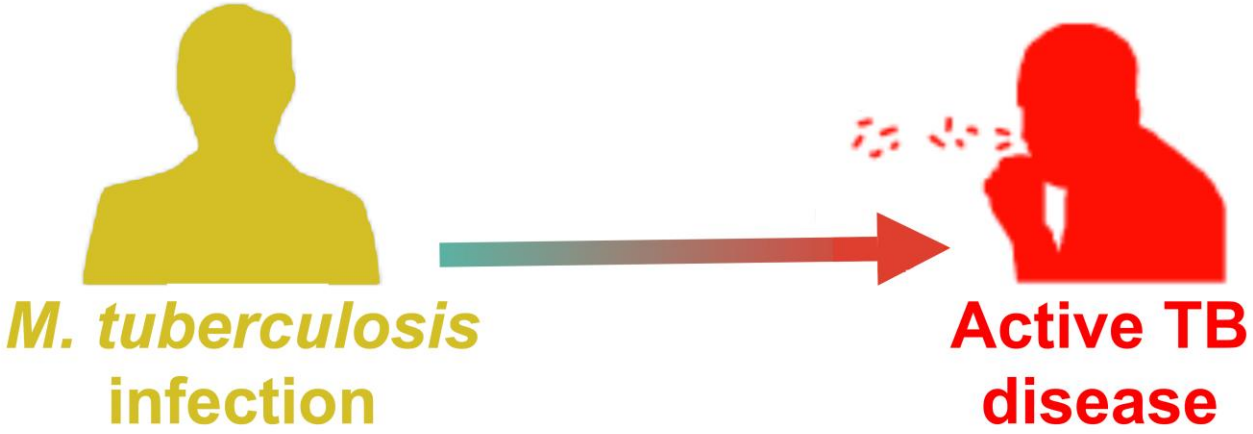
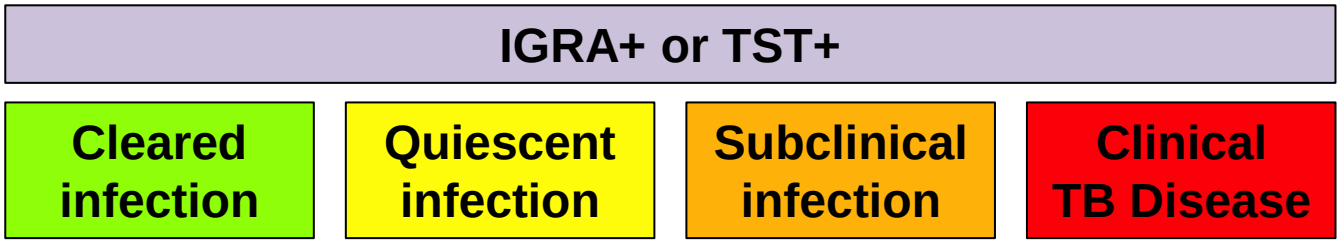
Genomic signatures of risk of TB disease



Tom Scriba, University of Cape Town

2nd Expert Workshop on the development of tests for progression of LTBI to active disease
1 July 2016

Possible consequences of *M. tuberculosis* infection



Identify all those who will progress to active TB disease?

Differentiate those at high risk from those who remain well?

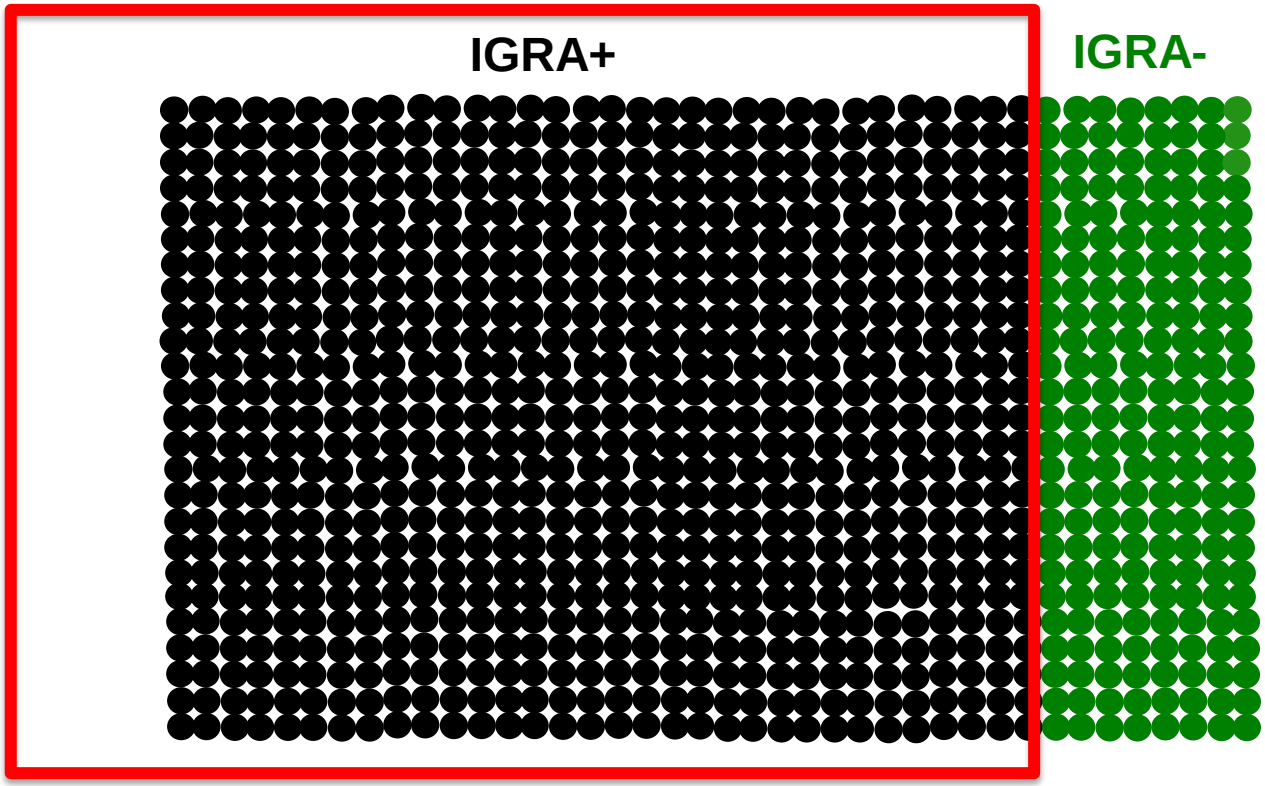
Intervene to prevent TB disease before transmission?

