Identification of *M. tuberculosis* antigens that induce dominant IL-17 responses during human infection

Paul Ogongo, PhD

Helen Hay Whitney Foundation Postdoctoral Fellow
Postdoctoral Scholar in the Ernst Lab
University of California, San Francisco
T cell responses to Mtb infection

CD4 T cells are essential for effective control of *M. tuberculosis* infection across species

### Cytokine Production

**IFN-γ dependent responses**
- IFN-γ knockout animals highly susceptible to Mtb
- Humans with inborn errors in IFN-γ signaling susceptible to Mtb infection

**IFN-γ production is necessary but not enough**

Cooper AM et al 1993; Flynn JL et al 1993; Feng GC et al 2006; Sologuren I et al 2011; Shabani M et al 2019

**IFN-γ independent responses**
- Polyfunctional TNF-α/IL-2/CD40L/CD107a
- Th22: contribute to CD4+ responses to Mtb; are depleted during HIV coinfection
- GMCSF: restrict Mtb growth


### Beyond the cytokines

**CD153**
- Mediates host protection against pulmonary Mtb across species
- Mtb specific CD4+CD153+ inversely correlate with bacterial load and disease severity in humans

**T cell differentiation**
- Less differentiated antigen specific cells provide long term control in mice
- Antigen expression/availability drives T cell differentiation

Moguche, Musvosvi et al 2017; Sallin MA et al 2018; Du Bruyn et al 2021; Clemmensen HS et al 2021

---

**No single T cell feature/readout is sufficient to define protective immunity**
Which Mtb antigens are targeted by CD4\(^+\) T cells?

- T cell epitopes in the classical immunodominant Mtb antigens are hyperconserved
- Comprehensive genomics revealed hotspots of sequence diversity

**Implication:** Human T cell recognition of the immunodominant epitopes has little impact on the survival and growth of Mtb

Comas I et al 2010

---

**Coscolla M et al 2015**

**Criteria:**
- Highest 5% nucleotide diversity
- Located in open reading frame
- Nonsynonymous substitution
- Lineage-wide presence

---

Paul Ogongo, Ernst lab

23 Feb 2022
Latent TB infected individuals and Mtb antigens

1. Household Contact Cohort

- Index TB case (smear+ or Xpert med/high)
- Household contacts screening (QuantiFERON TB-Gold)
- LTBI Cohort (QFT+/HIV-)
- Enrolled, 2year follow up

2. M. tuberculosis antigens
   - 60 distinct antigens as overlapping peptides covering the entire length of the protein

Whatney W. et al 2018
Study aim and hypotheses

*Do T cells that recognize novel antigens under diversifying evolutionary selection differ from T cells that recognize classical antigens?*

1. Human T cells with distinct Mtb antigen specificities differ in their phenotype, function, maturation state and trafficking potential

2. T cell features correlate with, and maybe responsible for, different Mtb infection outcomes in humans

- Identifying potential active TB progressors, before their progression, will reduce the overall cost of treatment and limit the rate of transmission
IFN-γ response in LTBI varies by participant and by antigen

At recruitment: IGRA+HIV-at high risk of progression to active TB

- At population level, fewer participants make IFN-γ to novel antigens.
- However, within responders, the magnitude of response is highly variable.

Courtesy: Devin Columbus
Novel Mtb antigens elicit high magnitude IL-17 response

**Classical antigens:** conserved T cell epitopes

- **IFN-γ**
  - % responders = 71%

- **IL-17**
  - % responders = 58%

**Novel antigens:** variable T cell epitopes

- **IFN-γ**
  - % responders = 55%

- **IL-17**
  - % responders = 79%

Confidential/Unpublished
Novel antigens elicit high magnitude IL-17 response

Confidential/Unpublished

Classical antigens

Novel antigens

IL-17 response

p = 0.0118
IL-17 response magnitude to novel antigens stable over 6-month period

Baseline

6-months

Data cumulative of 4 distinct novel antigens

Kisumu Kenya

Addis Ababa Ethiopia

No difference between IFN-γ and IL-17 responses to classical antigens
CD4 T cells producing IFN-γ+ to novel antigens are primarily central memory phenotype

Similar pattern for Rv0010c and LldD2

Confidential/Unpublished
Naïve-like memory CD4+ T cells in Mtb infection

Functional, Antigen-Specific Stem Cell Memory (T_{SCM}) CD4+ T Cells Are Induced by Human Mycobacterium tuberculosis Infection

Cheleka A. M. Mpande1, One B. Dintwe2, Munyaradzi Musvosvi, Simbarashe Mabwe, Nicole Bklek3, Mark Hatherill, Elisa Nemes1, Thomas J. Scriba4 and The SATVI Clinical Immunology Team

South African Tuberculosis Vaccine Initiative, Institute of Infectious Disease and Molecular Medicine, Division of Immunology, Department of Pathology, University of Cape Town, Cape Town, South Africa

Human CD4 T-Cells With a Naïve Phenotype Produce Multiple Cytokines During Mycobacterium Tuberculosis Infection and Correlate With Active Disease

Valentina Orlando1,2, Marco P. La Manna1,3, Delia Golelli1, Fabrizio Palmeri1, Elena Lo Presti2, Simona A. Joosten1, Carmela La Mendola1, Simona Bucchi3, Tom H. M. Ottenhoff1,4 and Nadia Caccamo1,2

1Catholic University of Sacred Heart and Biomedical Research (ICUS), University of Palermo, Palermo, Italy; 2Department of Bioprophylaxis, University of Palermo, Palermo, Italy; 3The National Research Unit, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy; 4Department of Infectious Diseases, Leiden University Medical Center, Leiden, Netherlands; 5Dipartimento di Medicina per l’Invecchiamento e Specializzazioni, University of Palermo, Palermo, Italy

A Subset of Mycobacteria-Specific CD4+ IFN-γ+ T Cell Expressing Naïve Phenotype Confers Protection against Tuberculosis Infection in the Lung

Jinyun Yuan, Janice Tenant, Thomas Pacatte, Christopher Eichhoff, Azra Blazevic, Daniel F. Hoft and Soumya Chatterjee

J Immunol published online 28 June 2019
http://www.jimmunol.org/content/early/2019/06/27/jimmunol.1900209

This information is current as of July 18, 2019.
Conclusion

1. CD4 T cells with distinct Mtb antigen specificities have different functional properties.

2. Individuals with undetectable levels of IFN-γ make other Mtb specific cytokines (IL-17, GMCSF and TNF-α).

3. Novel antigens are enriched for IL-17 producing T cells while classical antigens are skewed towards IFN-γ production.

4. For the novel antigens, CD4 effector memory T cells produce IL-17 more than IFN-γ; additionally higher frequency of central memory CD4 T cells produce either IL-17 or IFN-γ compared to SEB.

Currently testing the hypothesis that variation in T cell responses may be responsible for differences in TB outcomes in humans.

Specifically: We will compare IFN-γ and IL-17 responses to novel vs classical antigens in progressors vs nonprogressors.
Acknowledgements

Ernst Lab
Joel Ernst
Anthony Tran
Devin Columbus
Jason Limberis
Ernst Lab Members

KEMRI- Kisumu
Gregory Ouma
Samuel Gurrion, MD

TBRU-ASTRa
Clinical Core
Neel Gandhi, MD

Coordination
Lisa Sharling, PhD, MPH
Devin Columbus, MA, CCRC
Henry Blumberg, MD
Joel Ernst, MD

AHRI
Liya Wassie, PhD
Kidist Bobosha, PhD
Clinical research team

Funding
U19 AI 111211

Antigen Specific T-cell Responses and the control of TB