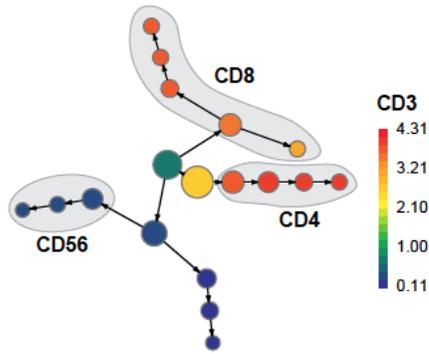
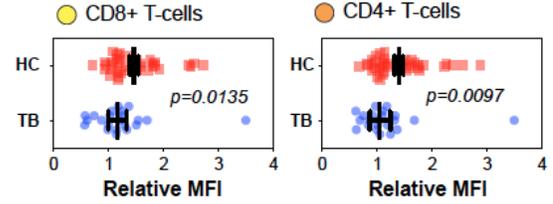
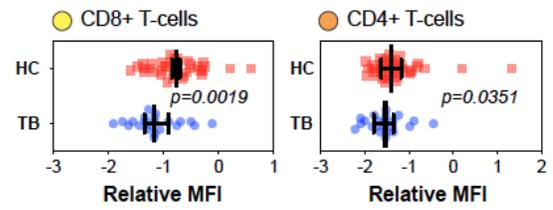


A Mtb immune response

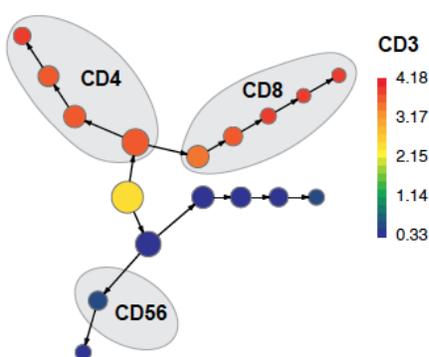


IFN γ

Ki67

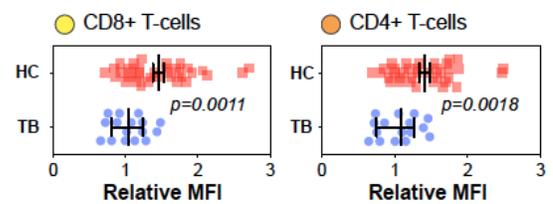
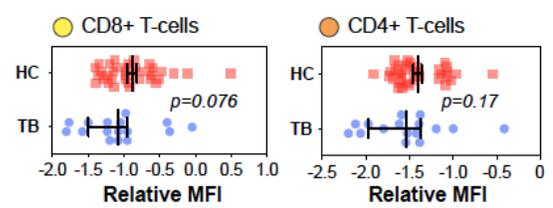