satvi

Adapted from Barry 3rd 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+

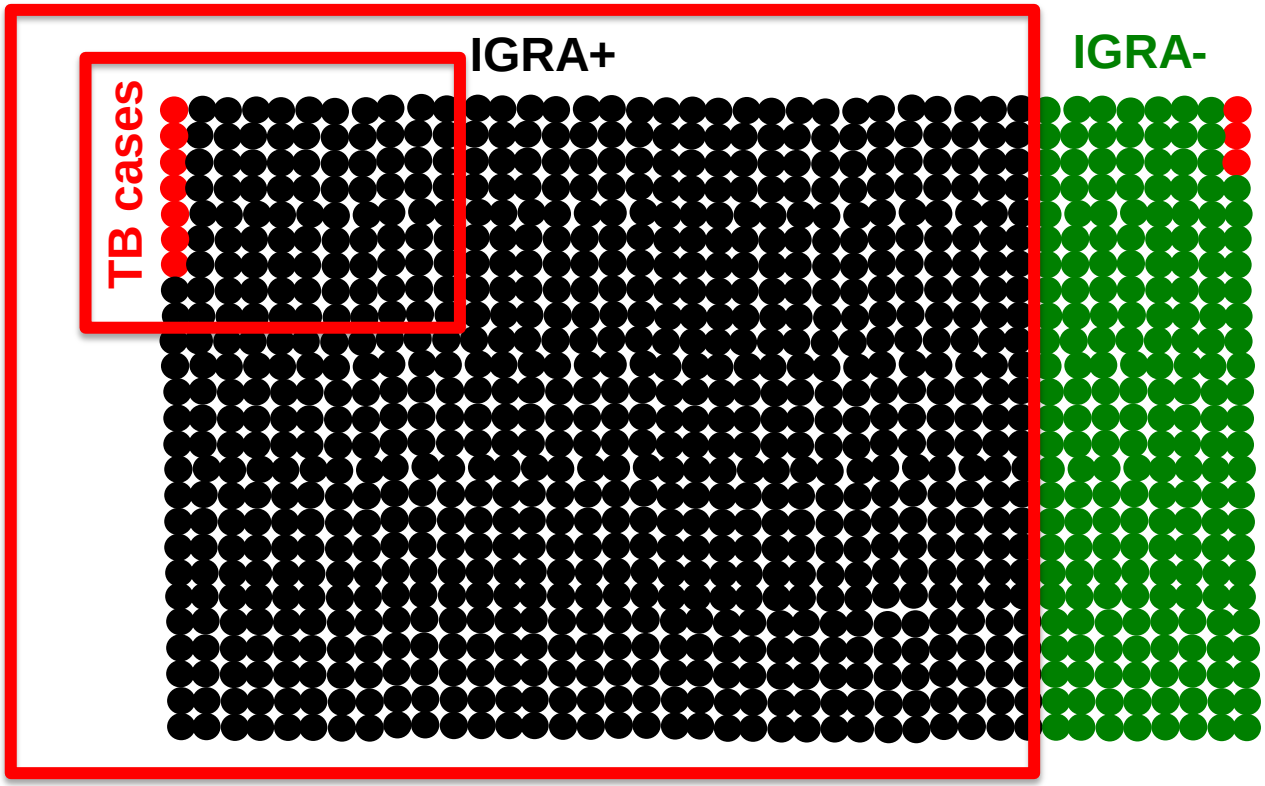
90% of latently infected people* will never develop TB disease

*HIV uninfected adults

satvi

High TB Burden Setting

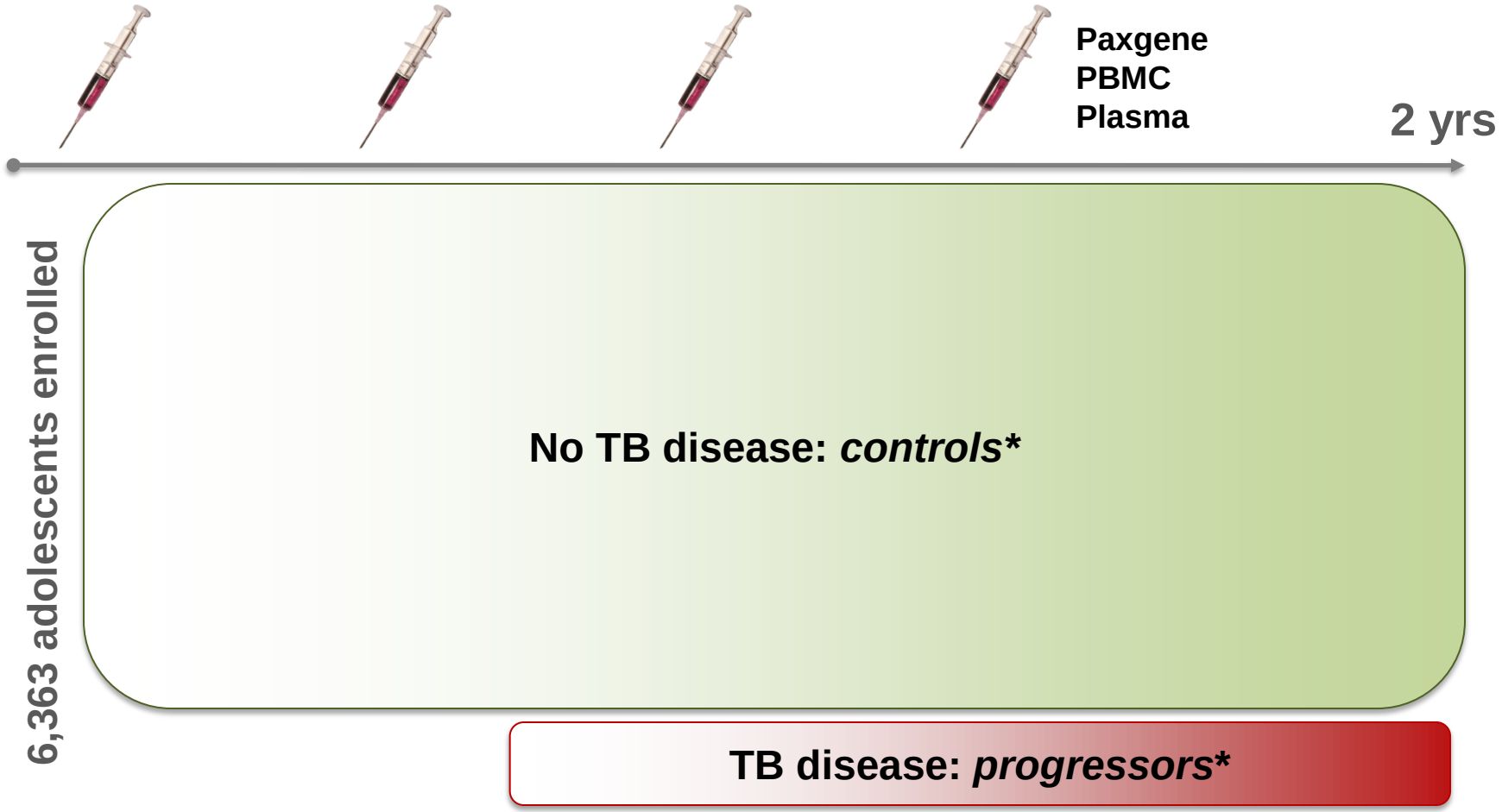
Preventive therapy for IGRA+ would treat most people unnecessarily



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

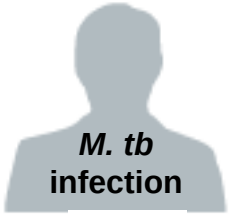
Adolescent Cohort Study (ACS)



satvi

Mahomed et al., IJTLD 2011; Mahomed et al., Tuberculosis 2013; Mahomed et al., Plos One 2013

ACS COR design: case/control



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

Enrollment

Follow up
2 years

Controls (n = 90)

Progressors (n = 44)

