

Oslo Life Science
15th-17th February 2017



OsloLifeScience

– Building the Life Science City

Systems Approaches to Studying the Immune Response in Infection
&
Research at The Francis Crick Institute

Anne O'Garra
The Francis Crick Institute
London, UK



Tuberculosis - A Major Human Threat



Caused by infection with *Mycobacterium tuberculosis*

Active TB:

1.4 million deaths per year

50% untreated mortality

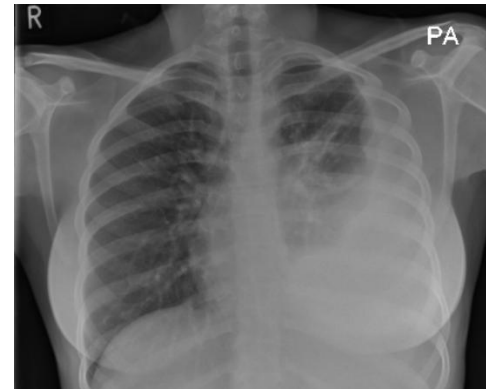
Diagnosis difficult (sputum difficult to obtain)

Vaccine variable

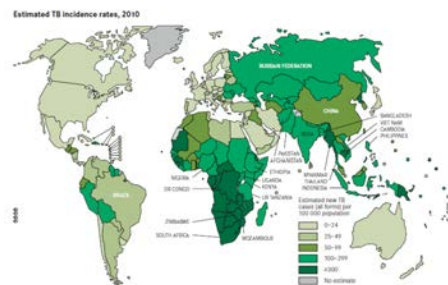
Treatment arduous

Need new drugs, MDR

Predominantly affects the lung



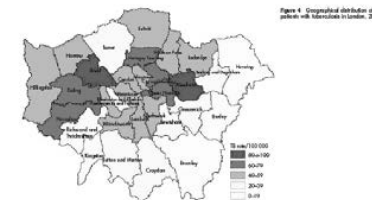
8.6 million cases per year



8000 cases in the UK in 2013



'London the tuberculosis capital of Europe'
(*The Telegraph*, Dec 2010)

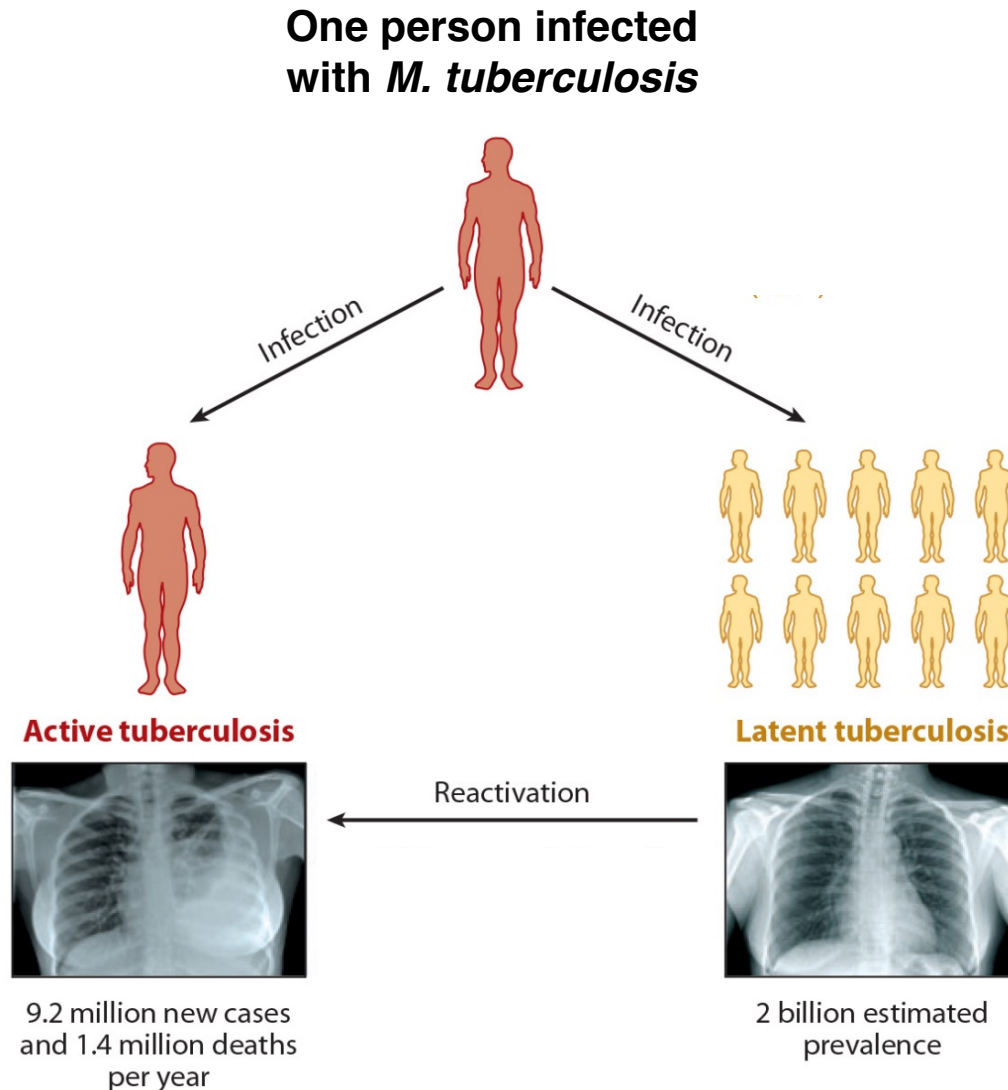


Latent TB:

2 billion infected - asymptomatic - skin test/chemical blood assay

10 - 20% - subclinical disease/will reactivate to active TB

Why do only certain infected individuals develop active tuberculosis?



Why do some individuals go on to develop active tuberculosis?
What factors in the immune response contribute to tuberculosis?

THE
FRANCIS
CRICK
INSTITUTE

A broad unbiased survey: Genomics?

Can human blood transcriptional signatures distinguish individuals with latent and active pulmonary tuberculosis?

