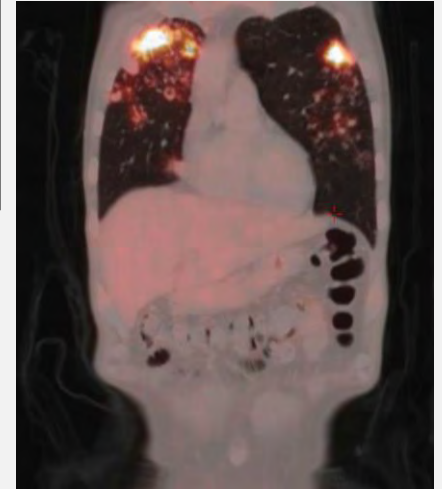


**A TOLLIP DEFICIENCY ALLELE,
RS5743854,
IS ASSOCIATED WITH
LNCRNA TOLLIP-AS1
EXPRESSION,
T-CELL MEMORY PHENOTYPE,
AND
INCREASED TB
SUSCEPTIBILITY**

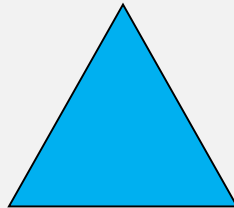
February 21, 2018

5th Global Forum on TB Vaccines

MULTIPLE FACTORS INFLUENCE VACCINE IMMUNITY AND TB SUSCEPTIBILITY



Pathogen



Exposure

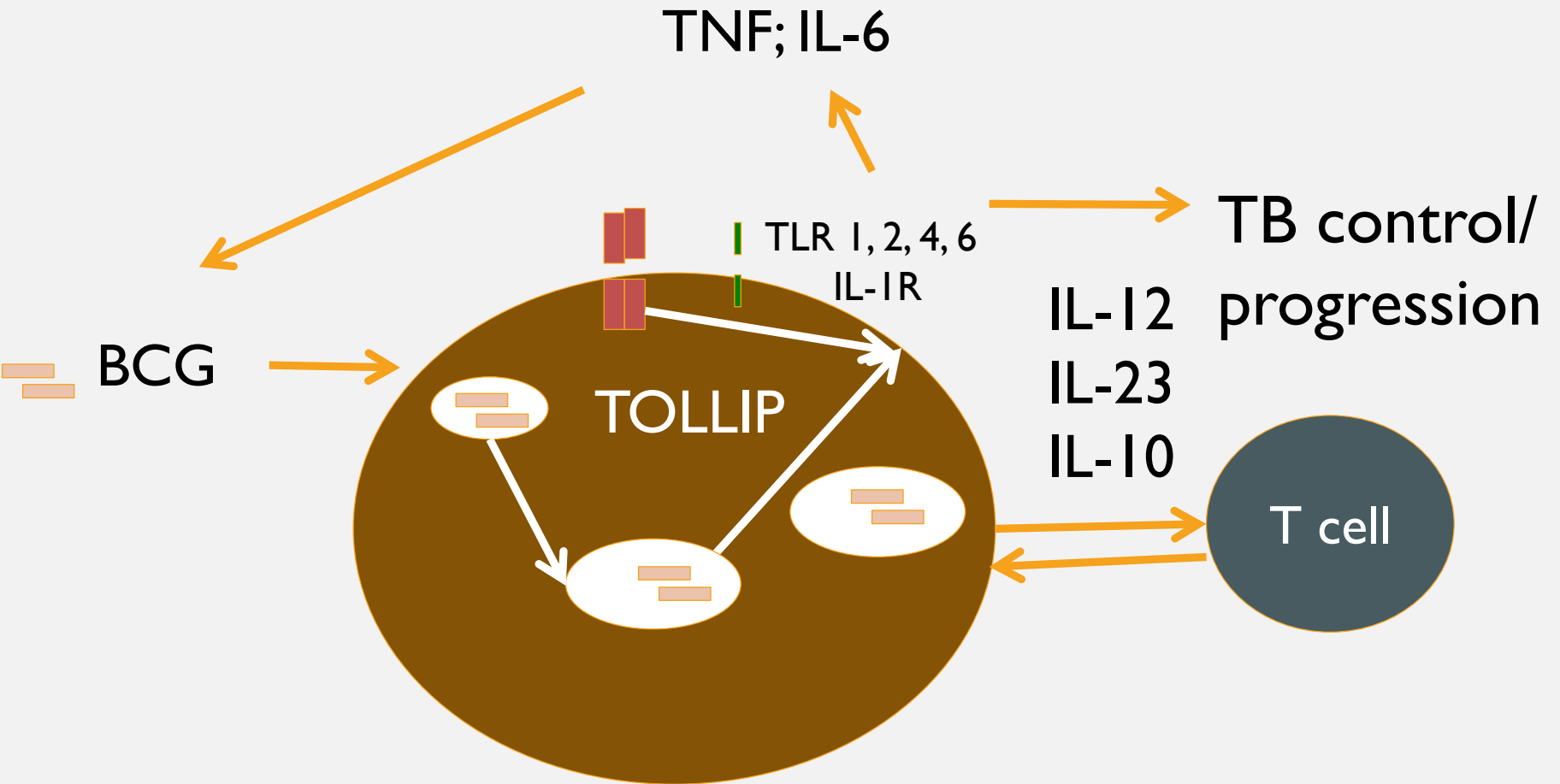
Host

Genetics

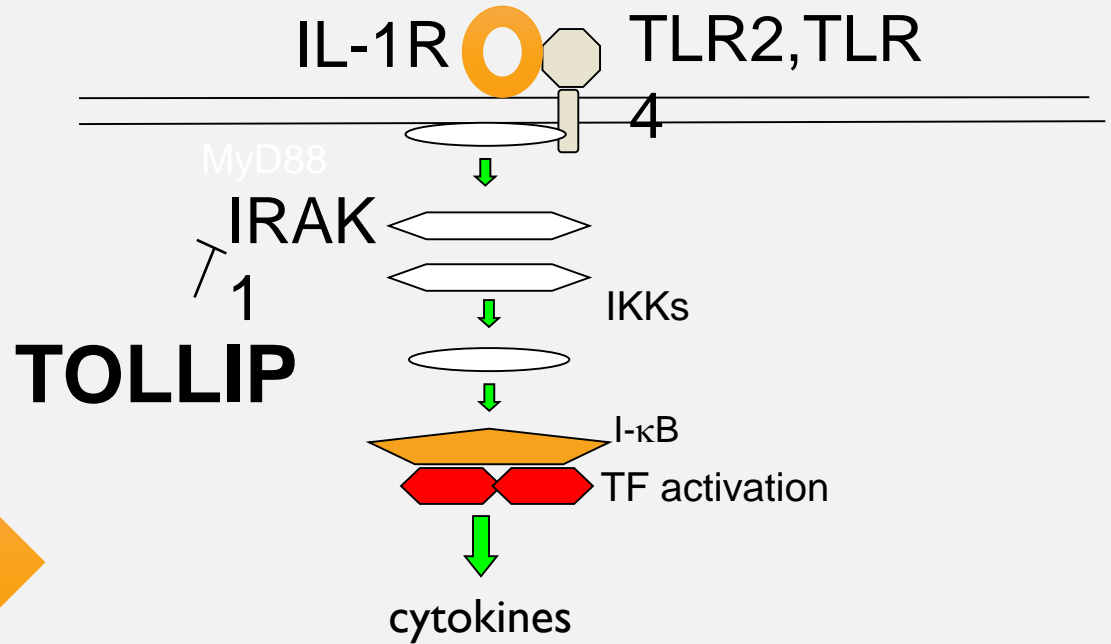