1. Training (n=74) 2. Validation (n = 16)	1. Training (n=36) 2. Validation (n = 8)

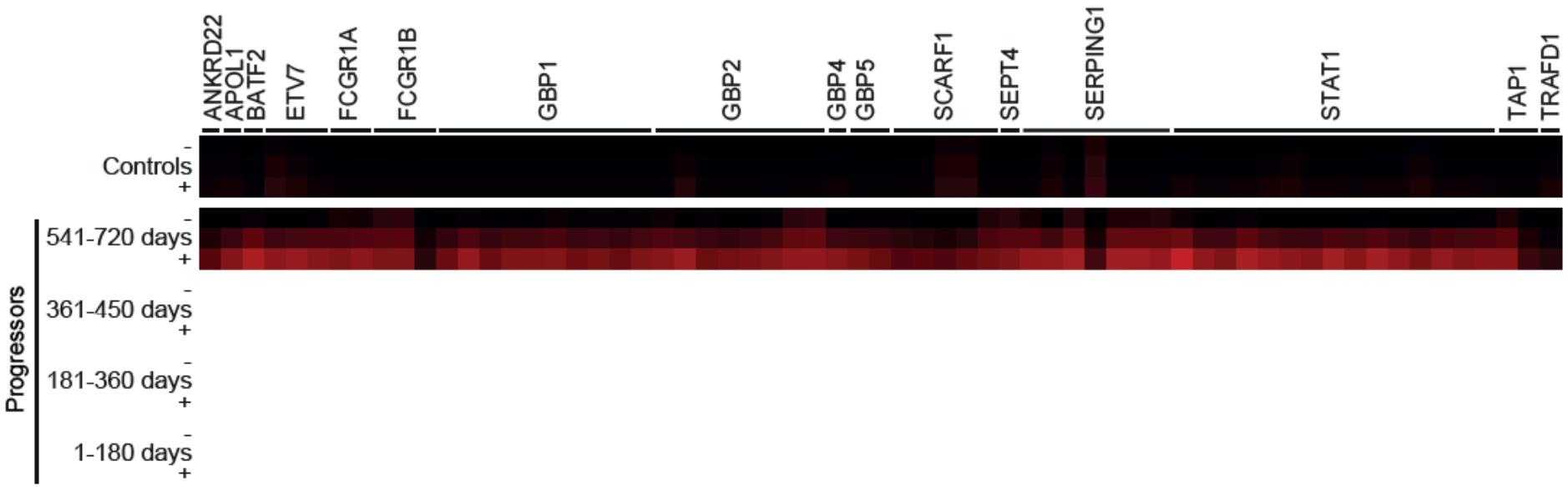
satvi

Center for Infectious Disease Research

Zak et al., Lancet 2016

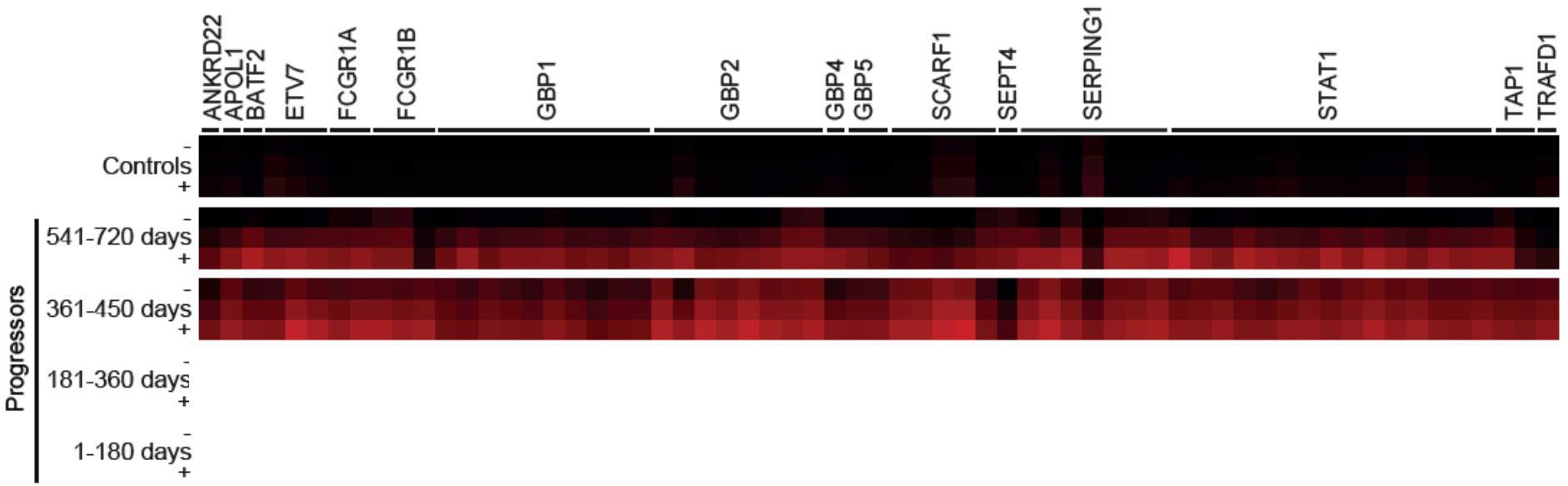
Center for Infectious Disease Research

Emergence of an IFN response signature during disease progression



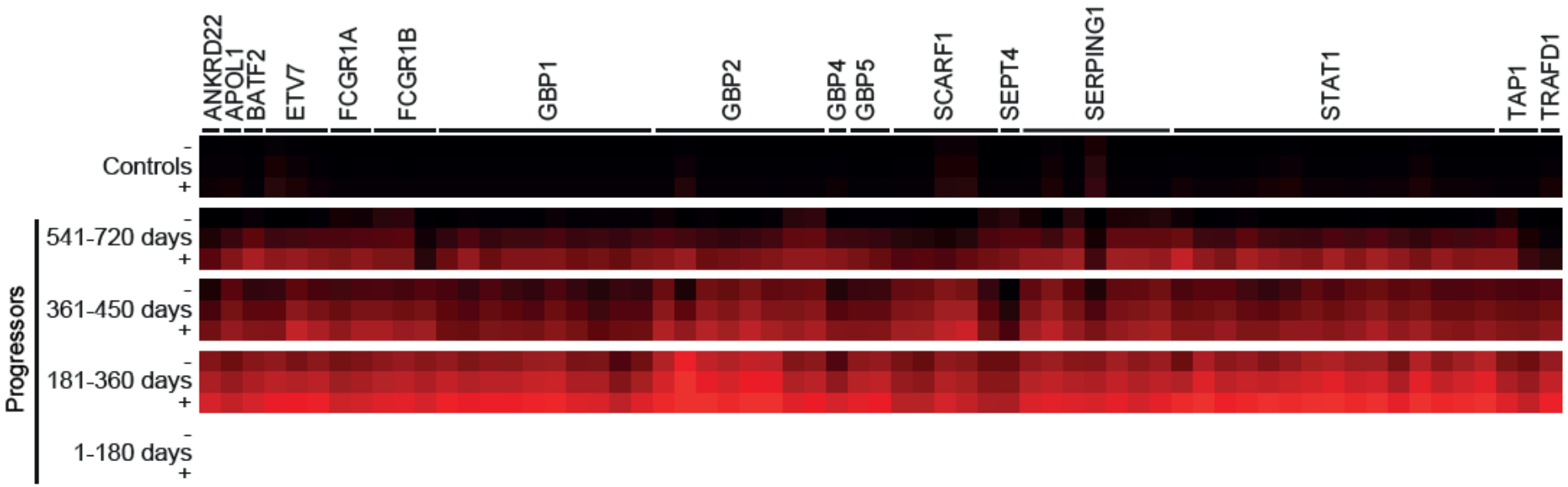
