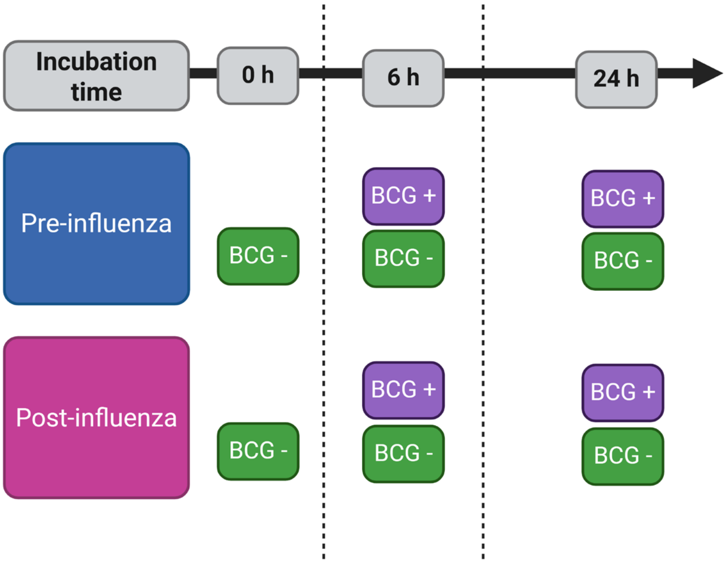
Extended Data

Extended Data Figure 1. Schematic overview of whole blood samples used for transcriptomics analyses. Each green and purple box represents a whole blood sample for RNA-sequencing, with each participant contributing 10 unique samples to the model.



Extended Data Figure 2. Genes significantly differentially expressed for the *Influenza: BCG* interaction and their associations with anti-mycobacterial immune responses. For each gene, the log2 fold change (LFC) and Benjamini-Hochberg (BH) adjusted p value (adj. p) are listed for the variables: *BCG:Influenza interaction, BCG, Influenza and BCG+ BCG:Influenza. BCG+ BCG:Influenza* describes the effect of BCG when influenza is also present. Where adj. p≤0.05, the box is shaded blue.

Ensembl gene ID	***Gene symbol***	**Gene name**	**BCG: Influenza LFC**	**BCG: Influenza adj. p**	**BCG LFC**	**BCG adj. p**	**Influenza LFC**	**Influenza adj. p**	**BCG+ BCG: Influenza LFC**	**BCG+ BCG: Influenza adj. p**	**Associations with anti-mycobacterial immune responses in the literature**
ENSG00000137959	*IFI44L*	Interferon induced protein 44 like	-1.67	2.07E-02	1.45	6.23E-04	3.57	4.37E-42	-0.22	6.40E-01	Interferon stimulated gene (ISG). Encodes anti-viral protein. Knockdown associated with increased intracellular survival of Mtb and reduced cell apoptosis[1]. Upregulated in tuberculosis (TB) disease[2].
ENSG00000183844	*FAM3B*	FAM3 metabolism regulating signaling molecule B	-1.54	2.07E-02	0.05	8.99E-01	0.05	8.88E-01	-1.49	1.66E-04	
ENSG00000160932	*LY6E*	Lymphocyte antigen 6 family member E	-1.42	1.05E-05	0.16	5.38E-01	2.43	2.93E-59	-1.26	1.86E-07	ISG. Modulates T cell receptor-mediated signalling, T cell activation and development[3]. Negatively modulates CD14 expression in monocytes and reduces their responsiveness to bacterial lipopolysaccharide (LPS) stimulation via downregulation of CD14/TLR4 pathways. Chronic *LY6E* upregulation, (e.g. in chronic HIV infection), may impair monocyte responses to bacterial pathogens and increase susceptibility to coinfections including *Mtb*[4.]
ENSG00000111331	*OAS3*	2'-5'-oligoadenylate synthetase 3	-1.39	3.61E-03	1.82	1.32E-09	2.45	1.94E-38	0.44	1.68E-01	Activates RNase L which cleaves cytoplasmic RNA and inhibits viral replication[5]. Upregulated in TB disease[6-8]. Suggested role in TB pathogenesis[9]. *OAS* expression in *Mtb*- and BCG- infected macrophages relates to pathogenicity: silencing of *OAS1-3* genes increases intracellular mycobacterial replication within macrophages and reduces IL-1β and TNF-α secretion[10]. Upregulated in TB disease[2].
ENSG00000260943	*LINC02555*	Long intergenic non-protein coding RNA 2555	-1.38	2.44E-02	0.75	4.35E-02	0.93	2.31E-04	-0.63	9.46E-02	
ENSG00000246016	*LINC01513*	Long intergenic non-protein coding RNA 1513	-1.37	2.07E-02	-2.96	6.19E-17	0.53	1.76E-02	-4.33	1.97E-31	
ENSG00000280270			-1.35	3.61E-03	1.04	5.71E-04	2.19	4.02E-30	-0.31	3.05E-01	

