Genomic signatures of risk of TB disease

M. tuberculosis infection → Active TB disease

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2nd Expert Workshop on the development of tests for progression of LTBI to active disease
1 July 2016
Possible consequences of \textit{M. tuberculosis} infection

Identify all those who will progress to active TB disease?

Differentiate those at high risk from those who remain well?

Intervene to prevent TB disease before transmission?

Adapted from Barry 3\textsuperscript{rd} et al., Nat Rev Micro 2009
High TB Burden Setting
IGRA+ individuals at higher risk of progression to disease

50-80% of adults in TB endemic countries are TST/IGRA+
90% of latently infected people* will never develop TB disease

*HIV uninfected adults
High TB Burden Setting
Preventive therapy for IGRA+ would treat most people unnecessarily

Shift focus from ‘treatment of latency’ to ‘preventive therapy for those at highest risk of progression to TB disease’
Developing a transcriptomic correlate of risk
Adolescent Cohort Study (ACS)

6,363 adolescents enrolled

No TB disease: controls*

TB disease: progressors*

Mahomed et al., IJTLD 2011; Mahomed et al.,
Tuberculosis 2013; Mahomed et al., Plos One 2013
ACS COR design: case/control

Enrollment

- QFT and/or TST positive
- No TB for first 6 months after enrollment
- HIV-negative

Follow up 2 years

Controls (n = 90)
1. Training (n=74)
2. Validation (n = 16)

Progressors (n = 44)
1. Training (n=36)
2. Validation (n = 8)

Zak et al., Lancet 2016
Emergence of an IFN response signature during disease progression

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Emergence of an IFN response signature during disease progression

Zak et al., Lancet 2016
Emergence of an IFN response signature during disease progression

Zak et al., Lancet 2016

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Inflammation module

Log2FC (progressors vs controls)

Time before diagnosis (days)
Emergence of an IFN response signature during disease progression

**Interferon module**

**Inflammation module**

**Time before diagnosis (days)**

**Log2FC**

(progressors vs controls)

- **Interferon module**

- **Inflammation module**

**Progressors**

- Controls
- 541-720 days
- 361-450 days
- 181-360 days
- 1-180 days

**Time before diagnosis (days)**

-800 -600 -400 -200 0

**Log2FC**

(progressors vs controls)

0 0.5 1.0 1.5
Emergence of an IFN response signature during disease progression

- CoR genes
- Interferon module
- Inflammation module

Time before diagnosis (days)

Log2FC (progressors vs controls)
Transcriptomic COR
Ensemble of transcript pairs

16 genes
62 PCR primers
257 primer pairs

Genes
ETV7
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COR Prognostic Performance

COR discriminates TB cases from controls up to 18 months before diagnosis

SA HIV-uninfected adults

70% Sensitivity and 84% Specificity for incident TB disease within 1 year of sampling (at 60% vote threshold)
A prognostic PCR test for incident TB

Control

COR-

COR+

progressor

Result in 2 days

93 samples per chip
Positive predictive value (PPV) of COR for South African adult population

Cumulative 2 year incidence: 2%
Effectiveness of IPT: 50%

Denkinger, Goletti et al.,
Number to treat (NNT) of COR for South African adult population

Cumulative 2 year incidence: 2%
Effectiveness of IPT: 50%
Denkinger, Goletti et al.,
The next steps: Correlate of Risk Targeted Intervention Study (CORTIS)

A Randomized, Partially-blinded, Clinical Trial of Isoniazid and Rifapentine (3HP) Therapy to Prevent Pulmonary Tuberculosis in High-risk Individuals Identified by a Transcriptomic Correlate of Risk

Screen approximately 10,000 HIV uninfected adults for transcriptomic COR
Enrol 3,200 COR+ and COR-
Randomize to COR+ Treated; COR+ Surveillance; COR- Surveillance

Screen for prevalent TB disease at baseline
Follow-up for incident TB disease x 15 months
The Correlate of Risk Targeted Intervention Study (CORTIS)
ClinicalTrials.gov NCT02735590
The landscape of TB preventive therapy is fundamentally changing: 3HP

A 12-dose, once-weekly, 3-month preventive therapy DOT regimen
Correlate of Risk Collaborators

- Mark Hatherill
- Adam Penn-Nicholson
- Willem Hanekom
- Sara Suliman
- Mbandi Kimbung
- Katrina Downing
- Fatoumatta Darboe
- SATVI Team

- Dan Zak
- Ethan Thompson
- Lynn Amon
- Gerhard Walzl
- Andre Loxton
- Jayne Sutherland
- Alan Aderem
- GC6 Team

- Gavin Churchyard
- Kogie Naidoo
- Richard White
- Tom Sumner
- Andrew Gartland