Memory, activation and functional profiles of *Mycobacterium tuberculosis*-specific CD4 T cells in recent QFT converters
Knowledge of *Mycobacterium tuberculosis* (*M.tb*)-specific classical T cell immunity is based on studies of individuals with remote *M.tb* infection and/or TB disease

Improved understanding of primary T cell responses during the early stages of *M.tb* infection in humans is critical to inform vaccine strategies.
BACKGROUND

- Knowledge of *Mycobacterium tuberculosis* (*M.tb*)-specific classical T cell immunity is based on studies of individuals with remote *M.tb* infection and/or TB disease
- Improved understanding of primary T cell responses during the early stages of *M.tb* infection in humans is critical to inform vaccine strategies.

AIM

*To determine functional and phenotypic (memory and activation) kinetics of T cell responses associated with QFT Conversion*
M.tb infection induces robust CD4+ T cell responses detectable by MHC Class II Tetramers

Cohort 1: Adolescents (12-18 years), n = 12
M. tb infection induces robust CD4+ T cell responses detectable by MHC Class II Tetramers

Cohort 1: Adolescents (12-18 years), n = 12

![Graph showing time since last uninfected visit (months) vs. IFN-γ (IU/ml) and TST Induration (mm)]

APC: CLIP Tet
PE: CLIP Tet

APC: CFP-10 Tet
PE: CFP-10 Tet
M. tb infection induces robust CD4+ T cell responses detectable by MHC Class II Tetrarians

Cohort 1: Adolescents (12-18 years), n = 12

QFT: IFN-γ (IU/ml)
TST: Induration (mm)

Time since last uninfected visit (months)

TETRAMER+ CD4 T CELLS (%)

IFN-γ (IU/ml)

TST: Induration (mm)

QFT: IFN-γ (IU/ml)

Time since last uninfected visit (months)
M. tuberculosis (M.tb) infection induces robust CD4+ T cell responses detectable by MHC Class II Tetraramers. M.tb infection induces M.tb (CFP10-ESAT6)-specific CD4+ T cells, which are detected upon M.tb infection and sustained throughout established M.tb infection (1 year post infection).
Does recent M.tb infection induce activated CD4+ T cells?

Increased T cell activation associated with TB disease (active M.tb replication)

Adekambi et al. 2015
Does recent M.tb infection induce activated CD4+ T cells?

Increased T cell activation associated with TB disease (active M.tb replication)

Recent M.tb-infection induces a highly activated (HLA-DR+) antigen specific T cells
Does recent M.tb infection induce polyfunctional M.tb-specific CD4 T cells?

Cohort 2: Adolescents (12-18 years)
QFT converters (n=11)
LTBI (n=11)

Follow Up Month

IFN-γ (IU/ml)

-6 0 +6 +12

0.00 0.25 0.50 0.75 1.0 2.0 3.0

Converters (ICS)
Does recent M.tb infection induce polyfunctional M.tb-specific CD4 T cells?

Cohort 2: Adolescents (12-18 years)
QFT converters (n=11)
LTBI (n=11)
Does recent M.t.b infection induce polyfunctional M.t.b-specific CD4 T cells?

Cohort 2: Adolescents (12-18 years)
QFT converters (n=11)
LTBI (n=11)
Does recent M.tb infection induce polyfunctional M.tb-specific CD4 T cells?

M.tb infection induces polyfunctional CD4+ T cells capable of producing IFN-γ±TNF-α±IL-2± in response to M.tb antigenic stimulation.

Cohort 2: Adolescents (12-18 years)
QFT converters (n=11)
LTBI (n=11)
Are similar proportions of M.tb-specific activated CD4+ T cells observed in recently M.tb infected and LTBI individuals?

Adekambi et al. 2015
Are similar proportions of M.tb-specific activated CD4+ T cells observed in recently M.tb infected and LTBI individuals?

Activated M.tb-specific CD4+ T cells from recently M.tb infected individuals are observed at higher proportions compared to LTBI individuals.
Does M.tb infection induce late differentiated effector T cells?

- CFP10-ESAT-6 pp
- BV570: CD45RA
- PEC: CCR7
- FITC: HLA-DR
- PerCP eFluor710: KLRG1

**Total CD4+ T cells**

**M.tb-specific (Total Cytokine+) CD4 T cells**
Does M.tb infection induce late differentiated effector T cells?

Total M.tb-specific CD4+ T cells

KLRG1 Expression

Proportion of CFP10-ESAT-6 sp CD4 T CELLS (%)

0.031 0.133

M12 M18

Follow Up Month

LTBI Conv LTBI Conv

M12 M18

Neg. Control CFP10-ESAT-6 pp

BV570: CD45RA

FITC: HLA-DR

PerCP eFluor710: KLRG1

Total CD4+ T cells

M.tb-specific (Total Cytokine+) CD4 T cells
Does M.tb infection induce late differentiated effector T cells?

Early (< 6 months) M.tb-specific responses from recent M.tb infected individuals are associated with reduced levels of KLRG1 expression and higher proportions of early effector CD4 T cells compared to LTBI individuals.
Recent M.tb infection:
Recent M.tb infection:

• Results in generation of detectable of M.tb-specific CD4+ T cells by MHC II tetramers and ICS
Recent M.tb infection:

- Results in generation of detectable of M.tb-specific CD4+ T cells by MHC II tetramers and ICS
- Induces highly activated CD4+ T cells, which significantly decrease during established M.tb infection
Recent M.tb infection:

- Results in generation of detectable of M.tb-specific CD4+ T cells by MHC II tetramers and ICS
- Induces highly activated CD4+ T cells, which significantly decrease during established M.tb infection
- Induces IFN-γ±TNF±IL-2± polyfunctional CD4+ T cells

CONCLUSIONS
Recent M.tb infection:

- Results in generation of detectable of M.tb-specific CD4+ T cells by MHC II tetramers and ICS
- Induces highly activated CD4+ T cells, which significantly decrease during established M.tb infection
- Induces IFN-\(\gamma\)-TNF-IL-2 polyfunctional CD4+ T cells

M.tb-specific functional (cytokine producing) are predominantly early effector \(T_E\) during established M.tb infection
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Established M.tb infection is characterised by a high proportion of HLA-DR- M.tb-specific CD4+ T cells that are predominantly \( T_\text{CM} \)
Recent M.tb infection does not induced late differentiated effector T cells

Early M.tb-specific responses from recent QFT converters are associated with reduced levels of KLRG1 expression and higher proportions of early effector CD4 T cells compared to LTBI individuals.