ENSG00000134321	*RSAD2*	Radical S-adenosyl methionine domain containing 2	-1.32	4.69E-02	1.48	5.71E-05	3.55	1.78E-54	0.17	6.82E-01	ISG. Encodes an anti-viral protein commonly called viperin[11]. In vitro, viperin restricts growth of intracellular bacterial pathogens including Listeria and Shigella[12]. *Mtb* induces macrophage expression of RSAD2[13.] Upregulated in TB disease[2].
ENSG00000174697	*LEP*	Leptin	-1.31	2.07E-02	4.22	2.62E-37	0.95	1.10E-04	2.92	2.40E-19	Encodes regulatory hormone leptin. Induces activation of neutrophils, macrophages and DCs; increases production of pro-inflammatory cytokines (e.g. IL-1, TNF and IL-6); enhances cytotoxicity of NK cells; increases proliferation of naive T cells and B cells; can polarise T_H cells towards a proinflammatory T_H1 subtype; reduces Treg cell proliferation and increases TH_{17} cell responses[14,15]. In murine models, leptin deficiency is associated with reduced mycobacterial control[16].
ENSG00000121236	*TRIM6*	tripartite motif containing 6	-1.27	1.27E-02	-0.86	7.35E-03	1.48	3.13E-17	-2.14	3.69E-12	The encoded protein is a member of the tripartite motif (TRIM) family, which are implicated in TB[17]. Role in T1-IFN signalling. TRIM6-deficiency associated with reduced T1-IFN induction and signalling in vitro[18]. Upregulated in TB disease[2].
ENSG00000107593	*PKD2L1*	Polycystin 2 like 1, transient receptor potential cation channel	-1.24	2.07E-02	0.31	3.78E-01	0.44	3.27E-02	-0.93	7.98E-03	
ENSG00000126709	*IFI6*	Interferon alpha inducible protein 6	-1.15	1.48E-02	0.98	5.32E-04	2.36	7.64E-42	-0.17	5.73E-01	ISG. Anti-viral protein. Regulator of type 1 IFN signalling[19]. Upregulated in TB disease[2].
ENSG00000137965	*IFI44*	Interferon induced protein 44	-1.15	2.95E-02	0.90	3.99E-03	2.67	3.24E-44	-0.25	4.45E-01	ISG. Upregulated in TB disease[2].
ENSG00000281162	*LINC01127*	Long intergenic non-protein coding RNA 1127	-1.14	2.62E-02	-0.77	1.23E-02	-0.86	2.53E-05	-1.91	2.39E-10	
ENSG00000225964	*NRIR*	Negative regulator of interferon response	-1.08	3.31E-02	0.80	6.50E-03	2.47	2.15E-42	-0.27	3.75E-01	Long non-coding RNA, induced by IFN-α, negative regulator of IFN response.[20]
ENSG00000125968	*ID1*	Inhibitor of DNA binding 1,	-1.07	2.32E-02	-1.82	1.37E-10	0.44	3.04E-02	-2.90	5.82E-24	Transcription factor. May promote type 1 IFN signalling[21]. Upregulated in *Mtb*- infected macrophages[22].
ENSG00000172426	*RSPH9*	Radial spoke head component 9	-1.07	2.32E-02	-0.80	5.01E-03	1.17	2.70E-11	-1.88	1.03E-11	

ENSG00000157601	*MX1*	MX dynamin like GTPase 1	-1.07	2.29E-02	1.47	9.43E-08	1.98	2.45E-30	0.40	1.71E-01	ISG. Encodes GTP-binding protein with antiviral activity. Blocks influenza virus transcription and replication[23]. Upregulated in TB disease[2].
ENSG00000233030		novel transcript, antisense to *FCGR1A*	-1.05	1.07E-02	0.87	4.90E-04	1.05	8.28E-11	-0.18	5.09E-01	
ENSG00000133106	*EPSTI1*	Epithelial stromal interaction 1	-1.04	1.06E-03	0.92	1.20E-05	2.03	3.88E-54	-0.12	6.03E-01	ISG. Highly expressed in macrophages exposed to IFN-γ and LPS. Possible modulatory role for macrophage activation and M1-M2 polarisation[24]. Upregulated in TB disease[2].
ENSG00000089127	*OAS1*	2'-5'-oligoadenylate synthetase 1	-1.02	3.34E-02	0.94	6.33E-04	2.39	2.68E-44	-0.07	8.14E-01	Activates RNase L which cleaves cytoplasmic RNA and inhibits viral replication[5]. Upregulated in TB disease[6-8]. Suggested role in TB pathogenesis[9]. *OAS* expression in *Mtb*- and BCG- infected macrophages relates to pathogenicity: silencing of *OAS1- 3* genes increases intracellular mycobacterial replication within macrophages and reduces IL-1β and TNF-α secretion[10]. *OAS1* polymorphisms have been associated with TB[25]. Upregulated in TB disease[2].
ENSG00000138646	*HERC5*	HECT and RLD domain containing E3 ubiquitin protein ligase 5	-1.00	2.51E-02	0.92	5.11E-04	1.74	7.54E-26	-0.08	7.83E-01	ISG. Encodes an enzyme that promotes conjugation of ISG15 to its targets (ISGylation), promoting IFN-γ release from NK cells and T cells[26]. Loss-of-function mutations of ISG15 in humans and mice are associated with increased susceptibility to mycobacteria[27,28]. Upregulated in TB disease[2].
ENSG00000257878		Novel transcript, antisense to *LTA4H*	-1.00	2.51E-02	-0.64	1.48E-02	-0.18	4.04E-01	-1.64	2.48E-10	
ENSG00000278330		Novel transcript, antisense to *MBP*	-0.98	2.44E-02	2.77	1.42E-28	0.18	4.23E-01	1.79	1.18E-12	
ENSG00000111335	*OAS2*	2'-5'-oligoadenylate synthetase 2	-0.97	9.94E-03	1.17	2.56E-07	1.76	8.58E-35	0.20	4.07E-01	Activates RNase L which cleaves cytoplasmic RNA and inhibits viral replication[5]. Upregulated in TB disease[6-8]. Suggested role in TB pathogenesis[9]. *OAS* expression in *Mtb*- and BCG- infected macrophages relates to pathogenicity: silencing of *OAS1- 3* genes increases intracellular mycobacterial replication within macrophages and reduces IL-1β and TNF-α secretion[10]. Upregulated in TB disease[2].
ENSG00000196141	*SPATS2L*	Spermatogenesis associated serine rich 2 like	-0.91	1.64E-02	0.79	5.08E-04	1.69	1.56E-33	-0.12	6.18E-01	Upregulated in TB disease[2].
ENSG00000270972			-0.89	3.83E-02	-0.10	7.26E-01	1.06	1.85E-11	-0.99	4.55E-05	