Vol 466 | 19 August 2010 | doi:10.1038/nature09247

nature

LETTERS

An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis

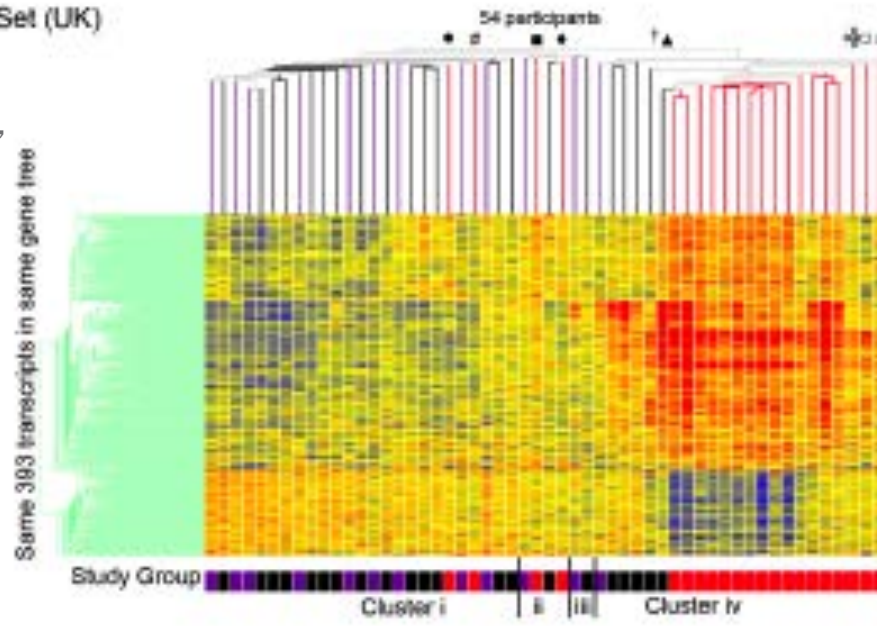
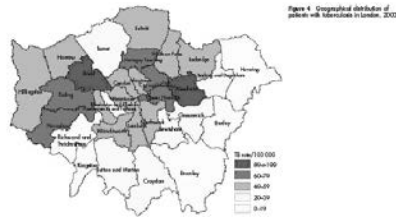
Matthew P. R. Berry¹, Christine M. Graham^{1*}, Finlay W. McNab^{1*}, Zhaohui Xu⁶, Susannah A. A. Bloch³, Tolu Oni^{4,5}, Katalin A. Wilkinson^{2,4}, Romain Banchereau⁹, Jason Skinner⁶, Robert J. Wilkinson^{2,4,5}, Charles Quinn⁶, Derek Blankenship⁷, Ranju Dhawan⁸, John J. Cush⁶, Asuncion Mejias¹⁰, Octavio Ramilo¹⁰, Onn M. Kon³, Virginia Pascual⁶, Jacques Banchereau⁶, Damien Chaussabel⁶ & Anne O'Garra¹

Outliers in Latent and Active Tuberculosis in London and South Africa



b. The Test Set (UK)

'London the tuberculosis capital of Europe'
(*The Telegraph*, Dec 2010)

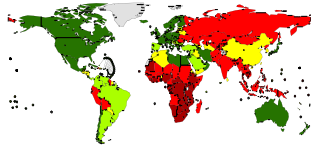


Study Group

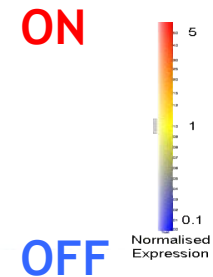
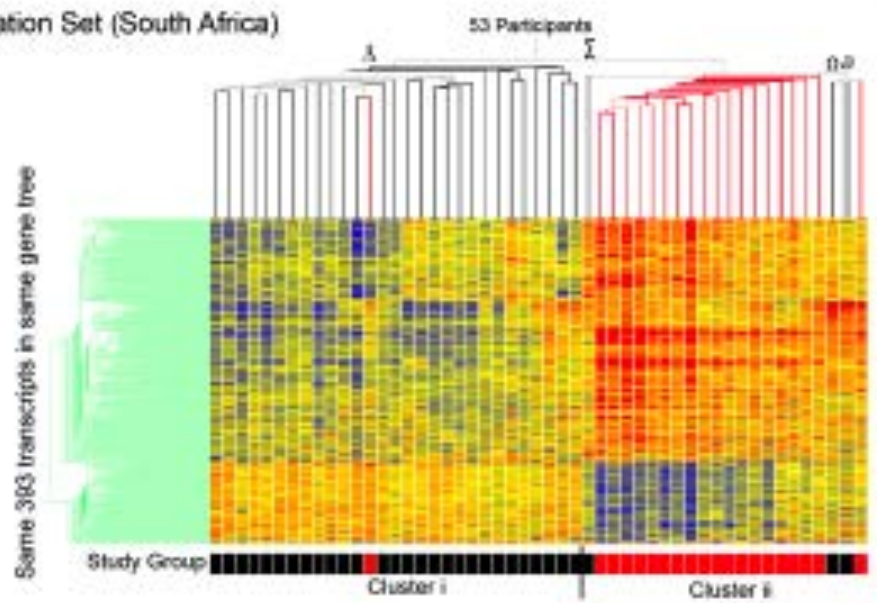
- Active
- Latent
- Control

c. The Validation Set (South Africa)

