TB Biomarker discovery: big data & bioinformatics

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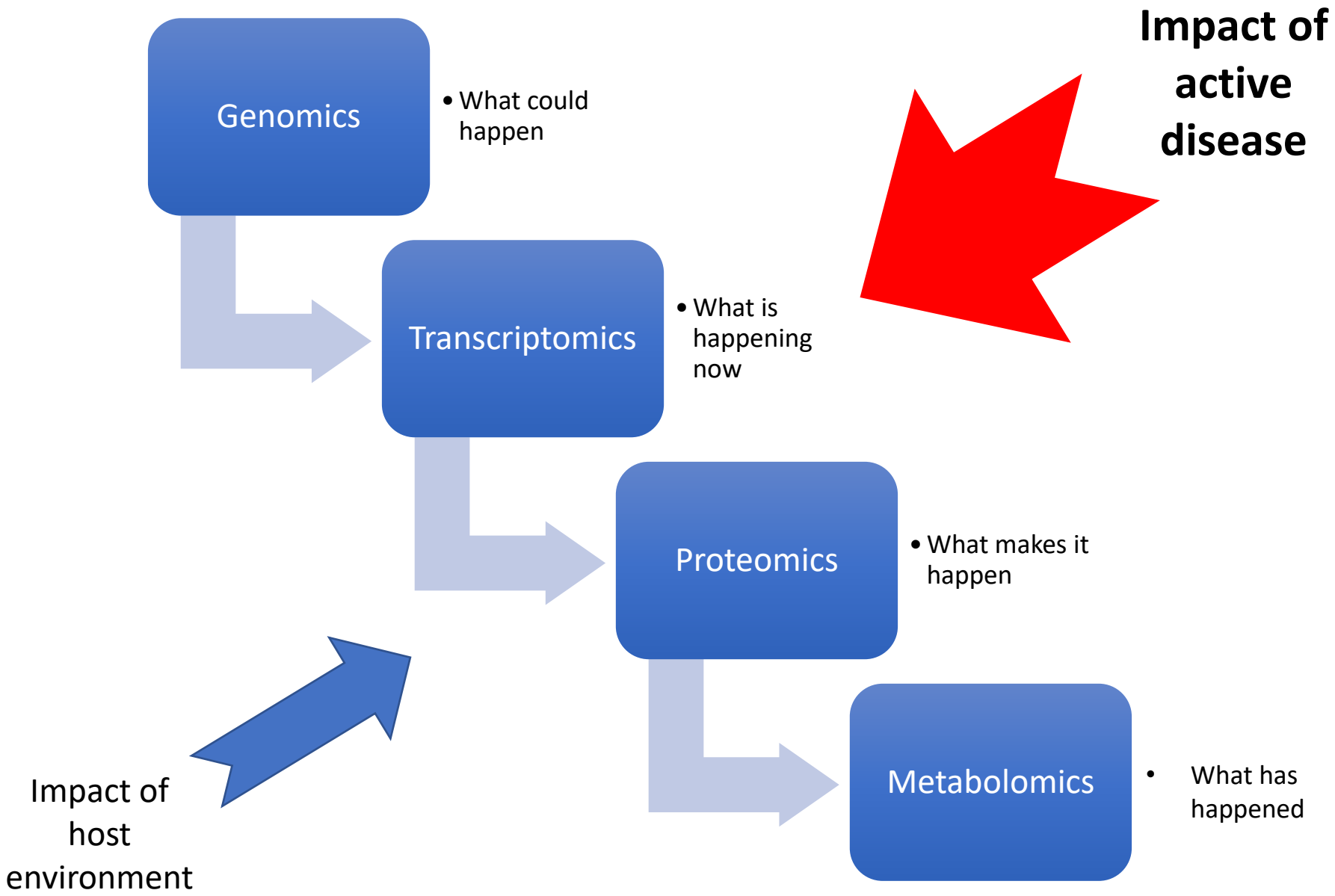
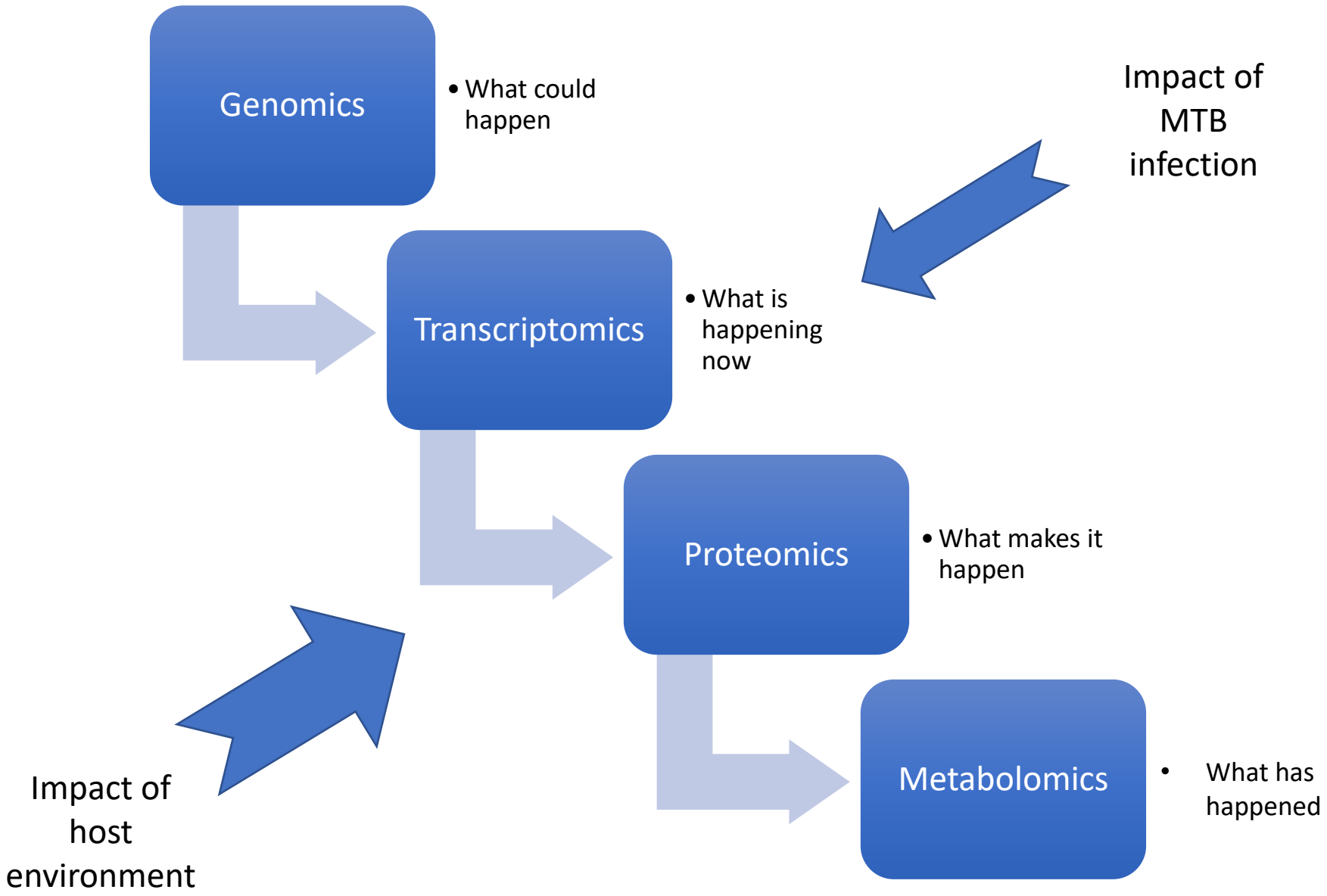