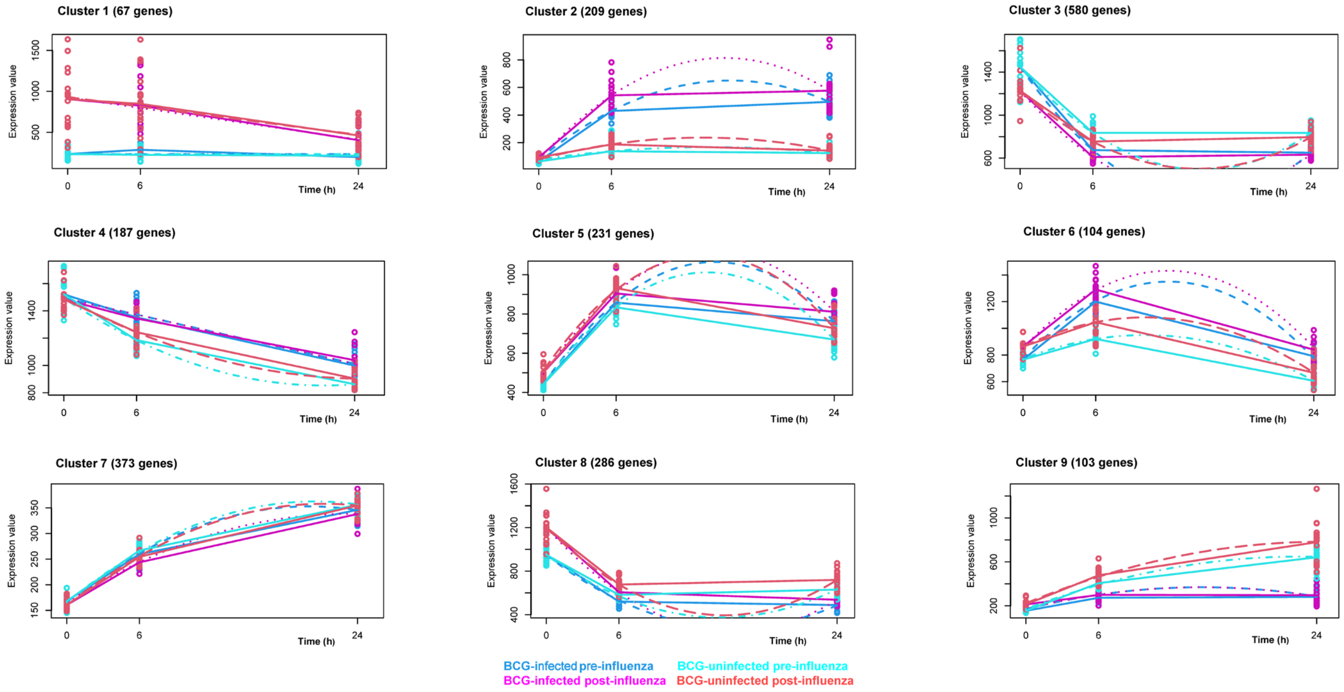
ENSG00000188313	*PLSCR1*	Phospholipid scramblase 1	-0.86	4.17E-03	1.32	2.49E-12	1.35	1.22E-29	0.46	1.70E-02	ISG. Antiviral protein.[29] Possible immunomodulatory roles[30]. Upregulated in TB disease[2].
ENSG00000173801	*JUP*	Junction plakoglobin	-0.80	9.94E-03	-0.52	6.48E-03	1.02	1.54E-17	-1.33	1.22E-12	
ENSG00000124762	*CDKN1A*	Cyclin dependent kinase inhibitor 1A	-0.80	2.26E-02	1.99	9.39E-23	0.69	6.14E-07	1.19	6.33E-09	Encodes the cyclin-dependent kinase inhibitor p21 which has immunomodulatory roles including T cell proliferation[31], macrophage activation[32] and inflammation[33]
ENSG00000136514	*RTP4*	Receptor transporter protein 4	-0.78	2.62E-02	1.07	1.46E-07	1.69	1.42E-39	0.30	1.63E-01	ISG. Anti-viral factor. Regulates type 1 IFN responses[34,35].
ENSG00000170458	*CD14*	CD14	-0.76	2.07E-02	0.34	8.84E-02	0.30	4.18E-02	-0.42	3.54E-02	Expressed on the surface of monocytes and some polymorphonuclear cells. Co-receptor for several TLRs; facilitates activation of the innate immune response by bacterial LPS; functions as a pattern recognition receptor (PRR)[36]. Increased CD14+ cells observed in the blood of patients with TB disease and show upregulated expression of ISGs[37].
ENSG00000137628	*DDX60*	DExD/H-box helicase 60	-0.75	3.71E-02	1.07	1.40E-07	1.51	3.18E-32	0.32	1.31E-01	ISG. Role in type 1 IFN signalling[38]. Upregulated in TB disease[2].
ENSG00000130489			-0.73	3.61E-03	-0.30	6.60E-02	1.04	7.54E-26	-1.03	4.13E-11	
ENSG00000258922			-0.69	3.83E-02	1.49	6.73E-16	-0.01	9.62E-01	0.80	2.17E-05	
ENSG00000161929	*SCIMP*	SLP adaptor and CSK interacting membrane protein	-0.68	3.71E-02	-1.36	9.85E-14	0.39	2.71E-03	-2.04	3.70E-29	Universal adaptor for multiple Toll like receptors, promoting macrophage production of proinflammatory cytokines[39,40].
ENSG00000068079	*IFI35*	Interferon induced protein 35	-0.66	4.24E-02	0.40	3.46E-02	1.15	1.69E-23	-0.26	1.70E-01	Modulates type 1 IFN activity in influenza infection[41] . Role in bacterial sepsis as a damage associated molecular pattern (DAMP) molecule, activating the NF-κB proinflammatory signalling pathway of adjacent macrophages[42]. Upregulated in TB disease[2].