B SEB immune response

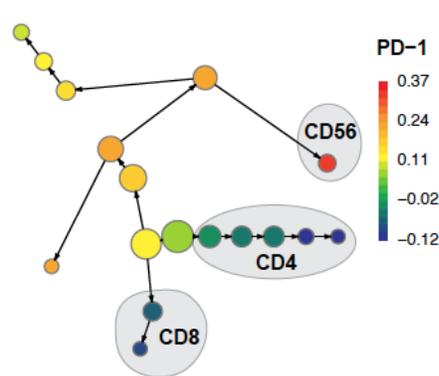


IFN γ

Ki67



C

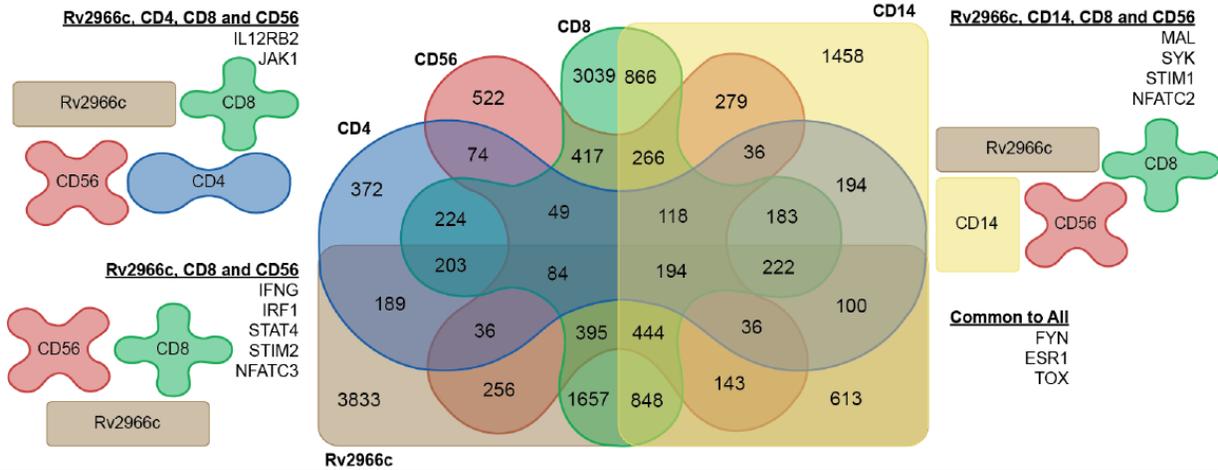


Supplemental Figure 1: TB patients exhibit an exhausted immune phenotype. PBMCs from individuals with Tuberculosis (TB; n = 29) and their asymptomatic household contacts (HC; n = 49) had their PBMCs divided into PBS vehicle non-stimulated control ("Nil stim"), BCG stimulated, ESAT-6 and CFP-10 stimulated and Staphylococcal-enterotoxin B (SEB) stimulated cells (0.5 – 1 x 10⁶ cells per condition). Cells were stimulated overnight with monensin and BFA for the final 12 hours. The BCG immune response is presented in Figure 1.

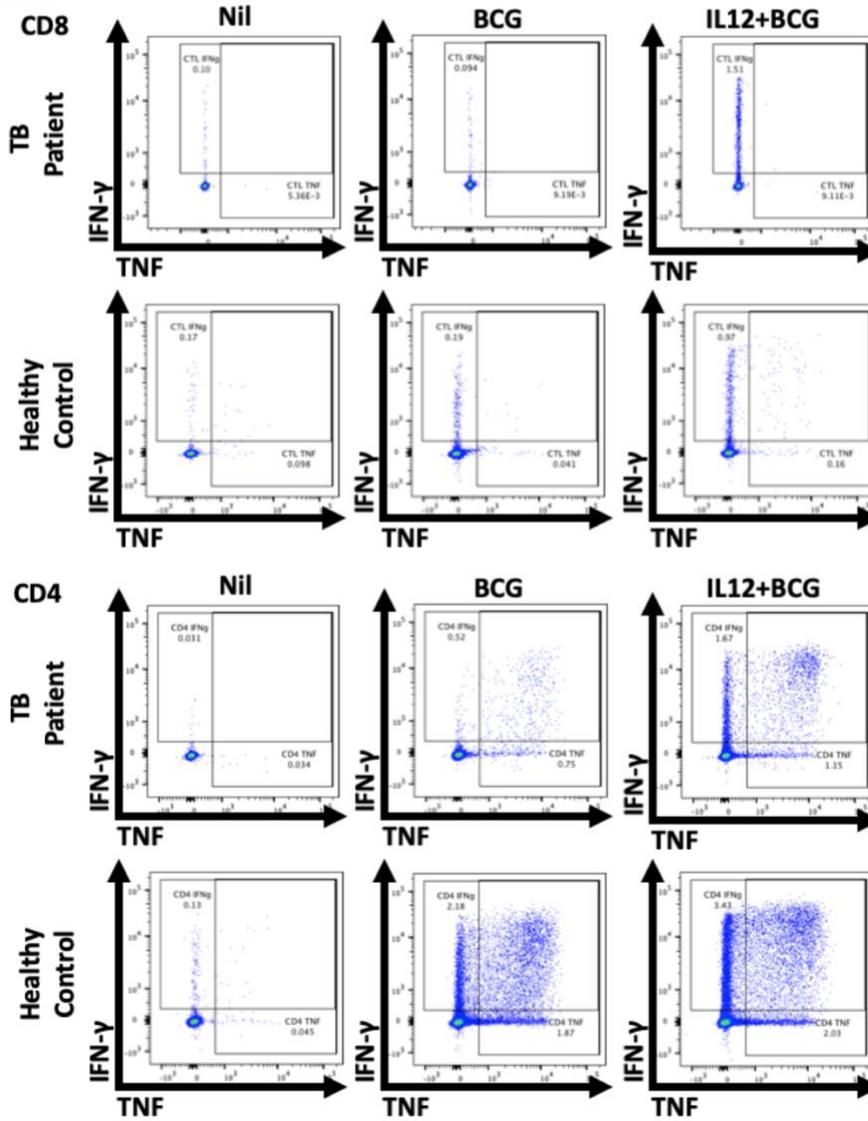
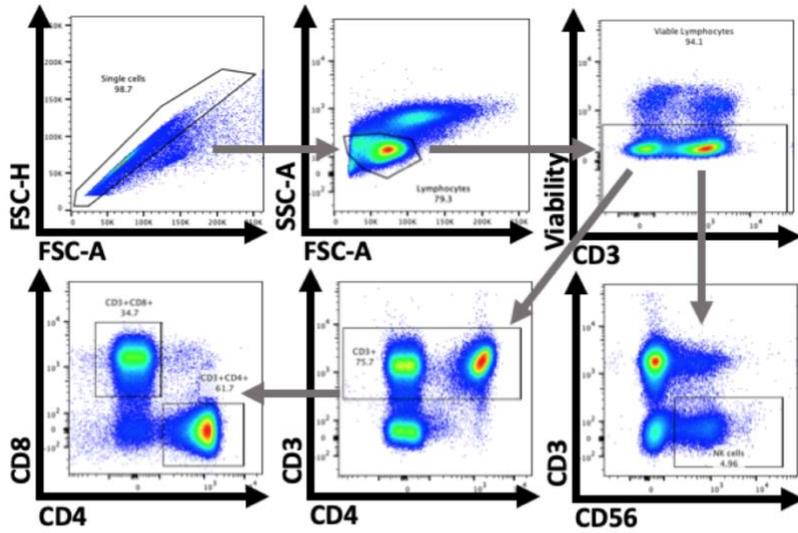
Citrus (cluster identification, characterization, and regression) identified CD4, CD8, CD3 and CD56 subsets.