Cape Town, South Africa

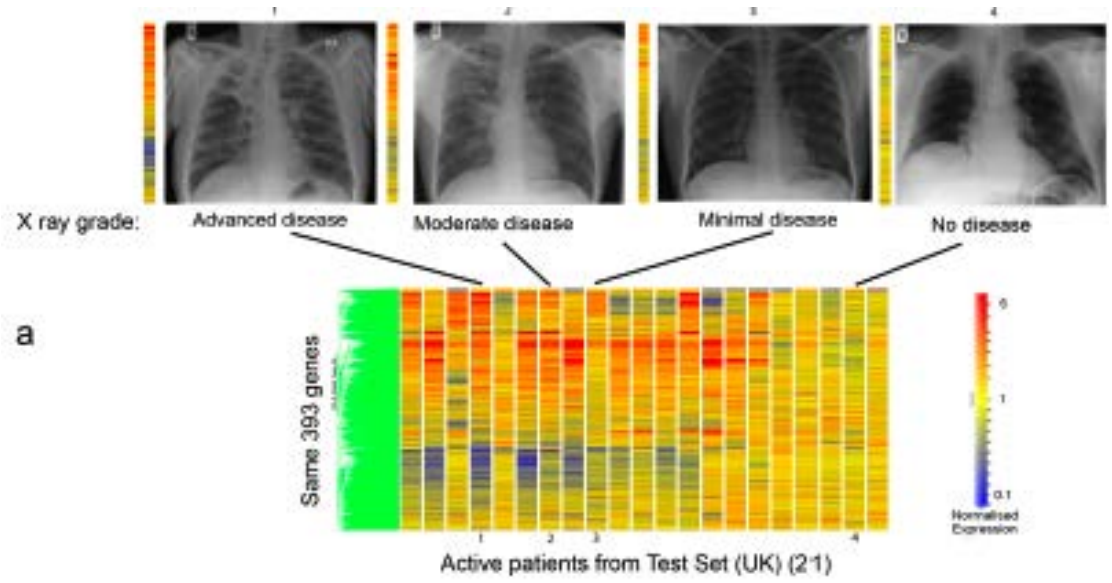


With Robert and Katalin Wilkinson

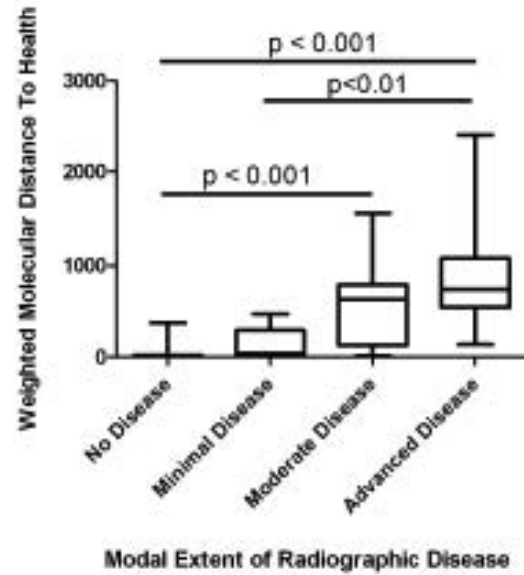


10 - 20% of Latent TB individuals cluster with Active TB

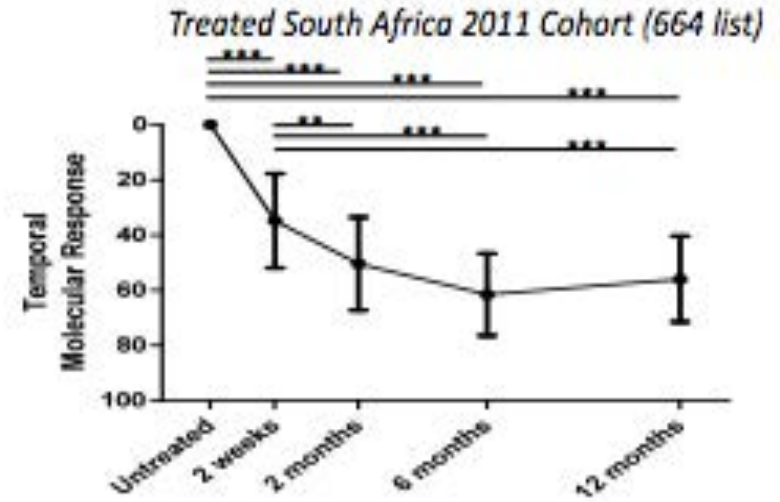
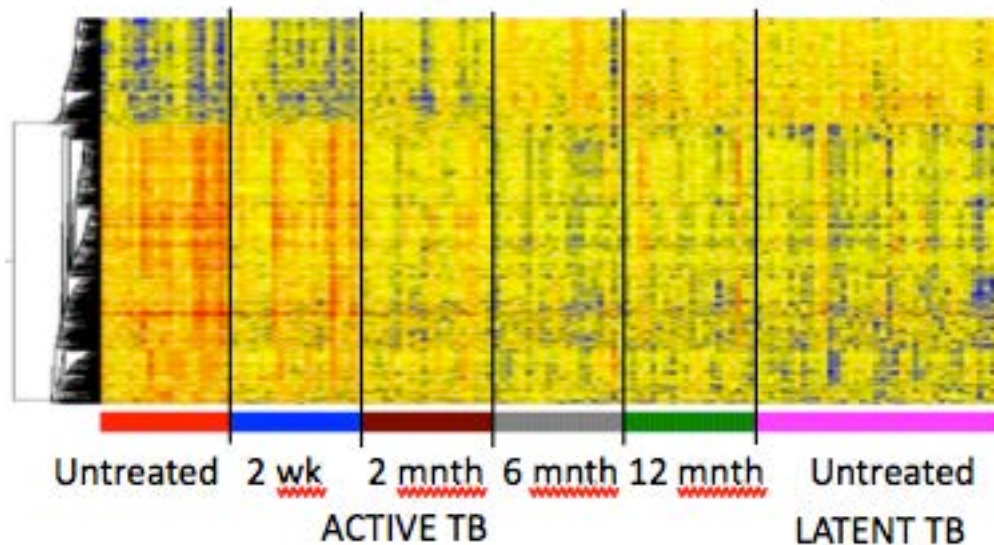
The transcriptional signature of Active TB correlates with radiographic extent of disease



b Correlation of XRay Grade and Transcriptional Perturbation for Training and Test Set Active and Latent patients judged by three independent clinicians



Treated South Africa 2011 Cohort (664 list)



OPEN ACCESS Freely available online

PLOS ONE

Detectable Changes in The Blood Transcriptome Are Present after Two Weeks of Antituberculosis Therapy

Chloe I. Bloom^{1*}, Christine M. Graham¹, Matthew P. R. Berry^{1,3}, Katalin A. Wilkinson^{2,4}, Tolu Oni^{4,5}, Fotini Rozakeas¹, Zhaohui Xu⁶, Jose Rossello-Urgell⁶, Damien Chaussabel^{6,7}, Jacques Banchereau⁶, Virginia Pascual⁶, Marc Lipman⁸, Robert J. Wilkinson^{2,4,5}, Anne O'Garra¹

PLOS ONE | www.plosone.org

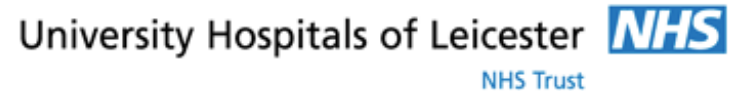
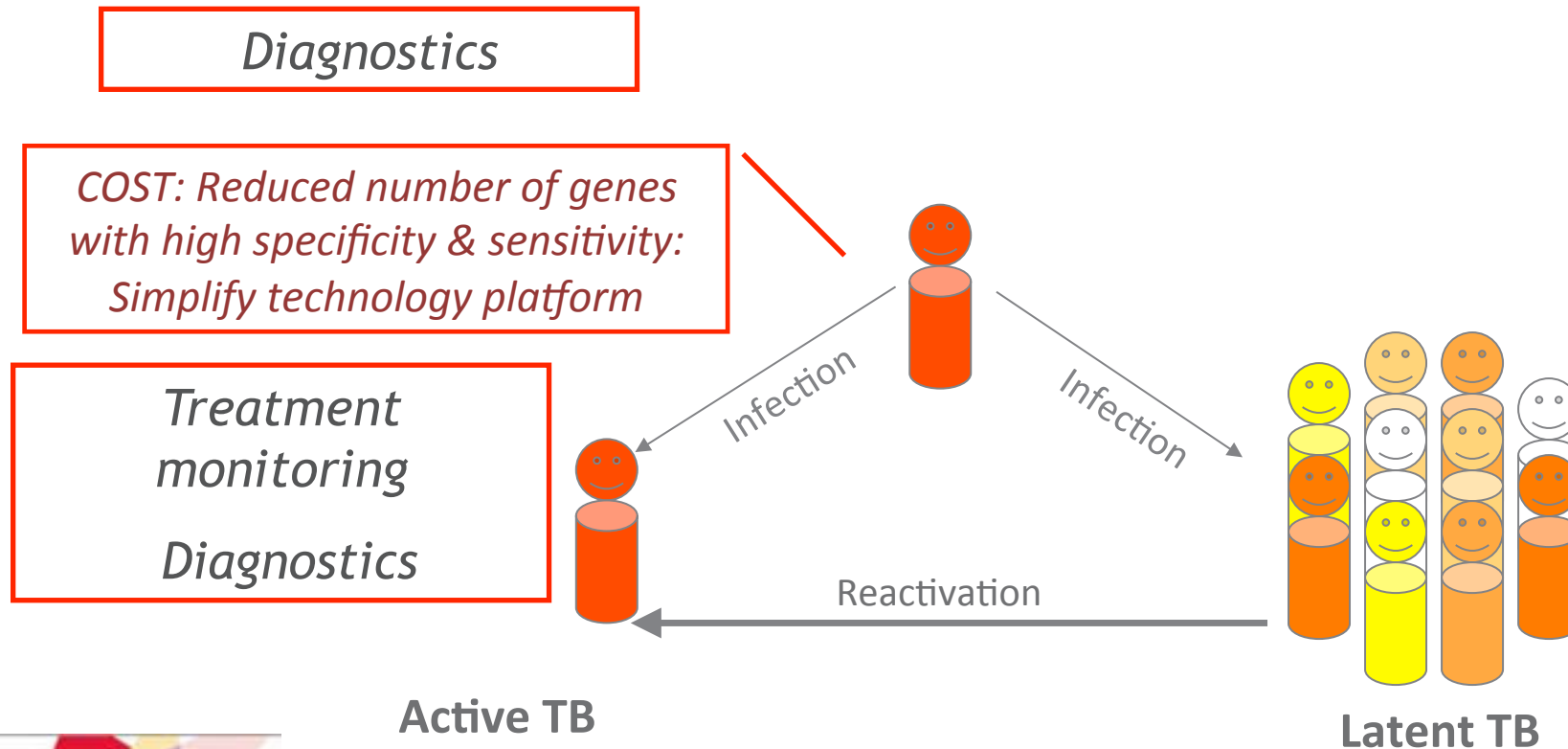
1