ENSG00000185507	*IRF7*	Interferon regulatory factor 7	-0.65	4.43E-02	0.95	1.10E-07	1.25	1.16E-28	0.30	1.03E-01	Key transcriptional regulator of type 1 IFN responses. Following activation of PRRs (including TLR3, 7, 8 and 9) by viral RNA/ DNA, IRF7 as well as IRF3 induce expression of IFN-α/β which further increase IRF7 expression in a positive feedback loop[43,44].IRF7-deficient humans and mice are vulnerable to severe viral infections[43,45,46]. In vitro, IRF7 expression is upregulated in *Mtb*-infected macrophages[47-49]. IRF7-/- knock out mice have higher *Mtb* bacillary burdens and lower survival rates[50]. IRF7 polymorphisms are linked to altered susceptibility to TB infection[51]. Upregulated in TB disease[2].
ENSG00000141664	*ZCCHC2*	Zinc finger CCHC-type containing 2	-0.64	6.98E-04	0.28	2.91E-02	0.90	2.08E-30	-0.36	4.90E-03	Association with type 4 hypersensitivity reactions[52].
ENSG00000151490	*PTPRO*	Protein tyrosine phosphatase receptor type O	-0.64	3.61E-03	-0.16	2.84E-01	0.55	7.74E-10	-0.79	5.83E-09	Immunoregulatory role in T cells, B cells, macrophages including TLR4/NFKB signalling[53].
ENSG00000116663	*FBXO6*	F-box protein 6	-0.62	2.60E-02	0.33	5.23E-02	0.94	1.60E-19	-0.29	8.37E-02	Activated by influenza A infection. Regulates type 1 IFN signalling via IRF3[54]. Upregulated in TB disease[2].
ENSG00000012171	*SEMA3B*	Semaphorin 3B	-0.59	2.14E-02	-0.66	1.17E-05	0.18	1.19E-01	-1.25	6.69E-17	Immunomodulatory effects in macrophages of rheumatoid arthritis patients[55].
ENSG00000025708	*TYMP*	Thymidine phosphorylase	-0.59	5.34E-03	-0.22	1.08E-01	0.71	7.52E-17	-0.81	9.28E-10	Upregulated in TB disease[2].
ENSG00000279236			-0.57	1.73E-02	-0.05	7.49E-01	0.76	2.45E-17	-0.62	1.04E-05	
ENSG00000197629	*MPEG1*	Macrophage expressed 1	-0.56	4.84E-02	-0.34	3.21E-02	-0.11	4.19E-01	-0.90	7.15E-09	Also known as Perforin-2. Pore-forming protein[56]. Knock out studies suggest role in control of intracellular bacterial and mycobacterial infections[57].
ENSG00000130487	*KLHDC7B*	Kelch domain containing 7B	-0.54	3.83E-02	0.26	9.81E-02	1.03	1.44E-27	-0.29	6.30E-02	Expression associated with STAT1-mediated IFN signalling pathway[58].
ENSG00000130303	*BST2*	Bone marrow stromal cell antigen 2	-0.54	2.07E-02	0.13	3.77E-01	0.95	3.42E-28	-0.41	3.17E-03	Protein also known as tetherin is an IFN-inducible transmembrane protein with anti-viral activities, including restricting virion release[59]. Induces activation of the NF-kB signalling pathway, promoting pro-inflammatory responses to pathogens including *Mtb*[60,61].
ENSG00000165185	*KIAA1958*	KIAA1958	-0.43	2.67E-02	-0.20	9.75E-02	0.46	9.15E-10	-0.63	3.69E-08	
ENSG00000113273	*ARSB*	Arylsulfatase B	-0.43	1.52E-02	0.64	8.39E-10	0.24	1.10E-03	0.21	5.14E-02	
ENSG00000124357	*NAGK*	N-acetylglucosamine kinase	-0.43	3.83E-02	0.52	7.74E-06	0.31	1.18E-04	0.09	4.54E-01	Upstream of NOD2, modifies bacterial cell wall peptidoglycan, enabling recognition by PRRs, triggering pro-inflammatory gene expression.[62]