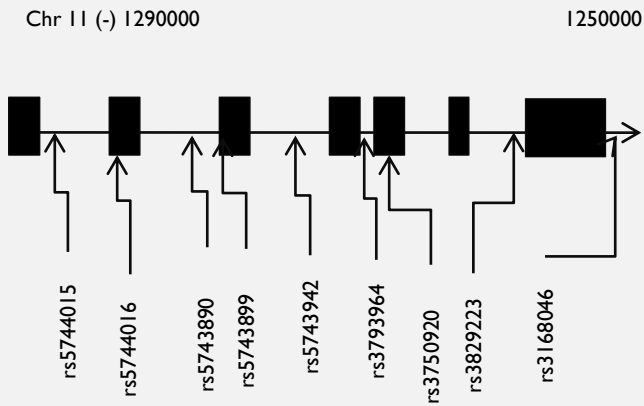
Age

- **Profile Genes Associated with Mycobacterial Susceptibility**
- **Determine Pathways Critical to Mycobacterial Control**
- **Improve Therapies and Vaccines**

BCG Activity



TOLLIP – CRITICAL REGULATOR OF IMMUNE ACTIVATION

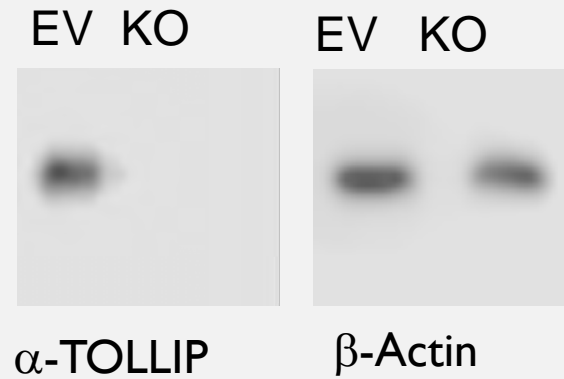


ESCRT Autophagy Ub binding
 Endosomal TLR2, TLR4,
 Localizatio IL-IR binding
 n

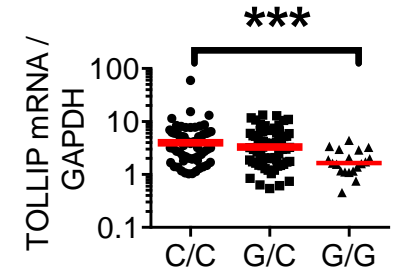
TOLLIP DEFICIENCY INDUCES INFLAMMATION

A.