October 2012 | Volume 7 | Issue 10 | e46191

Also reported by Cliff, Dockrell et al., *J.Infect.Diseases*, 2013

Improvement for monitoring TB treatment and testing new drugs:
Current test sputum-conversion >2 months; only in <50% patients

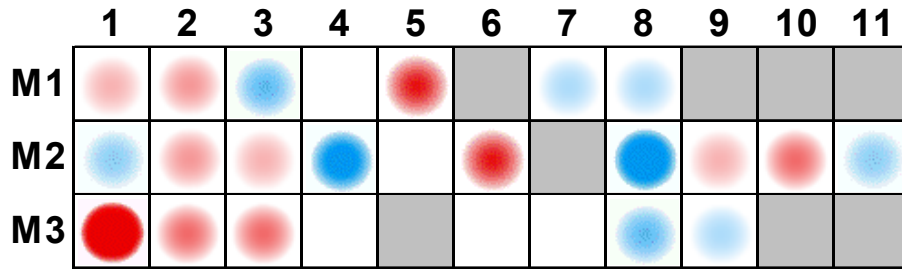
TB Signatures for Treatment Monitoring and Have Potential Use as Diagnostics and Prognostics



Identical Modular signature of Active TB: UK vs. South Africa

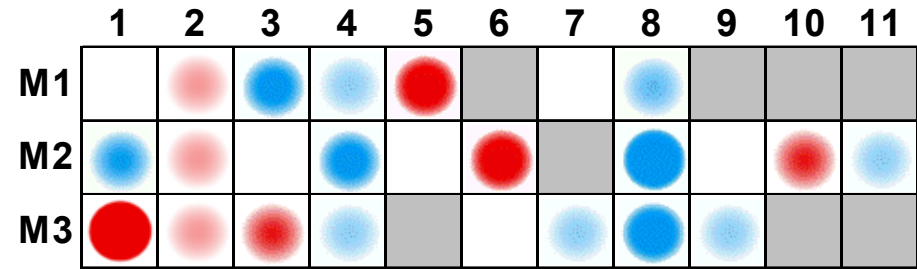


PTB UK Training



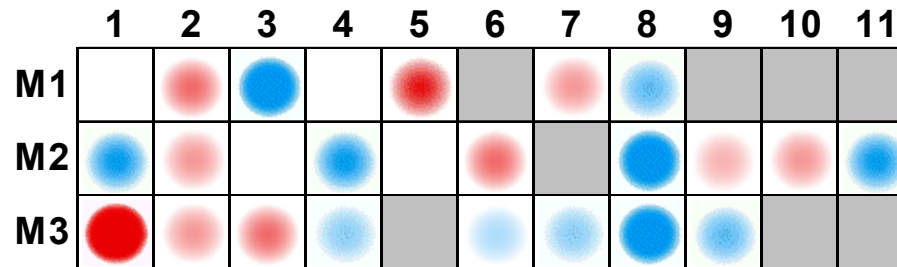
PTB n = 13/13, Control n = 12/12

PTB UK Test

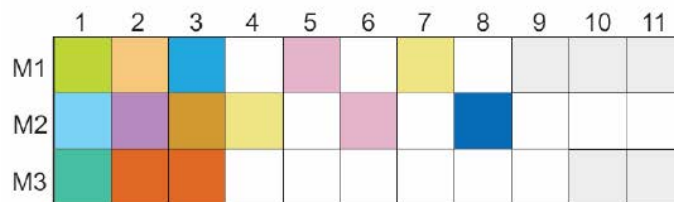


PTB n = 21/21, Control n = 12/12

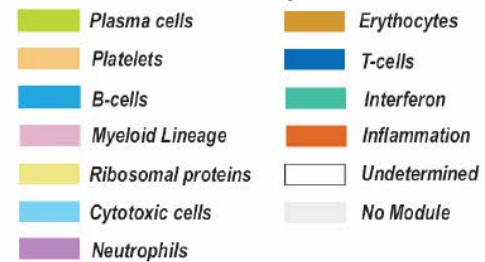
PTB SA Test



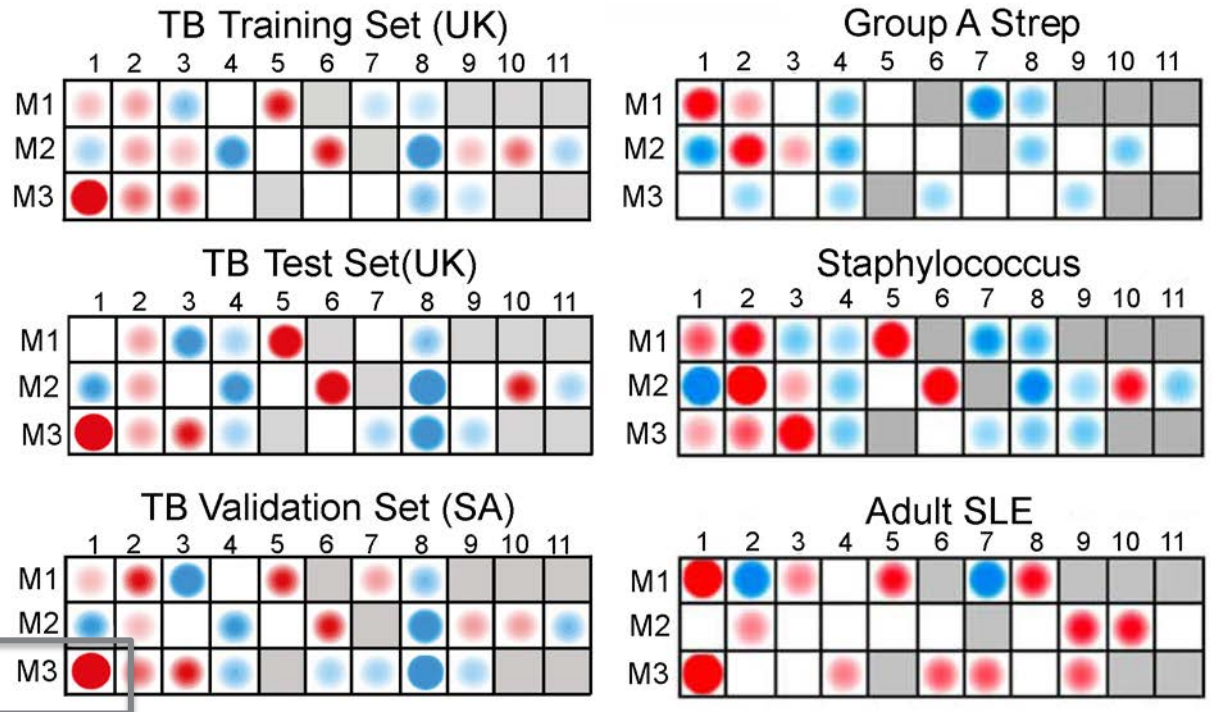
PTB n = 23/23, Control n = 12/12



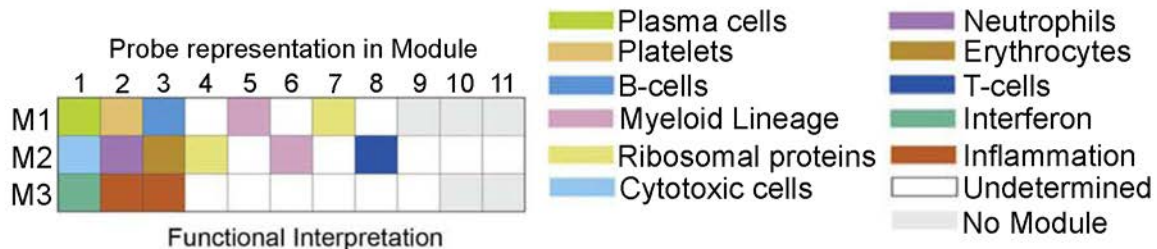
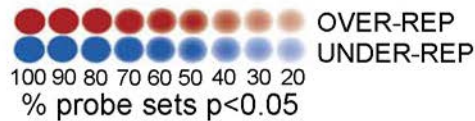
Functional Interpretation