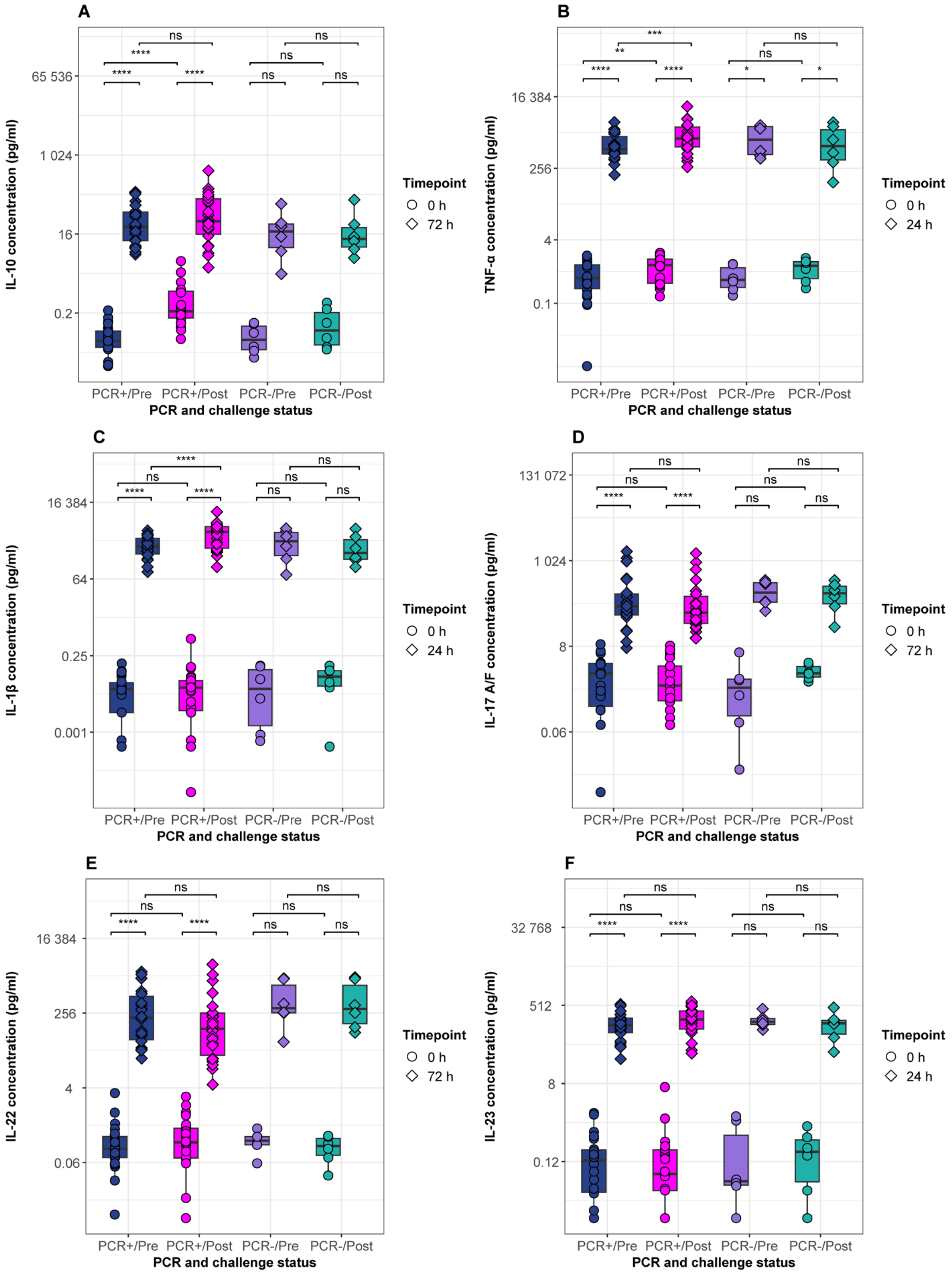
ENSG00000172936	*MYD88*	MYD88 innate immune signal transduction adaptor	-0.43	1.16E-02	0.31	2.68E-03	0.39	6.44E-09	-0.12	2.80E-01	Encodes downstream adaptor protein for most TLRs and the IL-1 receptor (IL-1R). After pathogen-sensing, the activated TLR activates MyD88, which in turn activates NF-kB, which mediates the induction of pro-inflammatory cytokines, and IRFs. MyD88-deficient children are vulnerable to severe pyogenic bacterial infections[63]. Mice with MyD88-deficiency are vulnerable to pathogens including *Mtb*[64].
ENSG00000163565	*IFI16*	Interferon gamma inducible protein 16	-0.40	2.29E-02	0.45	1.45E-05	0.59	1.51E-19	0.05	6.75E-01	Senses cytosolic viral RNA[65] and exogenous DNA[66] triggering type 1 IFN production. Role as *Mtb* DNA sensor in macrophages, increasing IFIT1 and IFN-β induction[13].
ENSG00000173786	*CNP*	2',3'-cyclic nucleotide 3' phosphodiesterase	-0.40	1.74E-02	0.61	6.09E-10	0.64	1.37E-24	0.21	3.84E-02	
ENSG00000180530	*NRIP1*	Nuclear receptor interacting protein 1	-0.36	1.52E-02	-0.10	2.72E-01	0.24	9.21E-05	-0.47	1.50E-07	Encodes Receptor-interacting protein 140. Coactivator for NFκB inflammation pathways. Deficiency leads to the inhibition of the proinflammatory gene expression in macrophages[67]
ENSG00000100220	*RTCB*	RNA 2',3'-cyclic phosphate and 5'-OH ligase	-0.29	5.34E-03	0.07	3.11E-01	0.42	2.65E-24	-0.22	9.83E-04	RTCB-depletion leads to increased type I and type III IFNs and proinflammatory cytokine responses in influenza infection. RTCB suppresses the expression of IFN and downstream ISGs[68].
ENSG00000106617	*PRKAG2*	Protein kinase AMP-activated non-catalytic subunit gamma 2	-0.27	2.44E-02	-0.17	2.02E-02	0.15	3.89E-03	-0.44	4.57E-10	In FoxA1+ regulatory T cells, the variant PRKAG2.2 is transcribed in response to IFN-β, with roles in FoxA1+ Treg differentiation and metabolic function[69].
ENSG00000231721	*LINC-PINT*	Long intergenic non-protein coding RNA, p53 induced transcript	0.21	3.65E-02	-0.20	5.22E-04	-0.16	4.21E-05	0.01	8.70E-01	
ENSG00000104450	*SPAG1*	Sperm associated antigen 1	0.30	3.83E-02	-0.13	1.26E-01	-0.12	6.34E-02	0.17	4.13E-02	
ENSG00000226380			0.36	2.07E-02	0.49	4.24E-08	-0.18	5.52E-03	0.84	1.31E-21	
ENSG00000134602	*STK26*	Serine/ threonine kinase 26	0.36	4.17E-03	0.26	1.35E-03	-0.06	3.48E-01	0.63	4.76E-15	Also known as MST4. Regulatory role in inflammation, downregulated in sepsis[70].
ENSG00000183150	*GPR19*	G protein-coupled receptor 19	0.42	2.44E-02	0.31	6.27E-03	-0.22	7.09E-03	0.72	5.30E-11	
ENSG00000109756	*RAPGEF2*	Rap guanine nucleotide	0.43	9.94E-03	0.60	1.55E-09	-0.20	7.55E-03	1.03	2.03E-25	

		exchange factor 2								
ENSG00000197965	*MPZL1*	Myelin protein zero like 1	0.66	3.83E-02	-2.04	2.30E-30	-0.74	4.51E-10	-1.38	1.62E-14	Downregulated in murine bone marrow-derived macrophages infected with hypervirulent versus hypovirulent *Mtb*[49].

