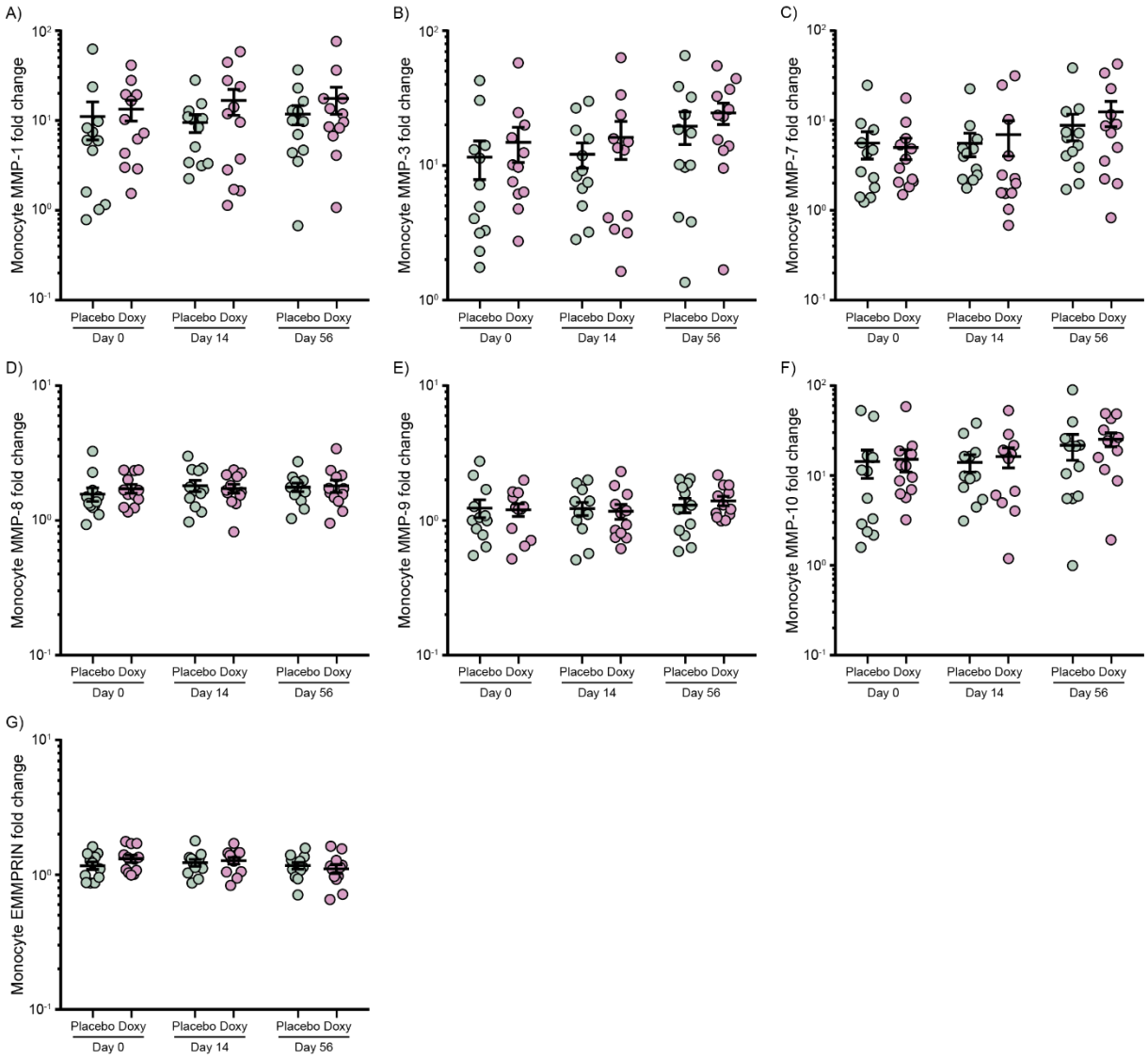
Supplemental Figure 6. Doxycycline divergently regulates multiple pathways relative to placebo. (A-B) EGSEA pathway analysis of genes significantly regulated by placebo and doxycycline treatment (Day 14 vs. Day 0) using Gene Ontology gene sets **(A)** and Hallmark signatures **(B)**. EGSEA analysis was performed individually for each arm. The top 10 ranked gene sets of each arm are shown. Gene sets are aligned in ascending value of their average rank in the doxycycline arm, and color intensity denotes the average rank of the gene set in each arm. **(C)** Gene set enrichment analysis of differentially regulated genes specific to doxycycline and placebo treatment (Day 14 vs. Day 0). Blood transcriptional modules (54) were used as gene sets. The top 17 enriched gene sets in doxycycline arm are shown. Dotted line marks adjusted *p*-value = 0.05. Red represents up-regulation and blue represents down-regulation of gene sets.