Zak et al., Lancet 2016

Emergence of an IFN response signature during disease progression



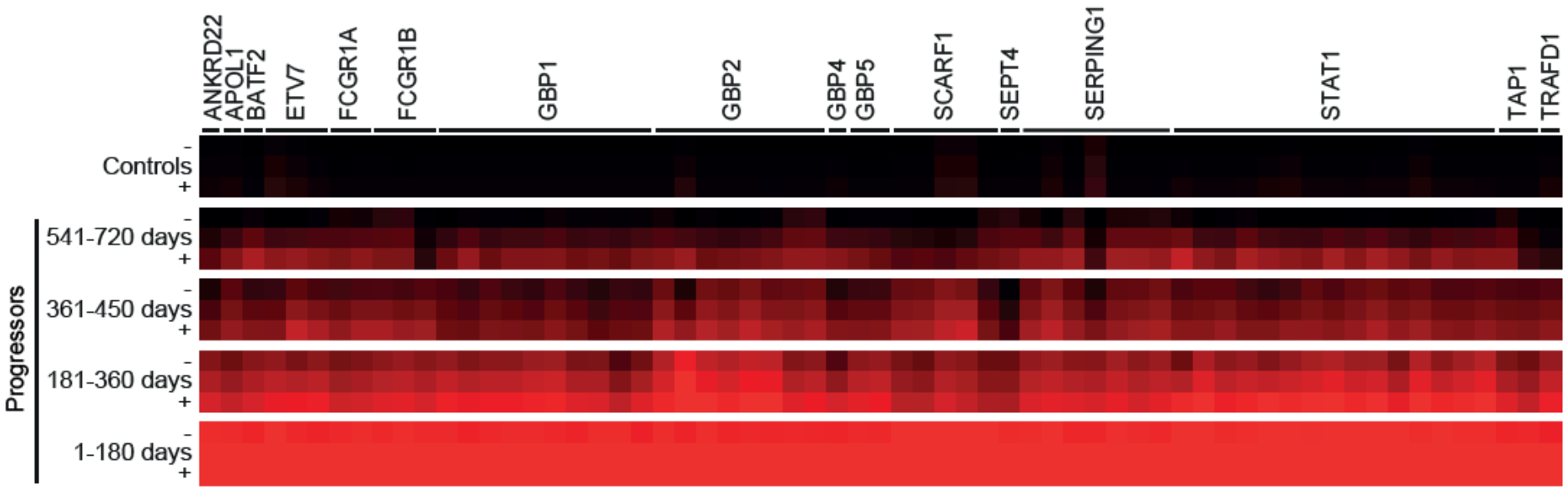
Zak et al., Lancet 2016

Emergence of an IFN response signature during disease progression



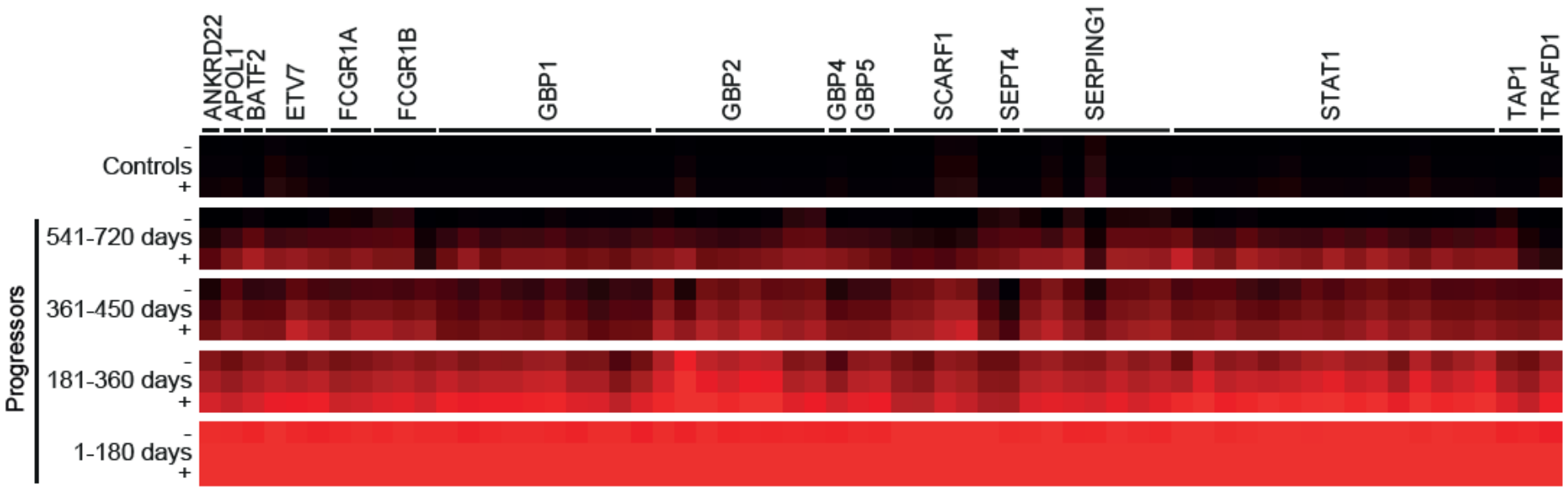
Zak et al., Lancet 2016

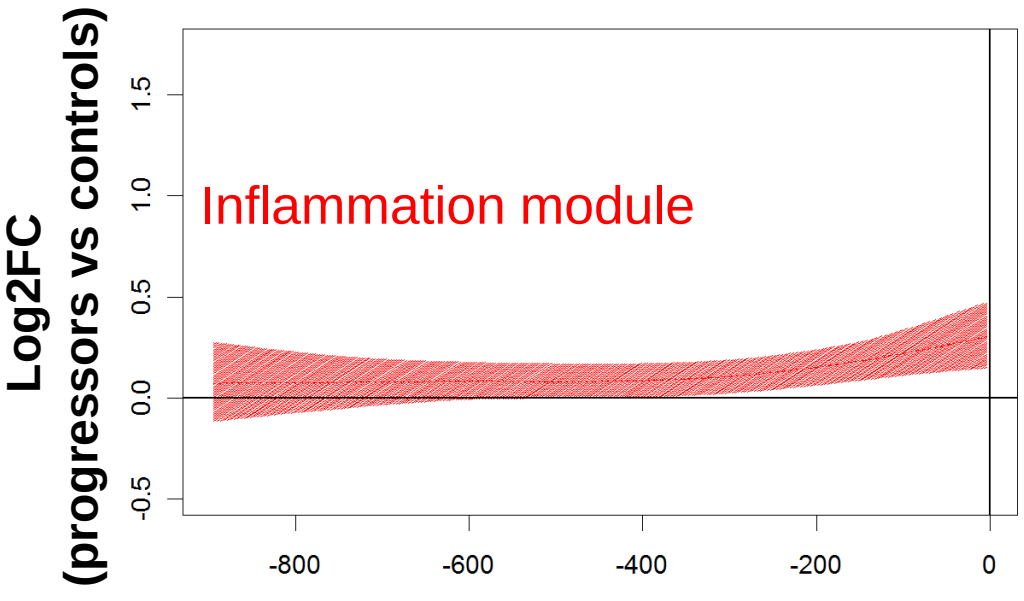
Emergence of an IFN response signature during disease progression