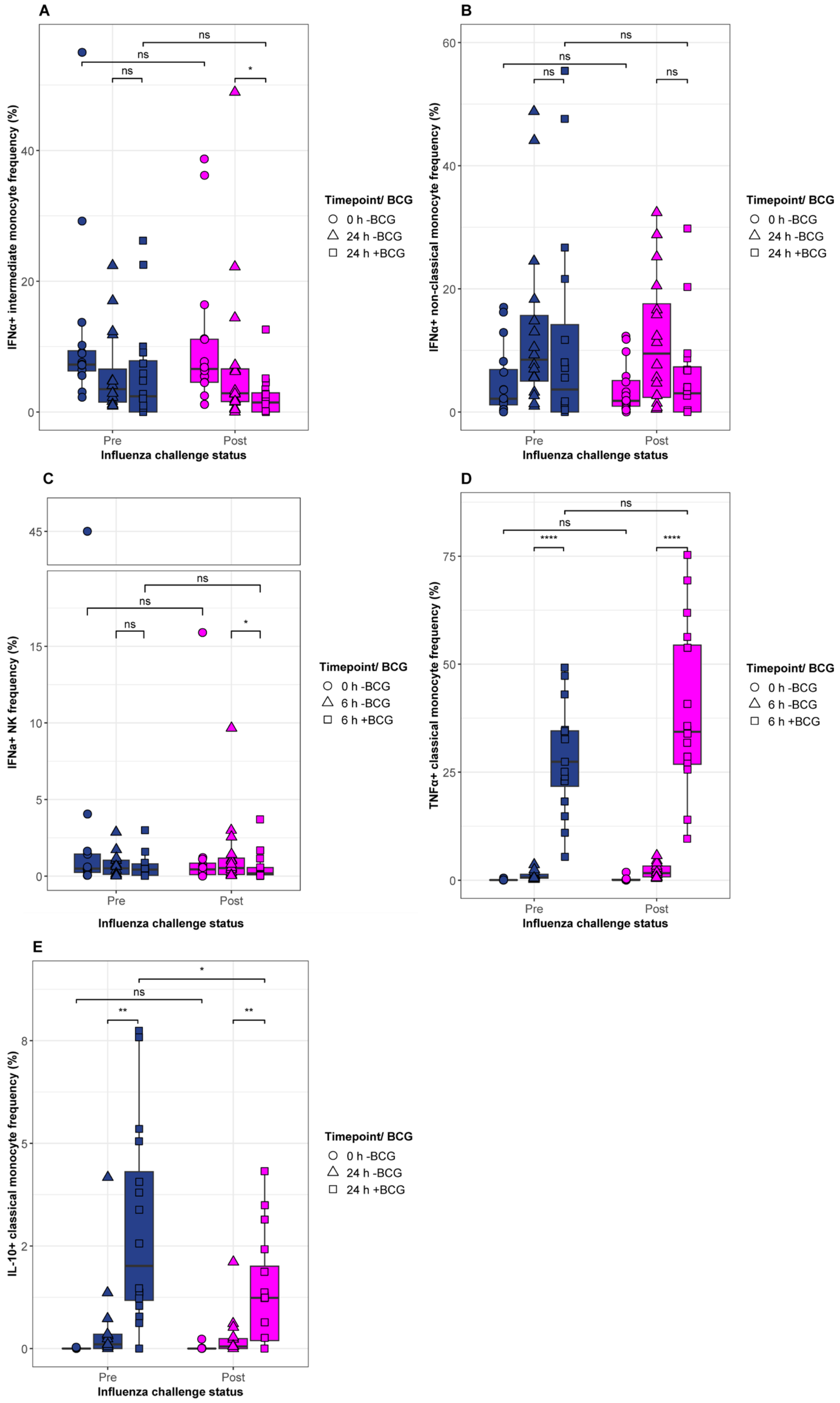
Extended Data Figure 3. Nine gene clusters identified by maSigPro. In total, 2,140 genes were identified as significantly differentially expressed (SDE) over time and between pre- *versus* post-influenza (adj. $p \leq 0.05$, $R^2>0.6$). The coefficients obtained were used to group together SDE genes into clusters with similar temporal expression patterns. Summary plots of gene expression over time for the BCG-infected pre-influenza (dark blue), BCG-infected post-influenza (pink), BCG-uninfected pre-influenza (light blue) and BCG-uninfected post-influenza (red) groups are shown. Solid lines connect the median expression to show the trends for each group, and the dashed lines show the regression curves fitted to the data.



Extended Data Figure 4. Cytokine responses to BCG *lux* infection, pre- and post-influenza. Concentrations of IL-10, TNF-α, IL-1β, IL 17-A/F, IL-22 and IL-23 were measured in the supernatants from BCG *lux*-uninfected blood at baseline (0 h incubation) and BCG *lux*-infected blood at 6, 24 and 72 h incubation. Plots showing baseline and maximal concentrations. Box and whiskers plots are shown for 22 influenza PCR+ and 6 PCR- participants, with the horizontal lines showing the medians. Paired comparisons of medians were made using two-tailed Wilcoxon rank sum between the pre- *versus* post-influenza samples, and baseline *versus* maximal concentrations, in the PCR+ and PCR- groups. In all plots, false discovery rate (FDR)-corrected p values are shown: ns p >0.05, *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001.



Extended Data Figure 5. **Changing frequencies of cell subsets over time.** Plots showing the frequency of (A) IFN-α+ intermediate monocytes, (B) IFN-α+ non-classical monocytes, (C) IFN-α+ NK cells, (D) TNF-α+ classical monocytes, (E) IL-10+ classical monocytes over time. For each cellular subtype, box and whiskers plots of frequency in BCG *lux*-uninfected blood at baseline (0h) and BCG *lux*- uninfected and infected blood at 6 h (C, D) and 24 h (A, B, E) are shown for 16 influenza PCR+ participants, before and after influenza infection, with the horizontal lines showing the medians. Paired comparisons of medians were made using two-tailed Wilcoxon rank sum between pre- *versus* post-influenza samples, and BCG *lux*-infected *versus* -uninfected samples. In all plots, false discovery rate (FDR)-corrected p values are shown: ns p >0.05, *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001.



Extended Data References

1. Jiang H, Tsang L, Wang H, Liu C. IFI44L as a Forward Regulator Enhancing Host Antituberculosis Responses. *Journal of Immunology Research* 2021; **2021**(1): 5599408.
2. Singhania A, Verma R, Graham CM, et al. A modular transcriptional signature identifies phenotypic heterogeneity of human tuberculosis infection. *Nature communications* 2018; **9**(1): 2308.
3. Yu J, Liu SL. Emerging Role of LY6E in Virus-Host Interactions. *Viruses* 2019; **11**(11).
4. Xu X, Qiu C, Zhu L, et al. IFN-stimulated gene LY6E in monocytes regulates the CD14/TLR4 pathway but inadequately restrains the hyperactivation of monocytes during chronic HIV-1 infection. *Journal of immunology (Baltimore, Md : 1950)* 2014; **193**(8): 4125-36.
5. Hornung V, Hartmann R, Ablasser A, Hopfner K-P. OAS proteins and cGAS: unifying concepts in sensing and responding to cytosolic nucleic acids. *Nature Reviews Immunology* 2014; **14**(8): 521-8.
6. Berry MP, Graham CM, McNab FW, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* 2010; **466**(7309): 973-7.
7. Maertzdorf J, Repsilber D, Parida SK, et al. Human gene expression profiles of susceptibility and resistance in tuberculosis. *Genes & Immunity* 2011; **12**(1): 15-22.
8. Ottenhoff TH, Dass RH, Yang N, et al. Genome-wide expression profiling identifies type 1 interferon response pathways in active tuberculosis. *PloS one* 2012; **7**(9): e45839.
9. Leisching G, Wiid I, Baker B. OAS1, 2, and 3: Significance During Active Tuberculosis? *The Journal of infectious diseases* 2018; **217**(10): 1517-21.
10. Leisching G, Cole V, Ali AT, Baker B. OAS1, OAS2 and OAS3 restrict intracellular M. tb replication and enhance cytokine secretion. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2019; **80s**: S77-s84.
11. Helbig KJ, Beard MR. The Role of Viperin in the Innate Antiviral Response. *Journal of Molecular Biology* 2014; **426**(6): 1210-9.
12. Helbig KJ, Teh MY, Crosse KM, et al. The interferon stimulated gene viperin, restricts Shigella. flexneri in vitro. *Scientific Reports* 2019; **9**(1): 15598.
13. Manzanillo PS, Shiloh MU, Portnoy DA, Cox JS. Mycobacterium tuberculosis activates the DNA-dependent cytosolic surveillance pathway within macrophages. *Cell host & microbe* 2012; **11**(5): 469-80.
14. Abella V, Scotece M, Conde J, et al. Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nature Reviews Rheumatology* 2017; **13**(2): 100-9.
15. Naylor C, Petri WA, Jr. Leptin Regulation of Immune Responses. *Trends in molecular medicine* 2016; **22**(2): 88-98.
16. Wieland CW, Florquin S, Chan ED, et al. Pulmonary Mycobacterium tuberculosis infection in leptin-deficient ob/ob mice. *International Immunology* 2005; **17**(11): 1399-408.
17. Chen Y, Cao S, Sun Y, Li C. Gene expression profiling of the TRIM protein family reveals potential biomarkers for indicating tuberculosis status. *Microbial pathogenesis* 2018; **114**: 385-92.
18. van Tol S, Atkins C, Bharaj P, et al. VAMP8 Contributes to the TRIM6-Mediated Type I Interferon Antiviral Response during West Nile Virus Infection. *Journal of virology* 2020; **94**(2).