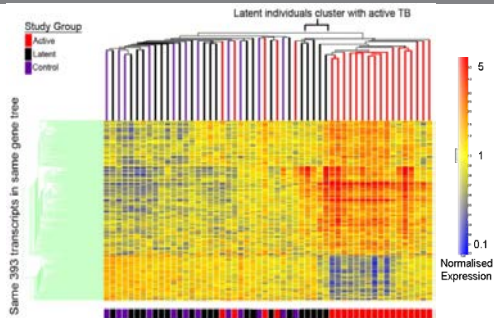
Modular Analysis Reveals a Transcriptional Signature in Active TB Patients Distinct from Other Diseases



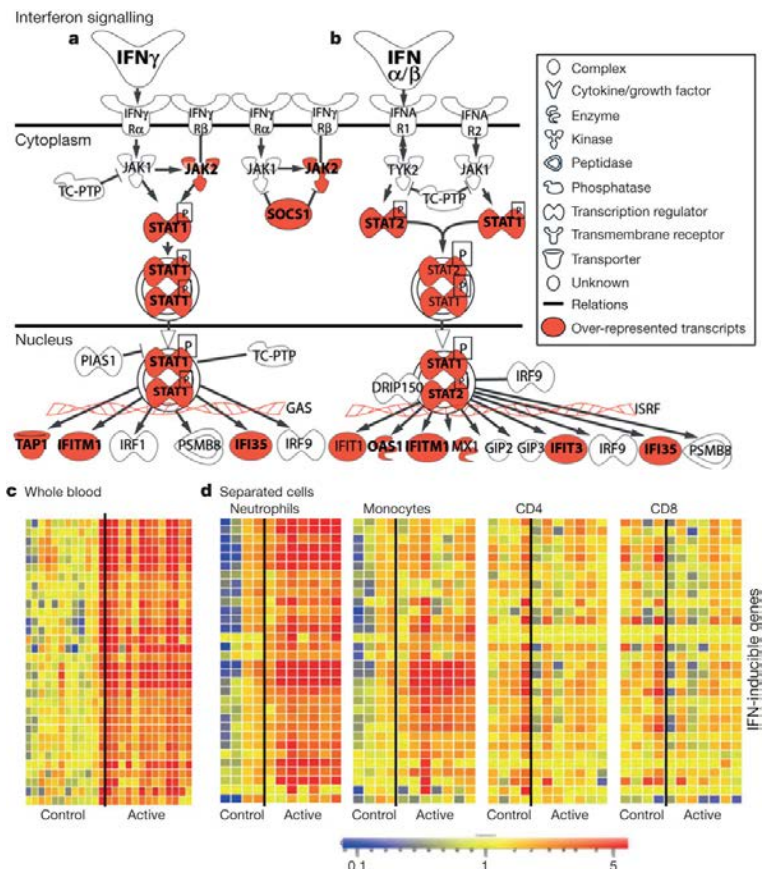
IFN-inducible genes



Blood Transcriptomics Reveal an Unappreciated Type I IFN-inducible Signature in Active TB

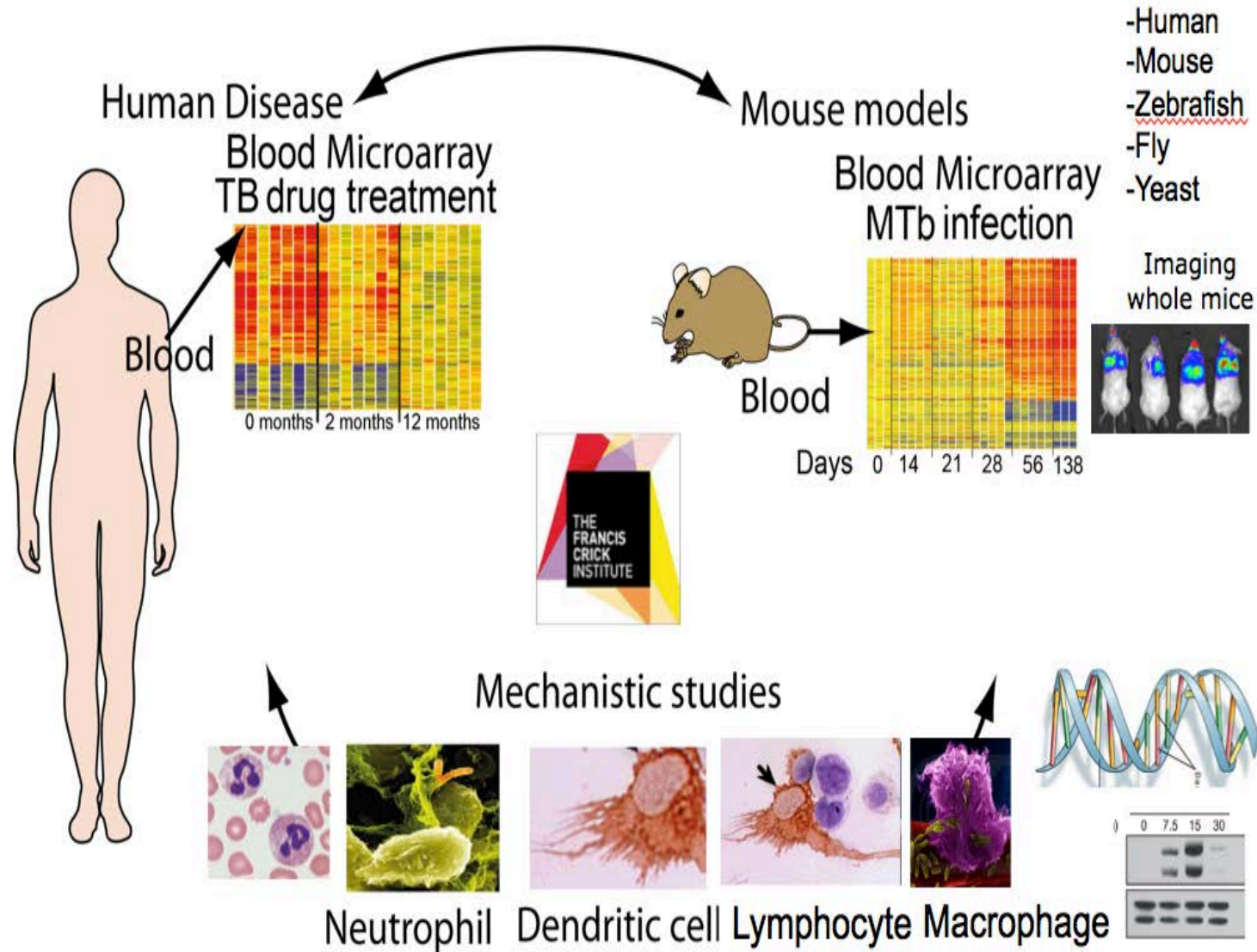


A 393 transcript signature is able to differentiate active pulmonary TB patients from healthy latent Mtb infected and healthy BCG vaccinated individuals¹.