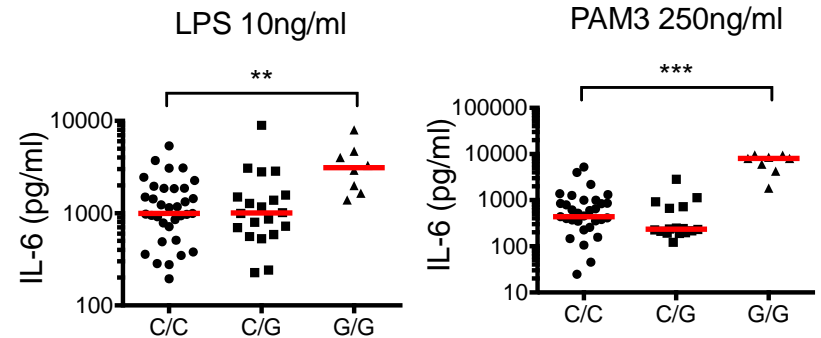
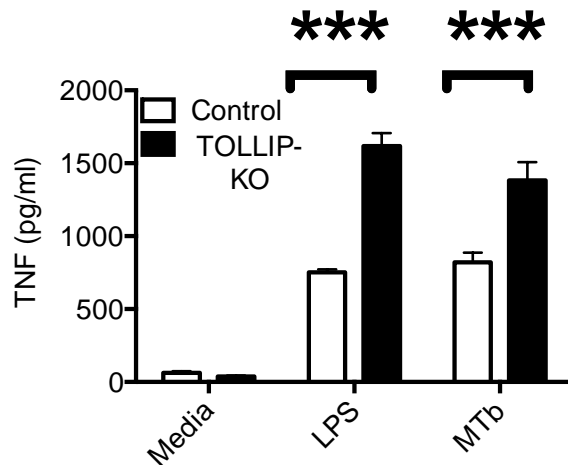
CRISPR/Cas9 knockout of TOLLIP in THP1s
Empty vector control (EV) vs TOLLIP-KO



Seattle Healthy Control Cohort



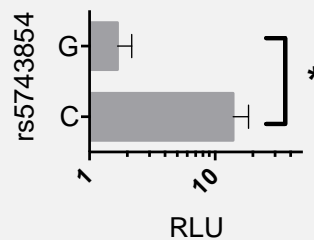
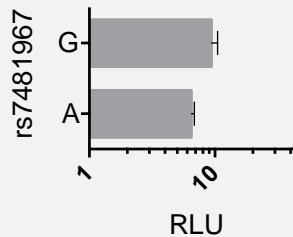
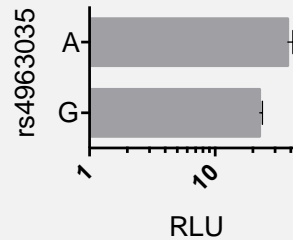
B.



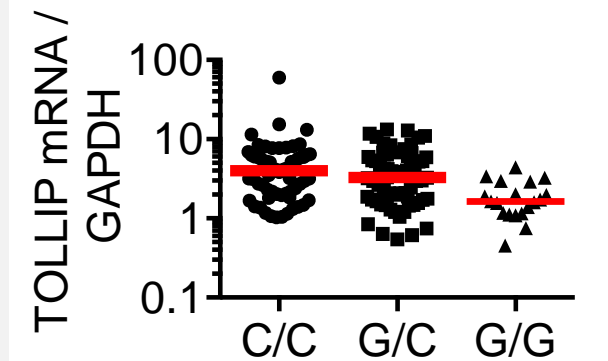
RS5743854 IS A **FUNCTIONAL** TOLLIP PROMOTER VARIANT



HEK293T cells
 TOLLIP promoter transfected with
 Luciferase protein
 Luminescence measured after 24hr