Zak et al., Lancet 2016

Emergence of an IFN response signature during disease progression

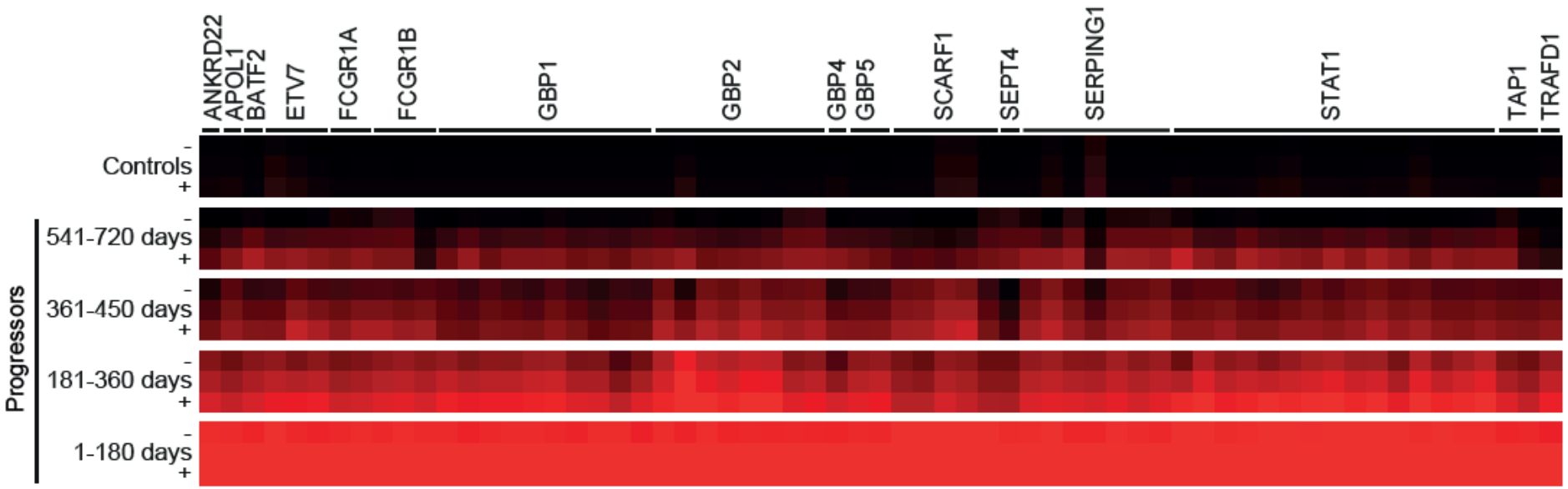


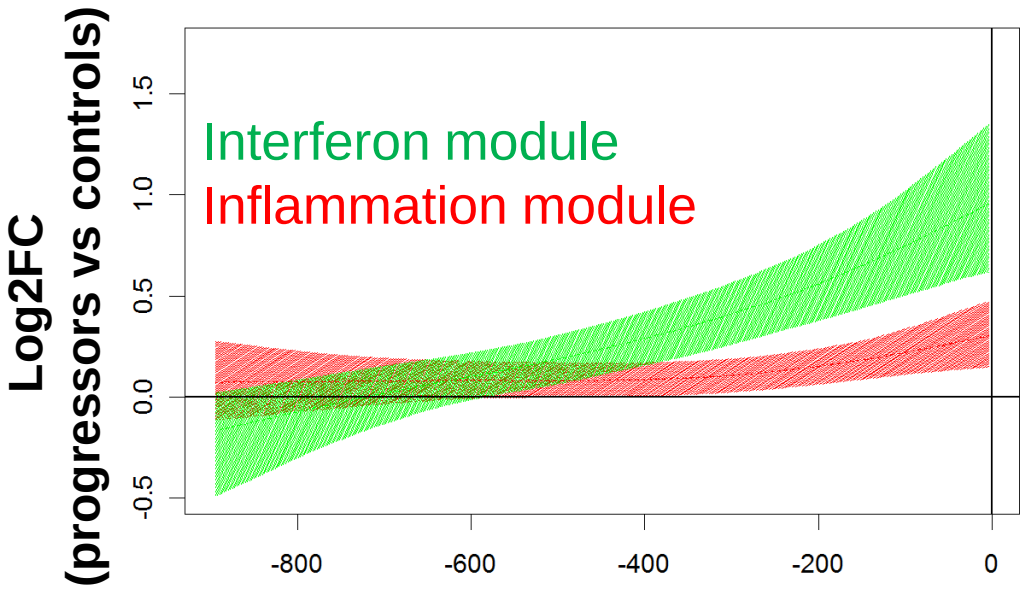


satvi

Center for Infectious Disease Research

Emergence of an IFN response signature during disease progression

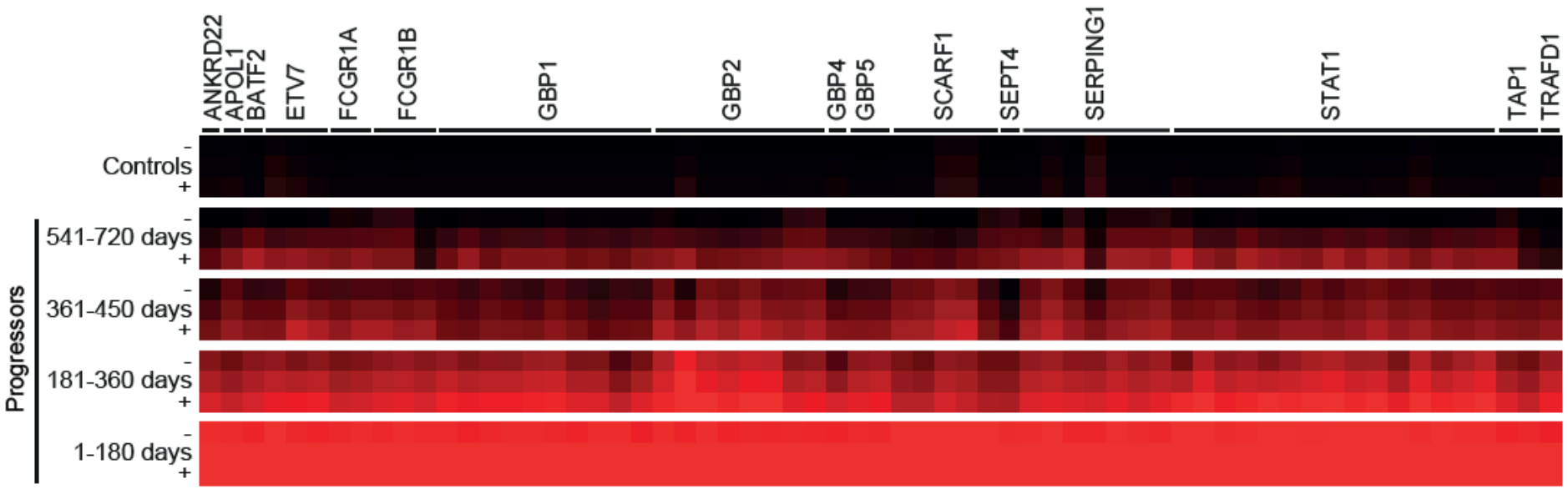


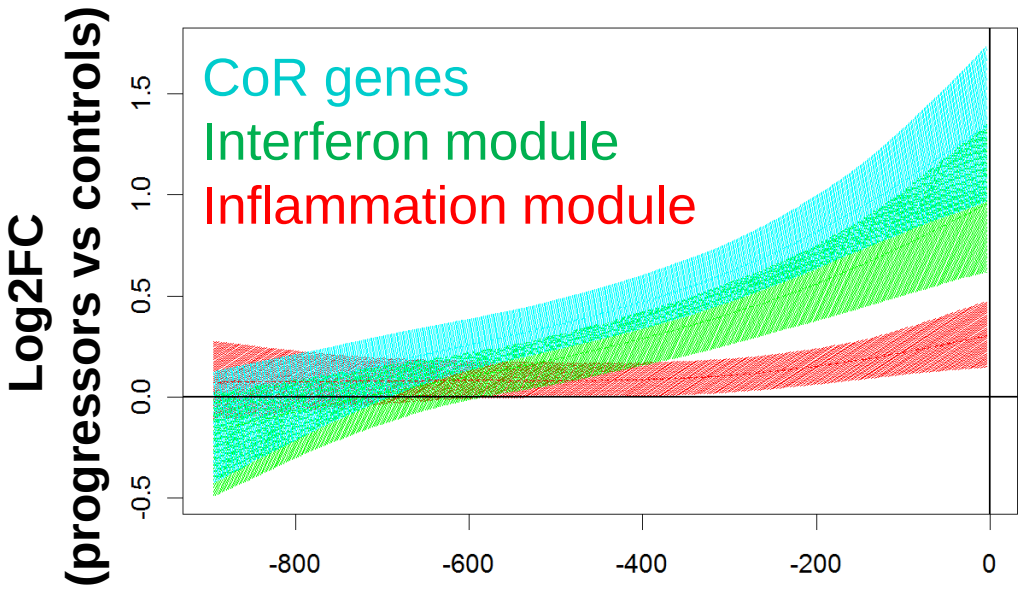


satvi

Center for Infectious Disease Research