Type I IFNs:
 Protect against viruses & cancer:
 Exacerbate bacterial infections

Crick strategies for elucidating determinants of immune and inflammatory responses in different systems: from human disease to experimental models



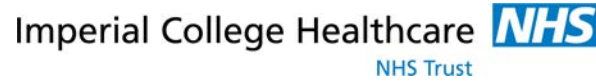
Acknowledgements



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Advanced Sequencing Facility



Onn Min Kon

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Hillingdon Hospital, UK

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Mimi Haselden

The Patients

Healthy Volunteers

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Damien Chaussabel (Sidra)

Zhaohui Xu

Nicole Baldwin

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Robert Wilkinson

Wellcome Trust SFCS

Katalin Wilkinson MRC



UCL

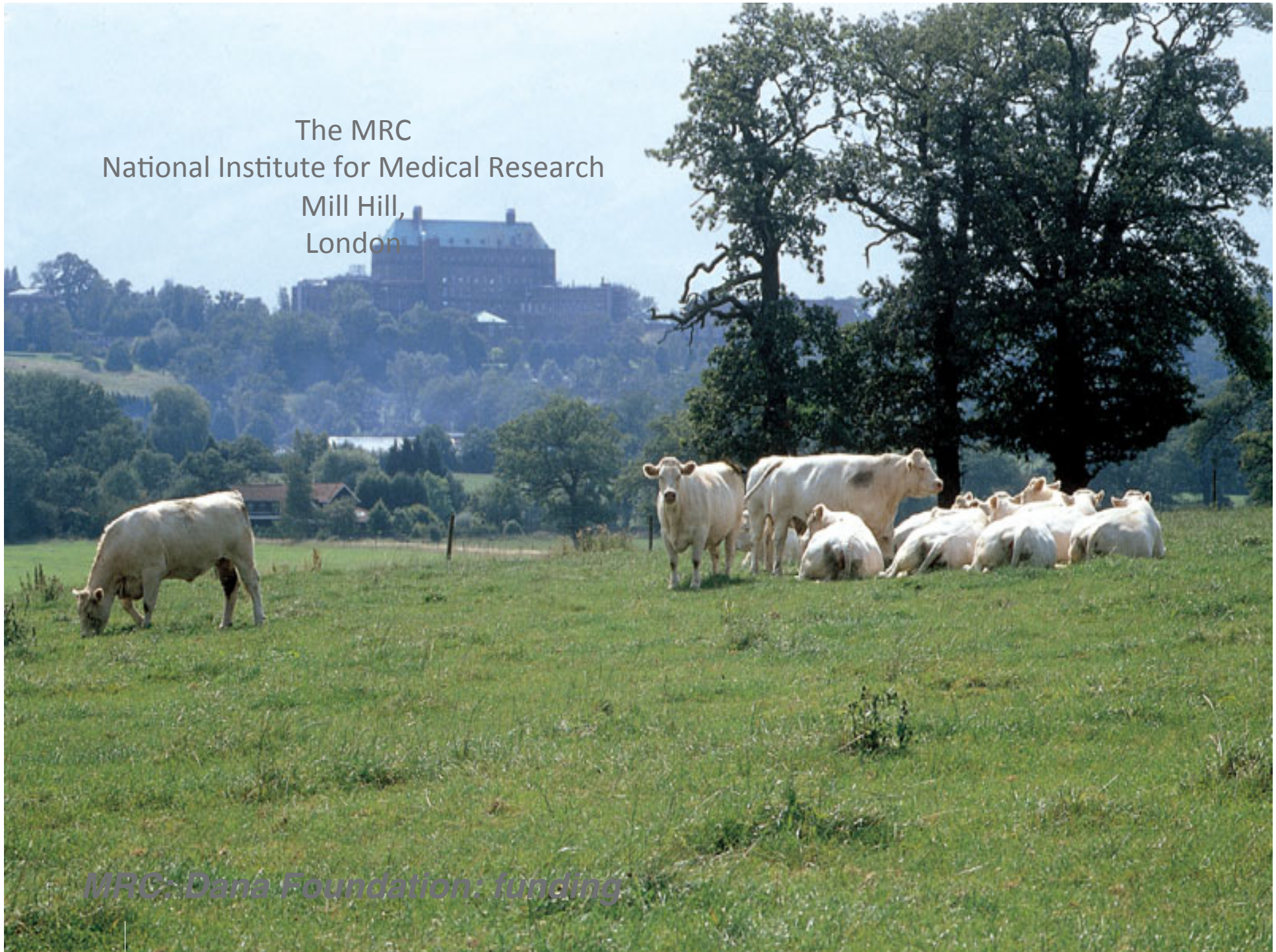
Marc Lipman

TB service & Ian Cropley

And other clinicians in Oxford, Paris, Lyon, Leicester

The MRC
National Institute for Medical Research
Mill Hill,
London

MRC: Dana Foundation: funding



FRANCIS CRICK INSTITUTE

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Anne O'Garra
Associate Research Director
Head, Laboratory of Immunoregulation & Infection



Imperial College
London



wellcome trust



What is The Crick?



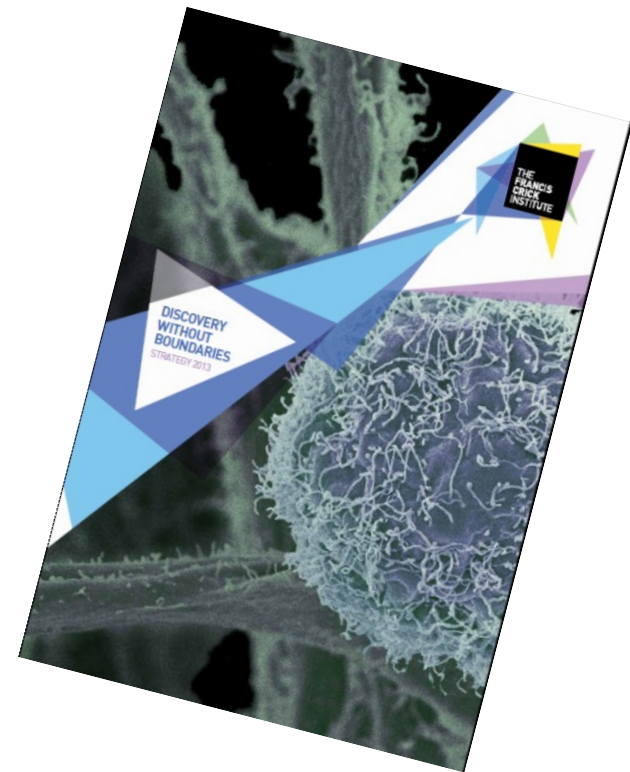
- Interdisciplinary biomedical research institute
- Partnership between:
 - Medical Research Council (National Institute for Medical Research)
 - Cancer Research UK (London Research Institute)
 - Wellcome Trust
 - UCL (University College London)
 - Imperial College London
 - King's College London
- Strategic partnership with Sanger Institute
- Funding:
 - Intramural from MRC, CRUK, Wellcome Trust
 - Response-mode funding
- Multi- and interdisciplinary working
- Strong clinical and translational links
- 1300 scientists, 120 research groups