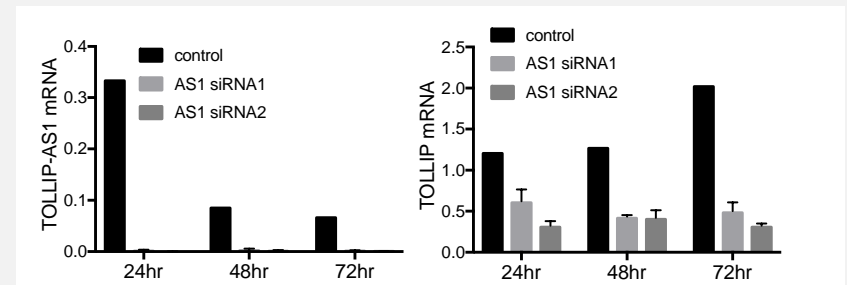
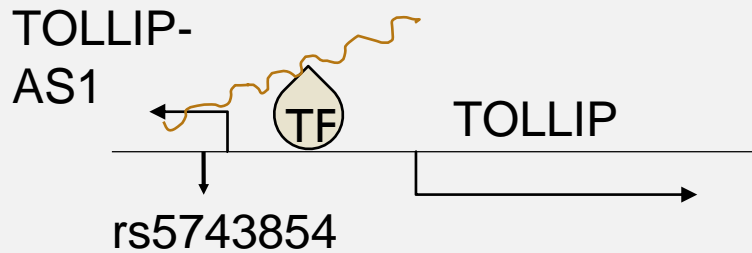