Emergence of an IFN response signature during disease progression



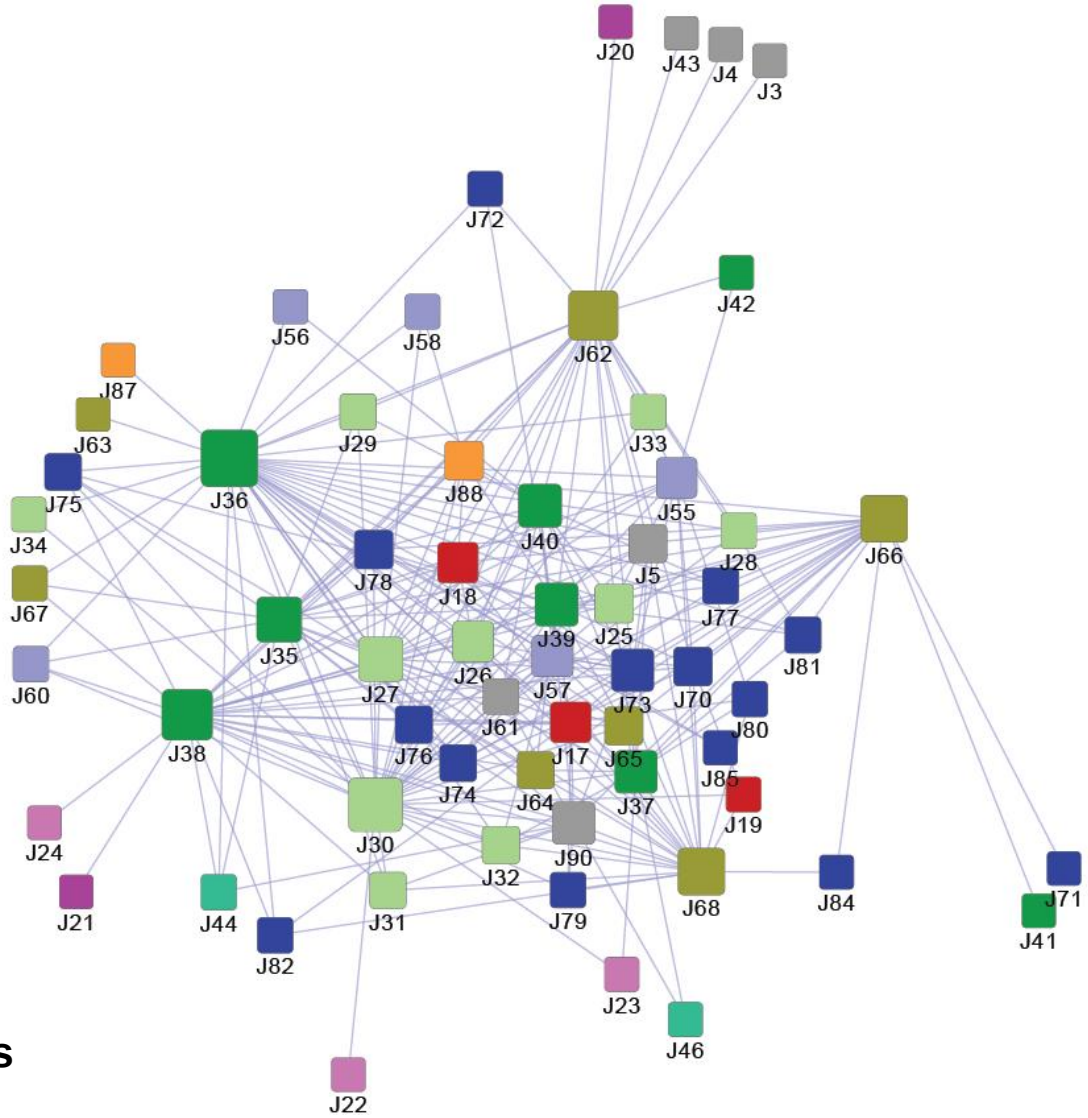


satvi

Center for Infectious Disease Research

Transcriptomic COR

Ensemble of transcript pairs



Genes

ETV7
FCGR1A
FCGR1B
GBP1
GBP2
GBP5
SCARF1
SERPING1
STAT1
TAP1
APOL1
ANKRD22
BATF2
GBP4
SEPT4
TRAFD1

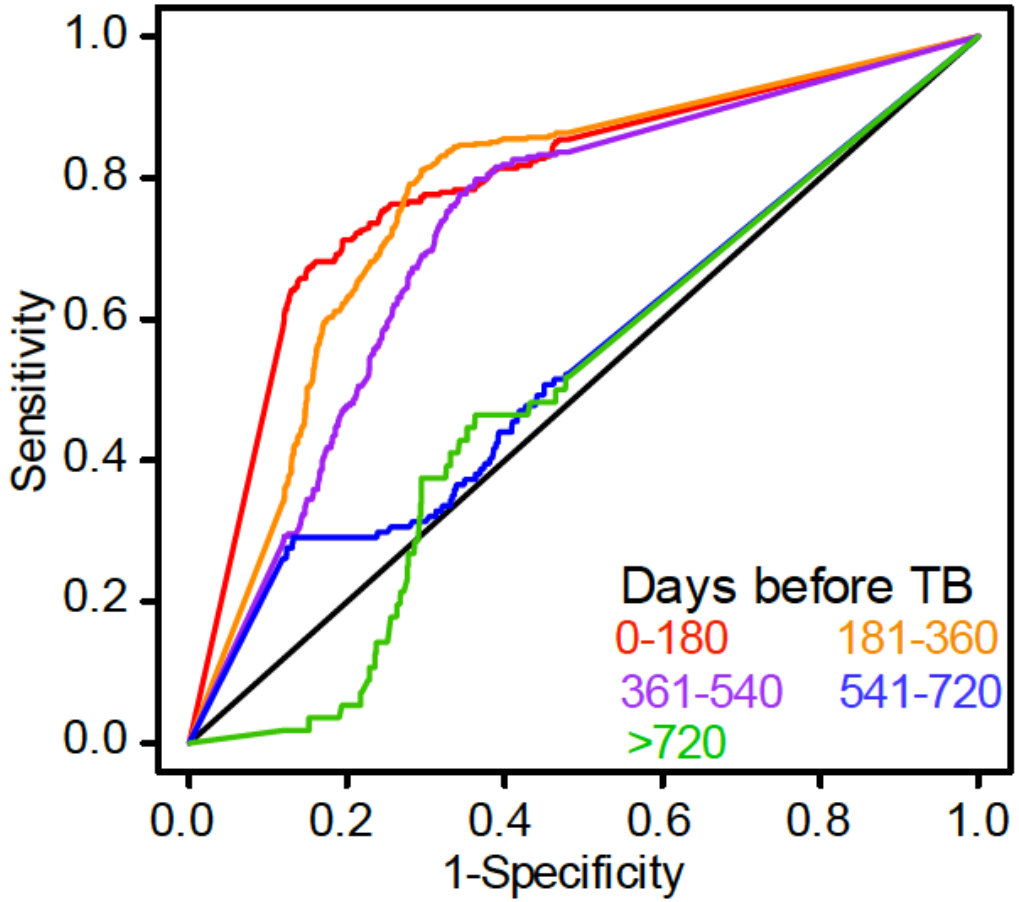
16 genes
62 PCR primers
257 primer pairs