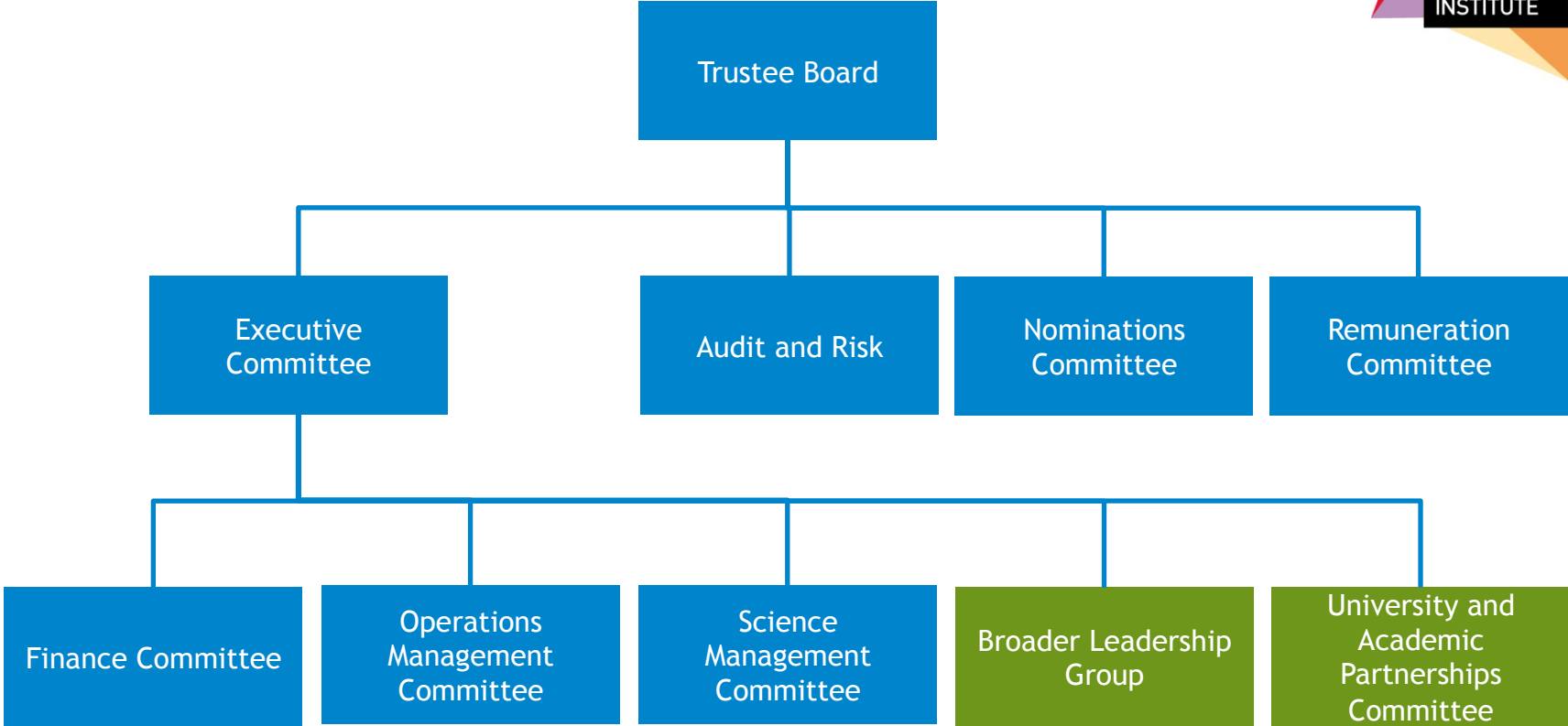
Crick's strategic priorities



- “Discovery without boundaries”
- Develop future science leaders
- Collaborate creatively to advance UK science and innovation
- Accelerate translation for health and wealth
- Engage and inspire the public
- Play a national role in supporting UK science endeavour



Crick's governance



Key:

- Decision-making
- Advisory



Crick Science Management Committee

- Director/CEO: Paul Nurse
- COO: David Roblin Operations & Translation
- Research Directors:
 - Steve Gamblin Director of Science Operations
 - Peter Ratcliffe Clinical Director
 - Richard Treisman Director of Research
- Associate Research Directors:
 - John Diffley - PhD & Postdoc Training
 - Julian Downward - Science Technology Platforms
 - Malcolm Irving - Crick University partners
 - Anne O'Garra - Group leader mentoring/development; Interest Grps

The design of the Crick



- Four lab floors plus plant above ground
- Three floor basement: animal, containment and imaging facilities
- Space for up to 1,300 researchers plus support staff
- Public access on ground floor - availability for community use
- Lecture theatre, seminar suite, meeting facilities
- Focus on practical sustainability
- High visual permeability
- Observable interior at street level



Collaboration & Multidisciplinarity

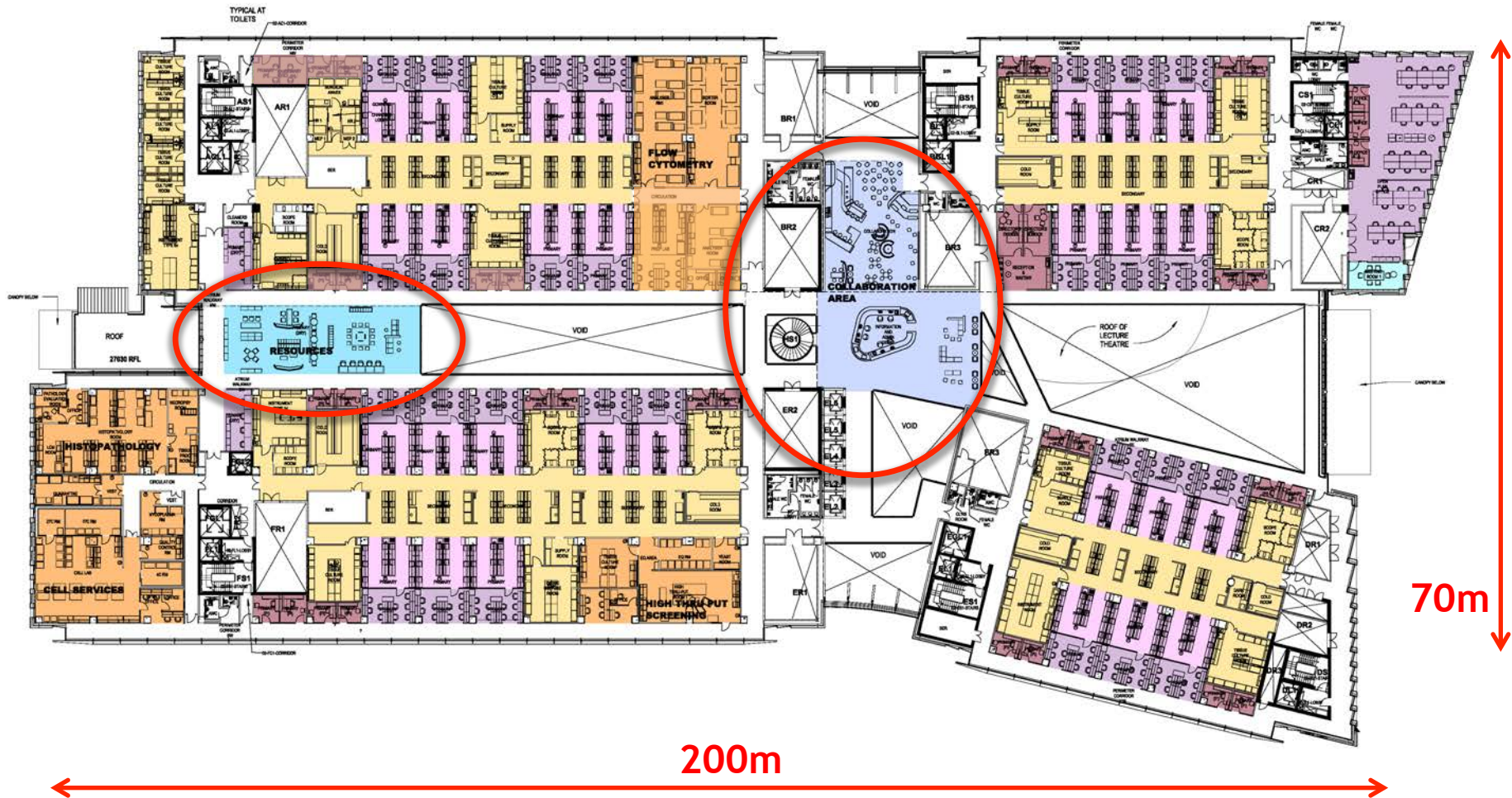


- Mix disciplines to encourage new ideas and interactions
- Bring together scientists from different institutions: UCL, King's, Imperial, Sanger Institute...
- Ensure proximity to intensively used core facilities
- Co-locate researchers with shared interests
- Maintain access to shared specialist research instruments



