Biomarkers for accurate prediction of activation of latent tuberculosis

Progress and needs

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Correlate of Risk Data

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- Adam Penn-Nicholson
- Willem Hanekom
- Sara Suliman
- Mbandi Kimbung
- Katrina Downing
- SATVI Team
- Dan Zak
- Ethan Thompson
- Lynn Amon
- Gerhard Walzl
- Andre Loxton
- Jayne Sutherland
- Alan Aderem
- GC6 Team

Bill & Melinda Gates Foundation

Institute of Infectious Disease and Molecular Medicine
Carnegie Corporation of New York
MRC The Gambia
Claude Leon Foundation
Center for Infectious Disease Research
50-80% of adults in TB endemic countries are TST/IGRA+

90% of latently infected people will not develop TB disease in their lifetime*

*HIV uninfected
High TB Burden Setting
Is it feasible to target preventive therapy for LTBI?

Shift focus from treatment of latency to preventive therapy for those at highest risk of progression to disease
Discovery & Validation of a Prognostic Correlate of Risk (COR) for TB Disease

To identify predictive gene expression signatures of risk of TB disease, following natural infection with *M. tuberculosis*

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**Sample Collection**

- **46 Cases**
- **107 Controls**
- 364 PAXgene whole blood samples over 2 years of follow up

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6,300 Healthy Adolescents

- **No TB Disease (Controls)**
  - TST+/QFN+

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**TB Disease (Cases)**

- TST+/QFN+, Microbiological confirmation + > 6 months

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Cases matched:
- Age, gender, ethnicity, school, prior episode of TB;
- TST/QFT+

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Controls | Cases

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Training Set | Test Set
2,515 genes differentially expressed

Red = Higher expression
Blue = Lower expression
2,515 genes significant

Red = Higher expression
Blue = Lower expression

*Also validation in household contacts (Walzl, GC6)
Exon junction-level expression

**sample is control**

**sample is progressor**

**Dan Zak, Ethan Thompson, Alan Aderem, Tom Scriba, Adam Penn-Nicholson, Willem Hanekom**
RNA Seq

Exon junction-level expression

Dan Zak, Alan Aderem, Tom Scriba, Adam Penn-Nicholson, Willem Hanekom
Network visualization

Gene-level Correlate of Risk (COR) Classifier

PSVM.1 Model
247 transcript pairs
47 PCR primers
16 genes

Red edges vote as progressors
Green edges vote as non-progressors

A sample predicted to be a progressor by PSVM.1
A sample predicted to be a non-progressor by PSVM.1
Translation of the COR to a qRT-PCR platform

RNA-Seq not practical for screening in high TB burden countries

- Anderson: 51 genes
- Anderson: 40 genes
- Kaforou: 53 genes
- Kaforou: 44 genes
- Kaforou: 27 genes
- Berry: 86 genes
- Berry: 393 genes
- COR: 16 genes

Biomark Fluidigm System (test 96 genes, 46 duplicate samples) → COR result in 2 days

Maximum capacity approximately 400 samples per week
Genes selected by algorithm for the COR classifier are up-regulated early.
Does the COR have potential as a triage test for prevalent TB at time of sampling?

**RNA-Seq model**

- **UK Training**
  - Berry et al. (2010)
  - Microarray re-parameterization
  - Fully locked down

- **(Illumina microarray)**

- Application of the COR classifier to blind prediction of published datasets
  - Berry et al. (2010): UK Test, SA Test (other disease)
  - Bloom et al. (2012): SA (TB Treatment)
  - Bloom et al. (2013): UK (other diseases)
  - Kaforou et al. (2013): SA; Malawi (TB/HIV, other diseases)
  - Anderson et al. (2014): SA; Malawi; Kenya (Pediatric TB, HIV, other diseases)
Does the COR have potential as a triage test for prevalent TB at time of sampling?

PSVM.1 re-parameterised to microarray data and used in blind prediction of published datasets
Could the COR be used as a triage test for TB?

HIV uninfected SA adults
130 prevalent TB cases and 230 controls

81 – 100% (97%) Specificity
80 – 90% (87%) Sensitivity

Published microarray datasets from HIV uninfected South African adults

Penn-Nicholson, Scriba
COR Prognostic Performance
COR discriminates TB cases from controls up to 18 months before diagnosis

70% Sensitivity and 84% Specificity for incident TB disease within 1 year of sampling (at 60% vote threshold)
COR performance decays exponentially over 21 months.
Hazard Ratio for TB disease decays from $15 \rightarrow 1$ (mean $\approx 7$)

*Acknowledgements: Andrew Gartland, Chris Gast, Steve Self (SCHARP)
Challenges?

Proof of concept in HIV uninfected persons
  Triage test
  Prognostic test
  Treatment response marker
  Treatment relapse marker

Proof of concept in HIV infected persons

Move testing out of the laboratory, into the community
Screening at scale $\rightarrow$ point of care COR testing
Rapid and extensive coverage

A ‘Screen & Treat’ Strategy
Couple COR testing with short-course preventive therapy
The 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

TE = Treatment Efficacy 3HP
RR COR = Relative Risk for incident TB in COR+ vs COR-
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