satvi

Center for Infectious Disease Research

COR Prognostic Performance

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



SA HIV-uninfected adults

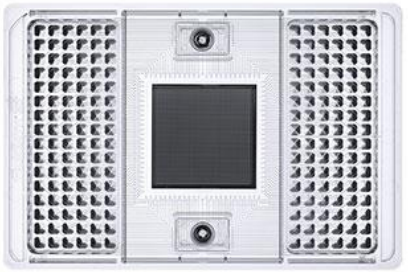
70% Sensitivity and 84% Specificity for incident TB disease within 1 year of sampling (at 60% vote threshold)

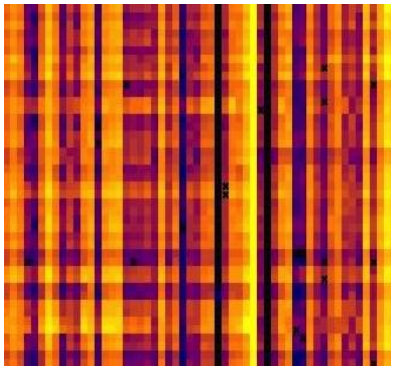
satvi

Center for Infectious Disease Research

A prognostic PCR test for incident TB

93 samples per chip





Control

COR-

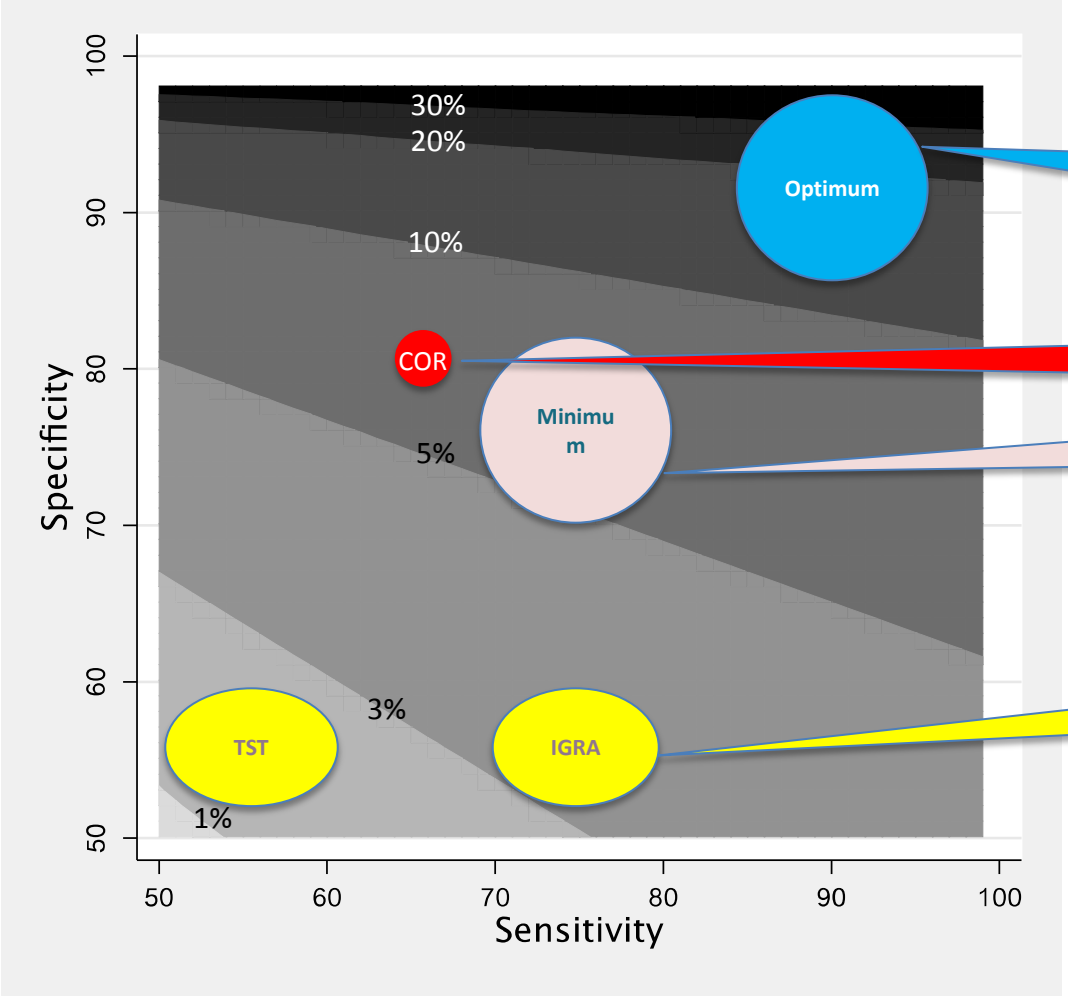
progressor

COR+

Result in 2 days

satvi

Positive predictive value (PPV) of COR for South African adult population



Optimum TPP
- PPV: ~16%

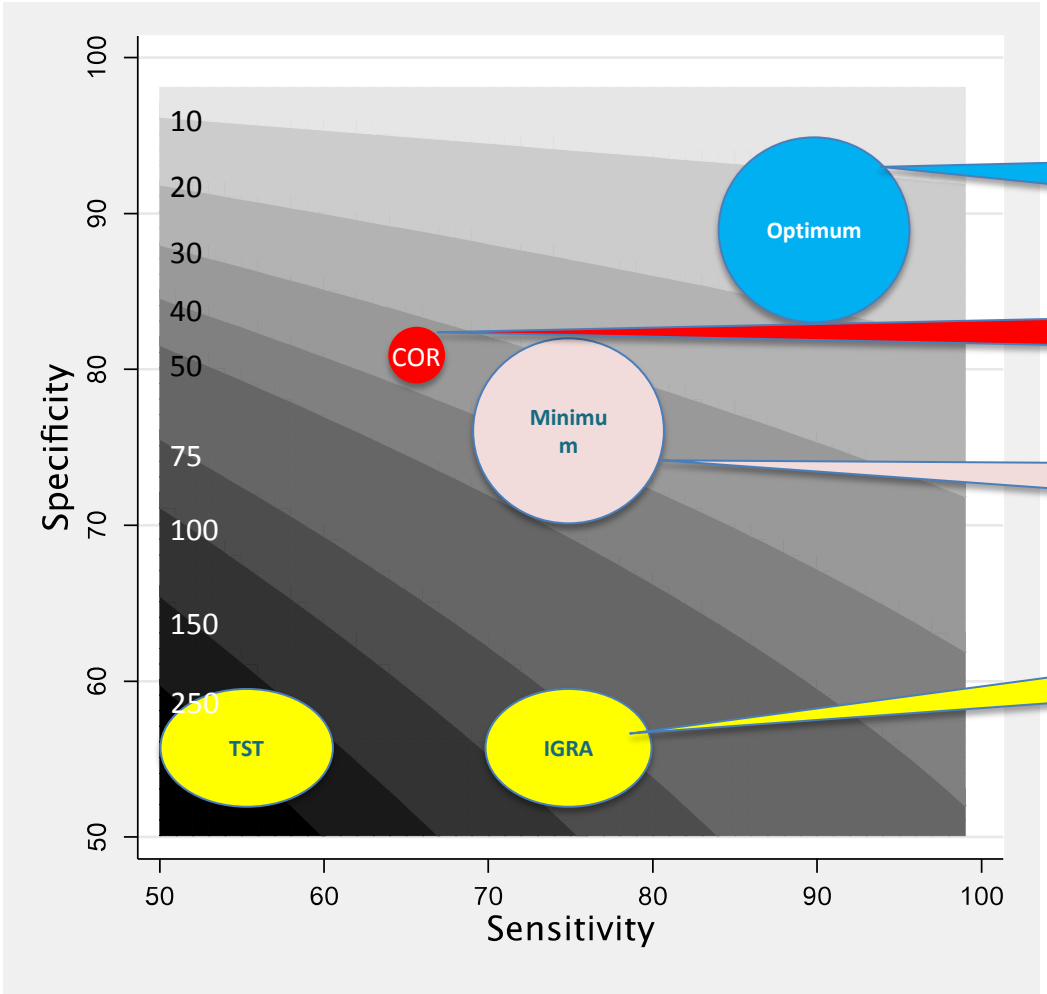
COR signature
- PPV: ~7%

Minimum TPP
- PPV: ~6%

TST / IGRA
- PPV: ~2% / ~3%

Cumulative 2 year incidence: 2%
Effectiveness of IPT: 50%
Denkinger, Goletti et al.,

Number to treat (NNT) of COR for South African adult population



Optimum TPP
- NNT: ~13

COR signature
- NNT: ~37

Minimum TPP
- NNT: ~40

TST / IGRA
- NNT: ~250 / ~85