South African cohort
 Infant Monocytes
 Community Control
 N = 155



* p = 0.008, Kruskal-Wallis test

RS5743854 INFLUENCES **TOLLIP-ASI** EXPRESSION AND **TOLLIP** MRNA TRANSCRIPTION



**HYPOTHESIS:
ONE OR MORE FUNCTIONAL TOLLIP
VARIANTS REGULATE *IN VIVO* IMMUNE
RESPONSES TO BCG & SUSCEPTIBILITY
TO TB**



Collaborators:
University of Cape Town



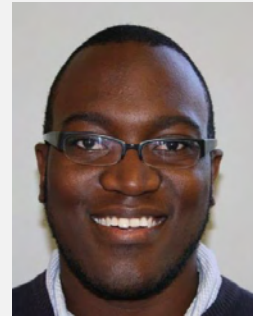
Willem
Hanekom



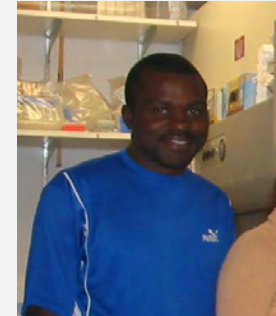
Mark
Hatherill



Tom Scriba



Munya
Musvosvi

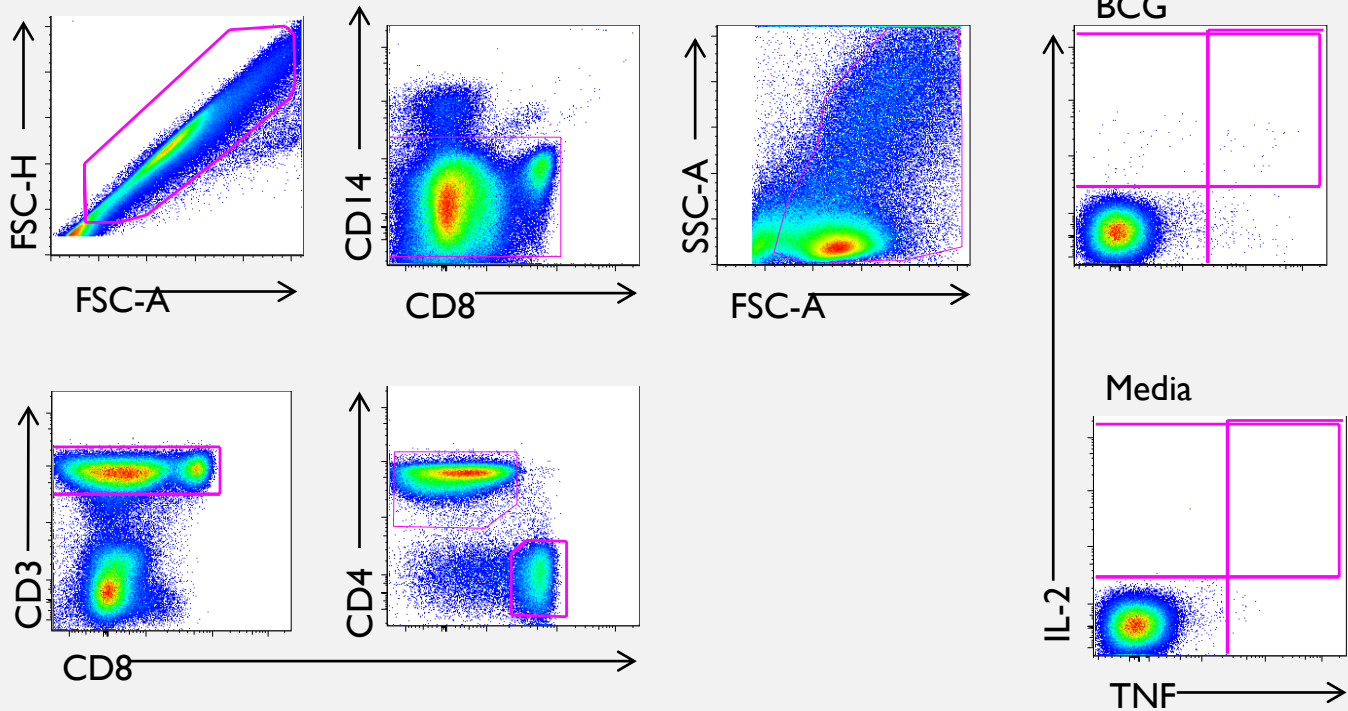


Muki Shey

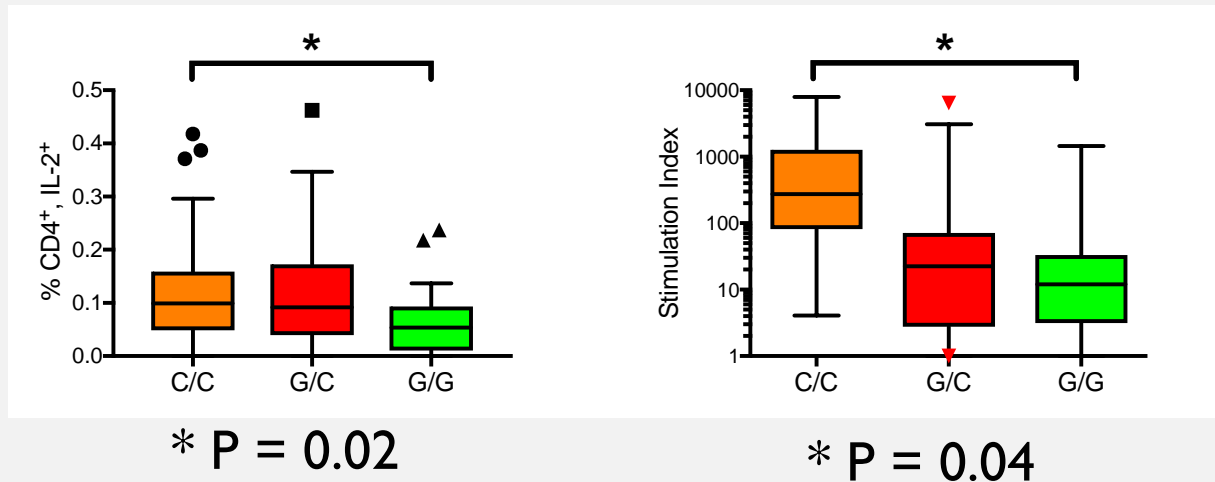
Evaluating BCG-specific T cell Immunity In TOLLIP-deficient infants