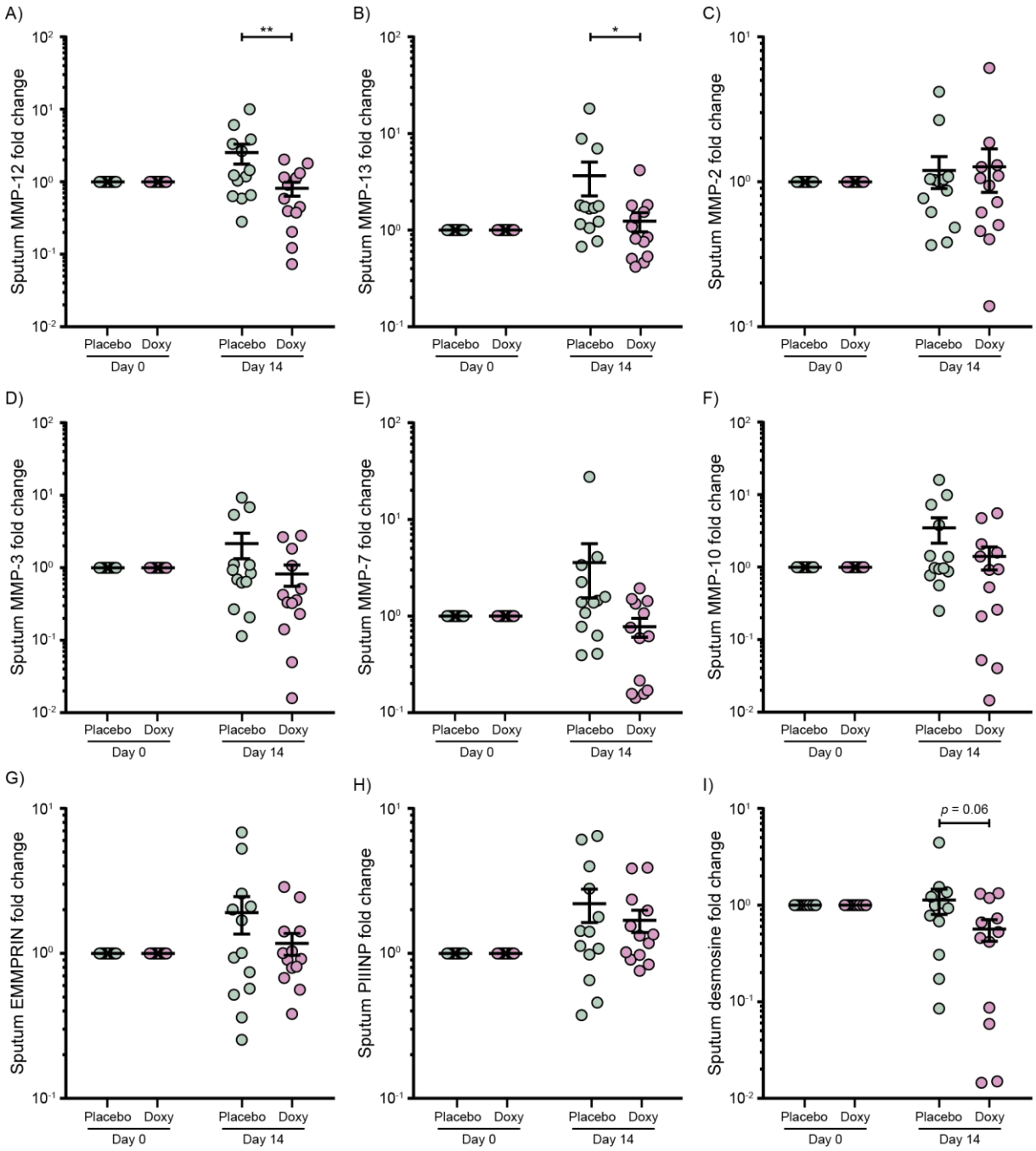
Supplemental Figure 7. Other plasma MMPs and matrix degradation products are unchanged in TB patients treated with doxycycline or placebo. Longitudinal analysis of plasma MMP-2 (**A**), MMP-3 (**B**), MMP-7 (**C**), MMP-9 (**D**), MMP-10 (**E**), EMMPRIN (**F**), PIIINP (**G**), and desmosine (**H**) concentrations at Day 0, 14 and 56 of placebo (n = 12, green) and doxycycline (Doxy, n = 13, purple) arms. Protein concentrations of each subject were normalized to their Day 0 values. Analysis by 2-way ANOVA with Sidak's multiple comparisons. Bars represent mean ± s.e.m.



Supplemental Figure 8. Neutrophil MMPs are unchanged in TB patients treated with doxycycline or placebo. Longitudinal analysis of neutrophil MMP-8 (**A**) and MMP-9 (**B**) concentrations at Day 0, 14 and 56 of placebo (n = 12, green) and doxycycline (Doxy, n = 12, purple) arms. Neutrophils of each subject were isolated and stimulated with live H37Rv or control media, and MMPs concentrations were normalized to control at each time point. Analysis by 2-way ANOVA with Sidak's multiple comparisons. Bars represent mean ± s.e.m.



Supplemental Figure 9. Monocyte MMPs are unchanged in TB patients treated with doxycycline or placebo. Longitudinal analysis of monocyte MMP-1 **(A)**, MMP-3 **(B)**, MMP-7 **(C)**, MMP-8 **(D)**, MMP-9 **(E)**, MMP-10 **(F)**, and EMMPRIN **(G)** concentrations at Day 0, 14 and 56 of placebo (n = 12, green) and doxycycline (Doxy, n = 12, purple) arms. Monocytes of each subject were isolated and stimulated with live H37Rv or control media, and MMPs concentrations were normalized to control at each time point. Analysis by 2-way ANOVA with Sidak's multiple comparisons. Bars represent mean ± s.e.m.



Supplemental Figure 10. Analysis of other sputum MMPs and matrix degradation products in TB patients treated with doxycycline or placebo. Longitudinal analysis of sputum MMP-12 (**A**), MMP-13 (**B**), MMP-2 (**C**), MMP-3 (**D**), MMP-7 (**E**), MMP-10 **(F)**, EMMPRIN **(G)**, PIIINP (**H**), and desmosine (**I**) concentrations at Day 0 and 14 of placebo (n = 13, green) and doxycycline (Doxy, n = 13, purple) arms. Protein concentrations of each subject were normalized to their Day 0 values. Analysis by 2-way ANOVA with Sidak's multiple comparisons. *Adjusted *p*-value < 0.05, **adjusted *p*-value < 0.01. Bars represent mean ± s.e.m.