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

BILL & MELINDA GATES foundation

SANOFI

satvi

UNIVERSITEIT STELLENBOSCH UNIVERSITY

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Statistical Center for HIV/AIDS Research & Prevention SCHARP

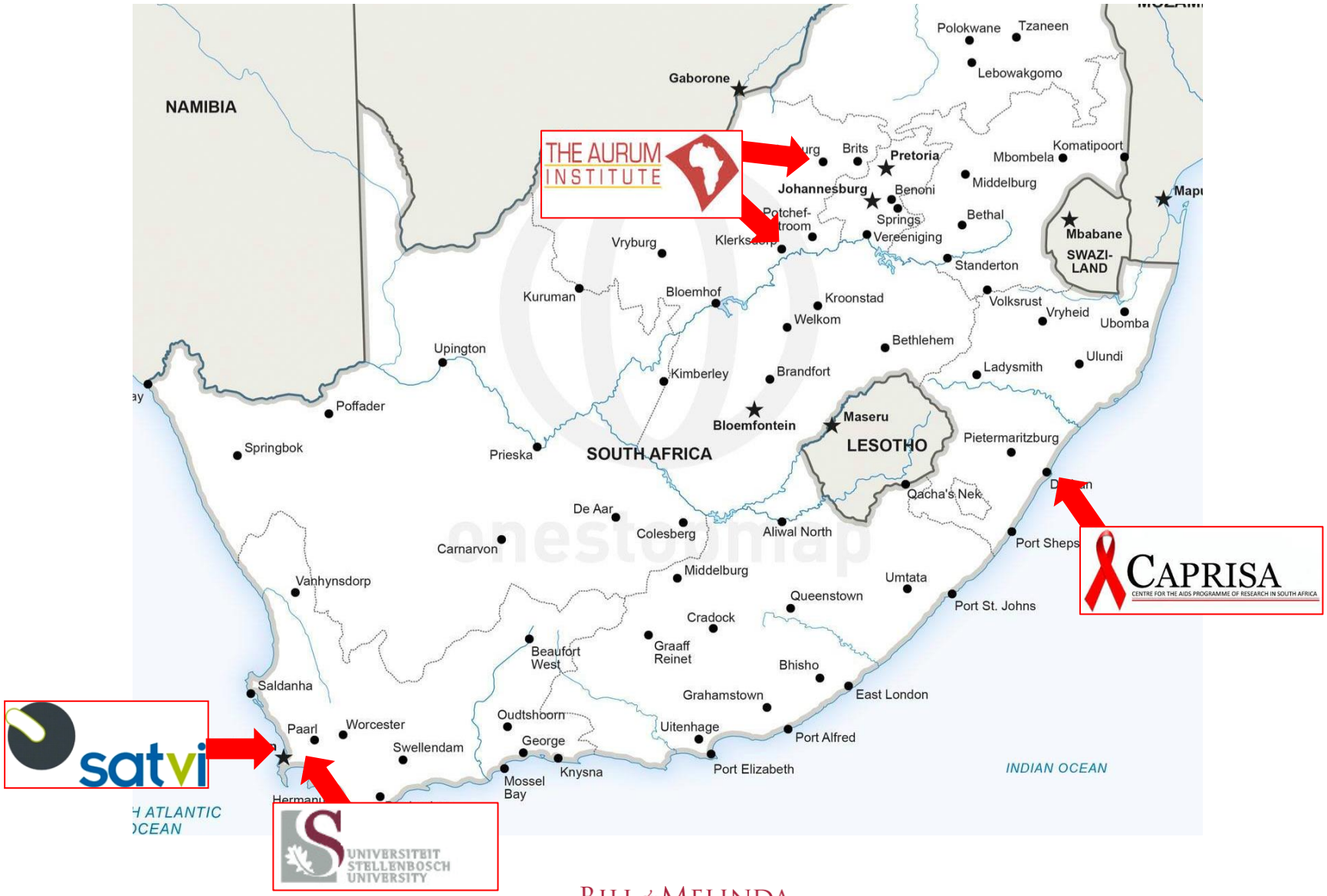
THE AURUM INSTITUTE

CAPRISA CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

IDM INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

The Correlate of Risk Targeted Intervention Study (CORTIS)

ClinicalTrials.gov NCT02735590



BILL & MELINDA GATES foundation

The landscape of TB preventive therapy is fundamentally changing: 3HP

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

→ **A 12-dose, once-weekly, 3-month preventive therapy DOT regimen**

satvi · Universiteit Stellenbosch University · London School of Hygiene & Tropical Medicine · Statistical Center for HIV/AIDS Research & Prevention SCHARP · The Aurum Institute · CAPRISA Centre for the AIDS Programme of Research in South Africa · SANOFI

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