N = 174
Infant Whole
Blood
BCG-specific T
Cell Cytokines

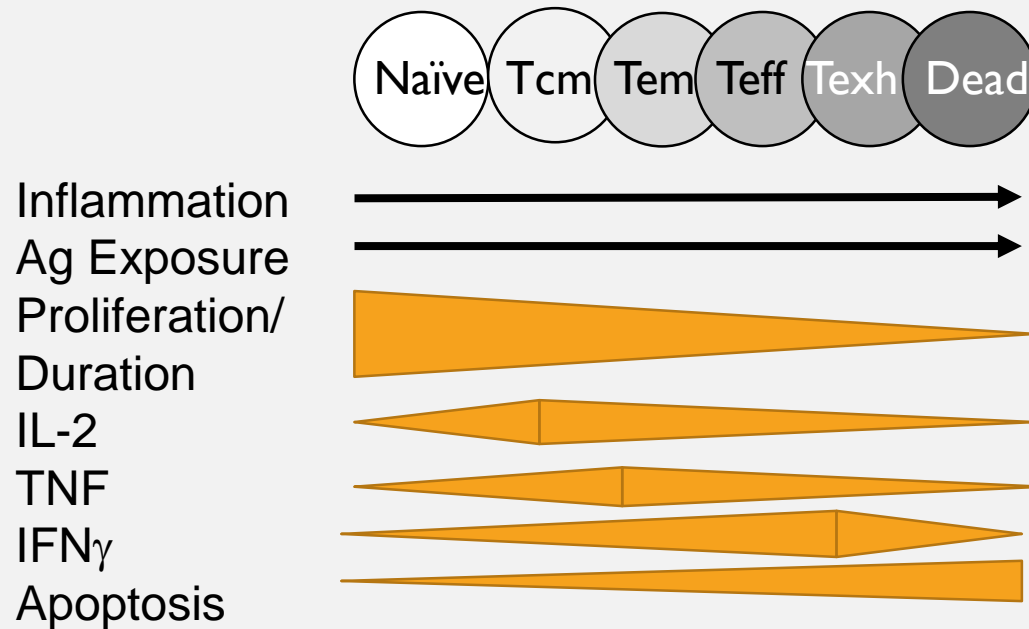
IL-2
TNF
IFN- γ
IL-17
IL-22
IL-4

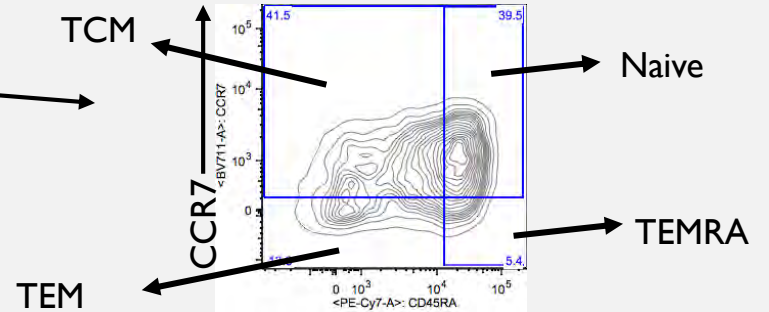
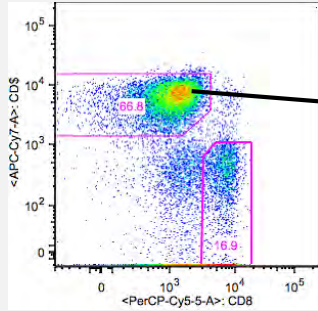
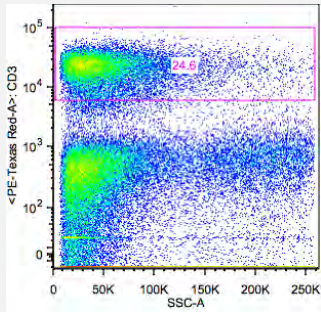
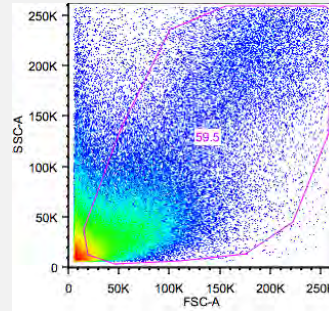
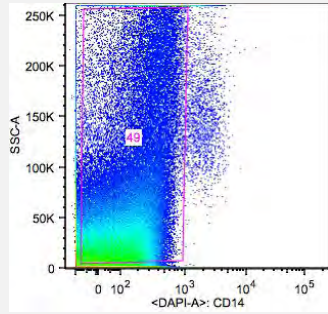
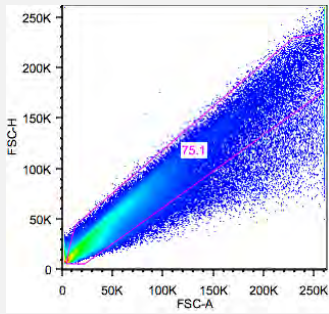


TOLLIP DEFICIENCY REDUCES BCG-SPECIFIC IL-2 AND PROLIFERATION IN CD4 T CELLS



MULTIPLE FACTORS INFLUENCE MEMORY T CELL PHENOTYPES

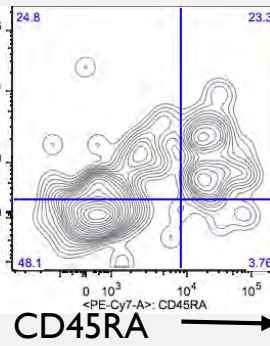




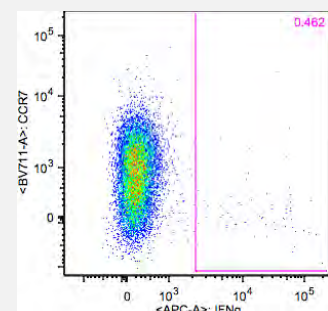
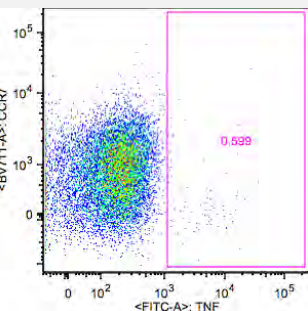
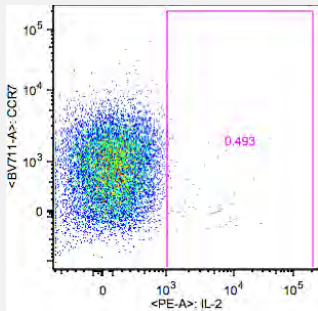
TEM

