



# **Transcriptomic Signatures of Progression to TB**

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**INSTITUTE FOR DISEASE MODELING** 

INTELLECTUAL VENTURES



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How do we identify incipient TB before progression to active disease?



How can we prevent progression from incipient to active TB disease to reduce *M.tb* transmission?





Red = Higher expression Blue = Lower expression

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\*Also validation in household contacts (Walzl, GC6)

A blood RNA signature for tuberculosis disease risk: a prospective cohort study



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### **TB risk classification model**

A 16-gene "Correlate of Risk" based on transcript voting pairs



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



**Biomark Fluidigm qRT-PCR platform** (test 96 genes, 46 duplicate) → COR result in 2 days

Maximum capacity approximately 400 samples per week



#### 16-gene Correlate of Risk (COR)

Discriminates TB cases from controls up to 18 months before diagnosis



Zak, Lancet 2016



## 16-gene COR predicts incipient TB disease >1 year before diagnosis Performance maximal at diagnosis



Can the 16-gene COR be used as a triage test to target curative and preventive therapy?





#### A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak\*, Adam Penn-Nicholson\*, Thomas J Scriba\*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡

#### Does the 16-gene COR have diagnostic potential?



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(re-parameterized to published microarrary data)



### A COR-targeted Test-&-Treat Strategy for TB?





**S**atvi

Scriba, Penn-Nicholson, Suliman, Darboe, Kimbung, many others

## 11-gene COR: A host blood RNA TB triage test?



#### **Prognostic Performance**

12-month incident TB cases vs non-progressors71% Sensitivity and 84% Specificity@ 60% vote threshold

#### **Diagnostic Performance**

Prevalent TB cases vs non-cases 86% Sensitivity and 94% Specificity @ 85% vote threshold



Scriba, Penn-Nicholson, Suliman, Darboe, Kimbung, many others (unpublished)

#### 16-gene COR signature can predict TB treatment (Catalysis Treatment Response Cohort Study, Walzl PI)

Thompson, Zak, Scriba, Walzl, Tuberculosis 2017



\*Low baseline expression of the 16-gene COR in TB patients is predictive of more rapid bacteriological conversion in response to treatment (p = 0.002)

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\*\*Both signatures identified treatment failure >4 weeks after Rx start



# Take Home Messages



Host blood RNA signatures of TB have been validated using qRT-PCR

Symmetrical expression during progression to TB disease, at diagnosis, during Rx

Potential as prognostic, triage and treatment-response biomarkers

Performance in HIV infection less optimal (viral load)

Smaller parsimonious RNA signatures being tested for POC "TB Test & Treat"