19. Villamayor L, Rivero V, López-García D, et al. Interferon alpha inducible protein 6 is a negative regulator of innate immune responses by modulating RIG-I activation. *Frontiers in immunology* 2023; **14**: 1105309.

20. Mariotti B, Servaas NH, Rossato M, et al. The Long Non-coding RNA NRIR Drives IFN-Response in Monocytes: Implication for Systemic Sclerosis. *Frontiers in immunology* 2019; **10**: 100.

21. Ren T, Chen H, Liu X, et al. ID1 inhibits foot-and-mouth disease virus replication via targeting of interferon pathways. *The FEBS Journal* 2021; **288**(14): 4364-81.

22. Roy S, Schmeier S, Kaczkowski B, et al. Transcriptional landscape of Mycobacterium tuberculosis infection in macrophages. *Scientific Reports* 2018; **8**(1): 6758.

23. Verhelst J, Parthoens E, Schepens B, Fiers W, Saelens X. Interferon-Inducible Protein Mx1 Inhibits Influenza Virus by Interfering with Functional Viral Ribonucleoprotein Complex Assembly. *Journal of virology* 2012; **86**(24): 13445-55.

24. Kim Y-H, Lee J-R, Hahn M-J. Regulation of inflammatory gene expression in macrophages by epithelial-stromal interaction 1 (Epsti1). *Biochemical and Biophysical Research Communications* 2018; **496**(2): 778-83.

25. Wu S, Wang Y, Chen G, Zhang M, Wang M, He JQ. 2'-5'-Oligoadenylate synthetase 1 polymorphisms are associated with tuberculosis: a case-control study. *BMC pulmonary medicine* 2018; **18**(1): 180.

26. Campbell JA, Lenschow DJ. Emerging roles for immunomodulatory functions of free ISG15. *Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research* 2013; **33**(12): 728-38.

27. Bogunovic D, Byun M, Durfee LA, et al. Mycobacterial disease and impaired IFN-γ immunity in humans with inherited ISG15 deficiency. *Science* 2012; **337**(6102): 1684-8.

28. Pohl C, Dikic I. Fighting mycobacteria through ISGylation. *EMBO reports* 2012; **13**(10): 872-3.

29. Xu D, Jiang W, Wu L, et al. PLSCR1 is a cell-autonomous defence factor against SARS-CoV-2 infection. *Nature* 2023; **619**(7971): 819-27.

30. Yang AX, Norbrun C, Sorkhdini P, Zhou Y. Phospholipid scramblase 1: a frontline defense against viral infections. *Frontiers in cellular and infection microbiology* 2025; **Volume 15 - 2025**.

31. Arias CF, Ballesteros-Tato A, García MaI, et al. p21CIP1/WAF1 Controls Proliferation of Activated/Memory T Cells and Affects Homeostasis and Memory T Cell Responses1. *The Journal of Immunology* 2007; **178**(4): 2296-306.

32. Lloberas J, Celada A. p21waf1/CIP1, a CDK inhibitor and a negative feedback system that controls macrophage activation. *European journal of immunology* 2009; **39**(3): 691-4.

33. Scatizzi JC, Mavers M, Hutcheson J, et al. The CDK domain of p21 is a suppressor of IL-1β-mediated inflammation in activated macrophages. *European journal of immunology* 2009; **39**(3): 820-5.

34. Lv X, Zheng T, Lei X, et al. RTP4 restricts influenza A virus infection by targeting the viral NS1 protein. *Virology* 2025; **603**: 110397.

35. He X, Ashbrook AW, Du Y, et al. RTP4 inhibits IFN-I response and enhances experimental cerebral malaria and neuropathology. *Proceedings of the National Academy of Sciences of the United States of America* 2020; **117**(32): 19465-74.

36. Zanoni I, Granucci F. Role of CD14 in host protection against infections and in metabolism regulation. *Frontiers in cellular and infection microbiology* 2013; **3**: 32.

37. Burel JG, Hillman H, Khan N, et al. Profiling the myeloid compartment of PBMC in active tuberculosis reveals substantial changes in CD14+ cells and upregulation of CD16 in pro-inflammatory dendritic cells. *The Journal of Immunology* 2022; **208**(1_Supplement): 161.02-.02.

38. Oshiumi H, Miyashita M, Okamoto M, et al. DDX60 Is Involved in RIG-I-Dependent and Independent Antiviral Responses, and Its Function Is Attenuated by Virus-Induced EGFR Activation. *Cell reports* 2015; **11**(8): 1193-207.

39. Luo L, Bokil NJ, Wall AA, et al. SCIMP is a transmembrane non-TIR TLR adaptor that promotes proinflammatory cytokine production from macrophages. *Nature communications* 2017; **8**(1): 14133.

40. Liu L, Lucas RM, Nanson JD, et al. The transmembrane adapter SCIMP recruits tyrosine kinase Syk to phosphorylate Toll-like receptors to mediate selective inflammatory outputs. *Journal of Biological Chemistry* 2022; **298**(5): 101857.