TCM

CCR7

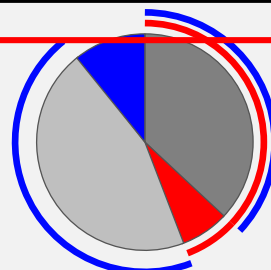
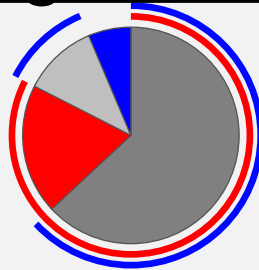


CD45RA

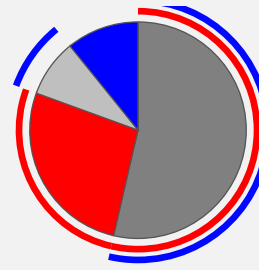
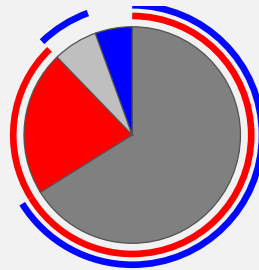


High Low TOLLIP

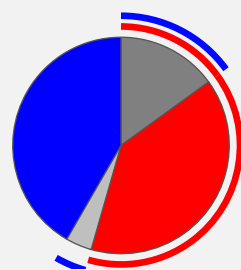
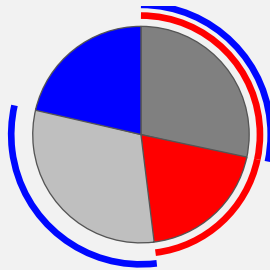
IL-2+



TNF+



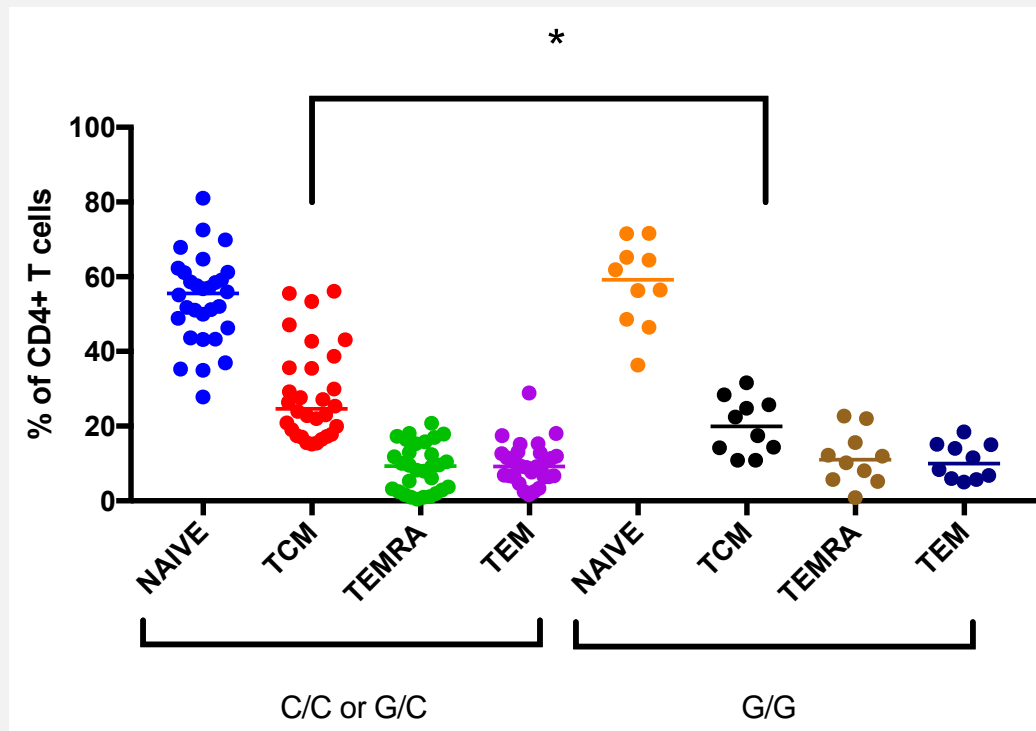
IL-2+
TNF+



*p = 0.02,
partial
permutation
test

- Naïve
- TCM
- TEM
- TEMRA

TOLLIP-DEFICIENT INFANTS DEMONSTRATE FEWER TCM OVERALL AT 10 WEEKS OF AGE



TOLLIP DEFICIENCY IS ASSOCIATED WITH ADULT TB SUSCEPTIBILITY

	N
Cord Blood Controls (N)	762
Adults with Pulmonary TB (N)	385
Adults with Meningeal TB (N)	307
HIV-infected (%)	0
Age (Mean)	38
Sex (% female)	37