The Francis Crick Institute

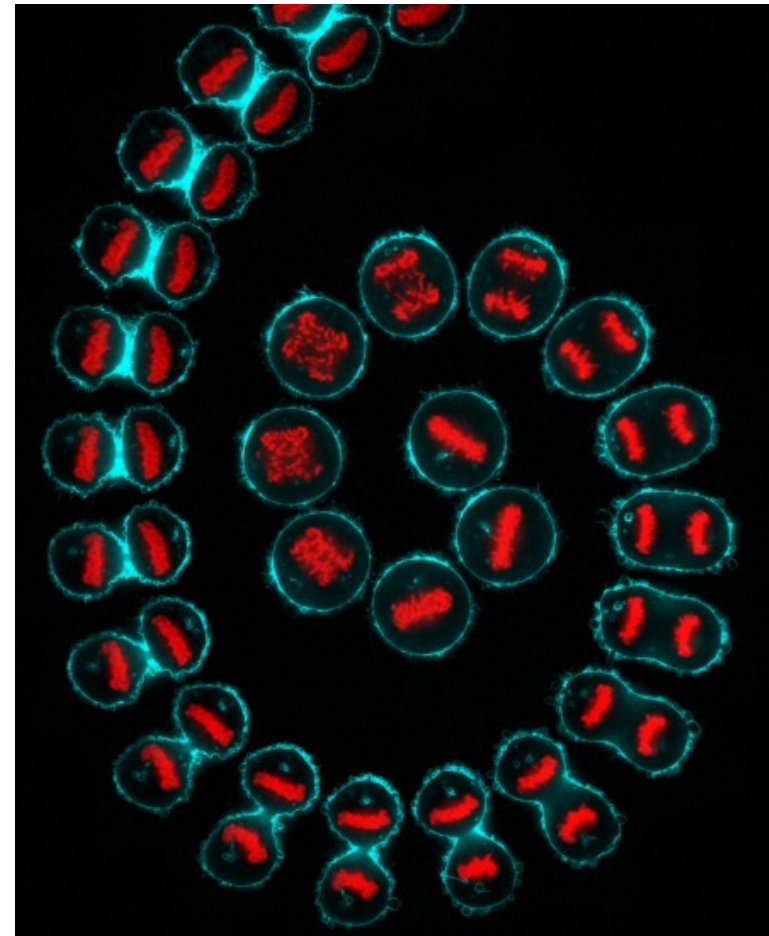
A research floor



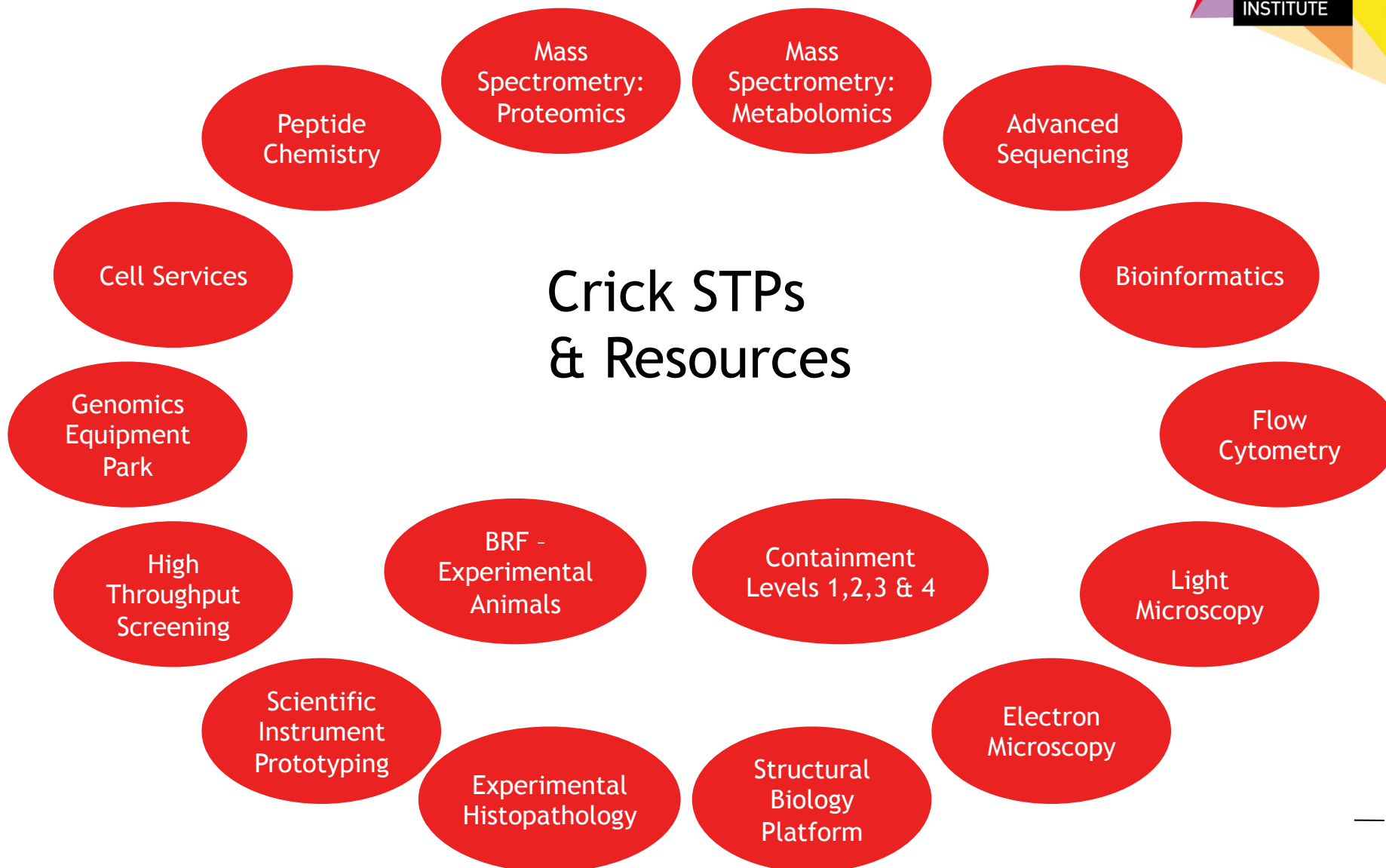
Outstanding discovery science at the Crick



- The initial areas of research strength at the Crick will be:
 - Cancer
 - Cell Biology & signalling
 - Chromosome biology
 - Computational & physical biology
 - Developmental biology & stem cells
 - Infection
 - Immunity
 - Neurosciences
 - Structural biology
- Each area of research has linked Interest Group seminars (Internal PhD & Postdocs; External invited speakers - advertised to partners & London)
- Bringing in chemistry, physics, translational & clinical research



Science Technology Platforms





crick.ac.uk



Imperial College
London



wellcome trust