41. Yang H, Winkler W, Wu X. Interferon Inducer IFI35 Regulates RIG-I-Mediated Innate Antiviral Response through Mutual Antagonism with Influenza Virus Protein NS1. *Journal of virology* 2021; **95**(11): 10.1128/jvi.00283-21.

42. Xiahou Z, Wang X, Shen J, et al. NMI and IFP35 serve as proinflammatory DAMPs during cellular infection and injury. *Nature communications* 2017; **8**(1): 950.

43. Honda K, Yanai H, Negishi H, et al. IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature* 2005; **434**(7034): 772-7.

44. Jefferies CA. Regulating IRFs in IFN Driven Disease. *Frontiers in immunology* 2019; **10**: 325.

45. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020; **370**(6515).

46. Ciancanelli MJ, Huang SX, Luthra P, et al. Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science* 2015; **348**(6233): 448-53.

47. Zhang G, Chen X, Chan L, et al. An SNP selection strategy identified IL-22 associating with susceptibility to tuberculosis in Chinese. *Sci Rep* 2011; **1**: 20.

48. Cheng Y, Schorey JS. Mycobacterium tuberculosis-induced IFN-β production requires cytosolic DNA and RNA sensing pathways. *The Journal of experimental medicine* 2018; **215**(11): 2919-35.

49. Leisching G, Pietersen RD, van Heerden C, van Helden P, Wiid I, Baker B. RNAseq reveals hypervirulence-specific host responses to M. tuberculosis infection. *Virulence* 2017; **8**(6): 848-58.

50. Zhang Z, Mai Q, Yang L, et al. MicroRNA-31 mediated by interferon regulatory factor 7 signaling facilitates control of Mycobacterium tuberculosis infection. *International journal of medical microbiology : IJMM* 2022; **312**(7): 151569.

51. Cubillos-Angulo JM, Arriaga MB, Melo MGM, et al. Polymorphisms in interferon pathway genes and risk of Mycobacterium tuberculosis infection in contacts of tuberculosis cases in Brazil. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2020; **92**: 21-8.

52. Velie BD, Shrestha M, François L, et al. Using an Inbred Horse Breed in a High Density Genome-Wide Scan for Genetic Risk Factors of Insect Bite Hypersensitivity (IBH). *PloS one* 2016; **11**(4): e0152966.

53. Xie F, Dong H, Zhang H. Regulatory Functions of Protein Tyrosine Phosphatase Receptor Type O in Immune Cells. *Frontiers in immunology* 2021; **12**: 783370.

54. Du X, Meng F, Peng D, et al. Noncanonical Role of FBXO6 in Regulating Antiviral Immunity. *The Journal of Immunology* 2019; **203**(4): 1012-20.

55. Martínez-Ramos S, Rafael-Vidal C, Malvar-Fernández B, et al. Semaphorin3B promotes an anti-inflammatory and pro-resolving phenotype in macrophages from rheumatoid arthritis patients in a MerTK-dependent manner. *Frontiers in immunology* 2024; **Volume 14 - 2023**.

56. McCormack RM, de Armas LR, Shiratsuchi M, et al. Perforin-2 is essential for intracellular defense of parenchymal cells and phagocytes against pathogenic bacteria. *eLife* 2015; **4**: e06508.

57. McCormack RM, Szymanski EP, Hsu AP, et al. MPEG1/perforin-2 mutations in human pulmonary nontuberculous mycobacterial infections. *JCI insight* 2017; **2**(8).

58. Jeong G, Bae H, Jeong D, et al. A Kelch domain-containing KLHDC7B and a long non-coding RNA ST8SIA6-AS1 act oppositely on breast cancer cell proliferation via the interferon signaling pathway. *Scientific Reports* 2018; **8**(1): 12922.

59. Yi E, Oh J, Kang HR, Song MJ, Park SH. BST2 inhibits infection of influenza A virus by promoting apoptosis of infected cells. *Biochem Biophys Res Commun* 2019; **509**(2): 414-20.

60. Poladian N, Orujyan D, Narinyan W, et al. Role of NF-κB during Mycobacterium tuberculosis Infection. *International journal of molecular sciences* 2023; **24**(2).

61. Tiwari R, de la Torre JC, McGavern DB, Nayak D. Beyond Tethering the Viral Particles: Immunomodulatory Functions of Tetherin (BST-2). *DNA and cell biology* 2019; **38**(11): 1170-7.

62. Stafford CA, Gassauer A-M, de Oliveira Mann CC, et al. Phosphorylation of muramyl peptides by NAGK is required for NOD2 activation. *Nature* 2022; **609**(7927): 590-6.

63. von Bernuth H, Picard C, Jin Z, et al. Pyogenic Bacterial Infections in Humans with MyD88 Deficiency. *Science* 2008; **321**(5889): 691-6.

64. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. *Annual review of immunology* 2013; **31**: 475-527.

65. Jiang Z, Wei F, Zhang Y, et al. IFI16 directly senses viral RNA and enhances RIG-I transcription and activation to restrict influenza virus infection. *Nature Microbiology* 2021; **6**(7): 932-45.

66. Unterholzner L, Keating SE, Baran M, et al. IFI16 is an innate immune sensor for intracellular DNA. *Nature Immunology* 2010; **11**(11): 997-1004.

67. Zschiedrich I, Hardeland U, Krones-Herzig A, et al. Coactivator function of RIP140 for NFκB/RelA-dependent cytokine gene expression. *Blood* 2008; **112**(2): 264-76.

68. Cao L, Hui X, Xu T, et al. The RNA-Splicing Ligase RTCB Promotes Influenza A Virus Replication by Suppressing Innate Immunity via Interaction with RNA Helicase DDX1. *Journal of immunology (Baltimore, Md : 1950)* 2023; **211**(6): 1020-31.

69. Mandatori S, Liu Y, Marturia-Navarro J, et al. PRKAG2.2 is essential for FoxA1(+) regulatory T cell differentiation and metabolic rewiring distinct from FoxP3(+) regulatory T cells. *Sci Adv* 2023; **9**(51): eadj8442.

70. Jiao S, Zhang Z, Li C, et al. The kinase MST4 limits inflammatory responses through direct phosphorylation of the adaptor TRAF6. *Nature Immunology* 2015; **16**(3): 246-57.