Jeremy Farrar

Sarah Dunstan

SNP	Group	Analysis	
		P	OR
rs5743854	control		(recessive)
	TB all	6.64E-07	1.7



The Hospital for Tropical Diseases

Pham Ngoc Thach Hospital for Tuberculosis

Oxford University Clinical Research Unit

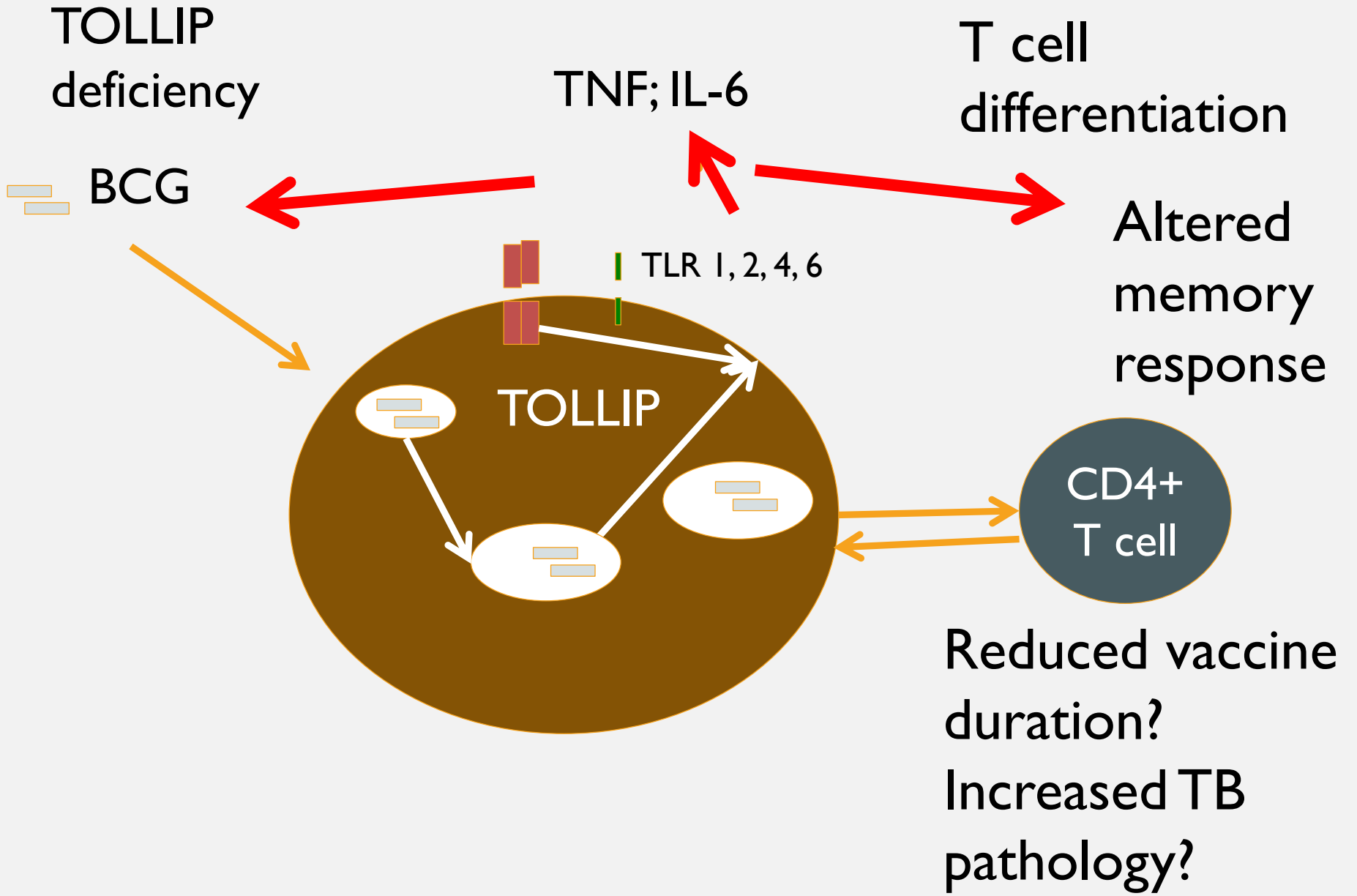
TOLLIP Deficiency is Associated with Latent Tuberculosis Susceptibility

	N
No LTBI (N)	116
Adults with LTBI (N)	150
HIV-infected (%)	0
Age (Mean)	42
Sex (% female)	46

David Horne; Masa Narita
King County Public Health Department
Harborview Medical Center
Seattle, WA

		Analysis	
SNP	Group	P (geno)	OR
rs5743854	No LTBI		(recessive)
	LTBI	7.0E-4	2.6 (1.1 – 7.1)





SUMMARY

- A functional single nucleotide polymorphism alters TOLLIP promoter activity in monocytes
- Antisense RNA TOLLIP-ASI influences TOLLIP expression (and perhaps innate immune responses)
- TOLLIP deficiency is associated with altered T cell phenotypes from a very early age
- TOLLIP variation is associated with TB in multiple genetic case control cohorts

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