(S1A) Mtb-specific (ESAT-6 and CFP-10) immune response: CITRUS was clustered based upon CD3, CD4, CD8 and CD56 surface markers with minimum of 10% population per node with CD3 signal depicted by color gradient. Grey shaded sub-clusters demonstrate nodes with decreased Mtb-specific (ESAT-6 and CFP-10) up-regulation of IFN- γ and Ki67 with an FDR <1%. (S1B) Staphylococcal-

enterotoxin B (SEB) immune response: CITRUS analysis demonstrates CD4, CD8 and NK cells with decreased Ki-67 and IFN- γ . **(S1C)** PD-1 NK cells: CITRUS analysis identifies TB patients to have increased abundance of PD-1 expressing NK cells compared to healthy controls



Supplemental Figure 2: Venn Diagram demonstrates overlap of in vivo DNA hyper-methylation in TB patients from Eswatini with previously published in vitro DNA hyper-methylation by Rv2966c as described by Sharma et al(24, 25). Venn diagram of genes with DNA hyper-methylation in CD4, CD8, CD56 and CD14 cells from this cohort of TB patients.



Supplemental Figure 3: Representative gating strategy and dot plots for data demonstrated in Figure 7 with no stimulation ("Nil"), BCG or IL-12 plus BCG stimulation.

Supplemental Table 3: Antibodies used for flow cytometry.

Target	Flor	Company	Catalog	Clone
CD8	BV786	BD Horizon	563823	RPA-T8
CD4	PE-Cyanine5.5	eBioscience	35-0047-42	SK3
CD279 (PD-1)	APC/Cy7	BioLegend	329922	EH12.2H7
CD56	BV605	BD Bioscience	562780	NCAM16.2
IFN- γ	Alexa Fluor [®] 700	BioLegend	506516	B27
T-bet	FITC	BioLegend	644812	4B10
CD3	BV711	BD Bioscience	563725	UCHT1
IL-4	BV421	BD Bioscience	562986	8D4-8
IL-13	APC	BioLegend	501907	JES10-5A2
IL-10	PE-CF594	BD Bioscience	562400	JES3-19F1
Perforin	PE	BioLegend	353304	B-D48
TNF- α	BV650 [™]	BioLegend	502938	Mab11
Ki-67	BUV395	BD Bioscience	564071	B56
GATA3	PE-Cy [™] 7	BD Bioscience	560405	L50-823