Genomics
• What could happen
Impact of active disease
Transcriptomics
• What is happening now
Proteomics
• What makes it happen
Impact of host environment
Metabolomics
• What has happened

TB disease studies until 2013

study	reference	population	sample collection	# TB patients initial, independent	type of sample
1	Mistry R, JID, 2007: 195, 357	active TB disease vs healthy infected controls	South Africa	n = 10	whole blood
2	Jacobsen M, J Mol Med, 2007: 85, 613	active TB disease vs healthy infected controls	Germany	n = 9	PBMC
3	Berry MP, Nature, 2010: 466, 973	active TB disease vs healthy infected & uninfected controls vs other inflammatory disorders (SLE, Stills, Streptococcus, Staphylococcus)	United Kingdom (test), South Africa (validation)	n = 13, n = 20	whole blood
4	Maertzdorf J, Genes & Immunity, 2011: 12, 15	active TB disease vs healthy infected & uninfected controls	South Africa	n = 33	whole blood
5	Maertzdorf J, PLoS ONE, 2011: 6, e26938	active TB disease vs healthy infected & uninfected controls	The Gambia	n = 46	whole blood
6	Maertzdorf J, PNAS, 2012: 109, 7853	active TB disease vs healthy infected & uninfected controls & sarcoidosis	Germany	n = 8	whole blood
7	Cliff J, JID, 2013: 207, 18	active TB disease over time during treatment	South Africa	n = 27, n = 9	whole blood
8	Ottenhoff TH, PLOS ONE, 2012: 7, e45839	active TB disease over time during treatment vs healthy controls	Indonesia	n = 23	PBMC

doi:10.1371journal.pone.0073230.t002

Joosten SA, Fletcher HA, Ottenhoff THM (2013) A Helicopter Perspective on TB Biomarkers: Pathway and Process Based Analysis of Gene Expression Data Provides New Insight into TB Pathogenesis. PLOS ONE 8(9): e73230. doi:10.1371/journal.pone.0073230
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0073230


Genomics
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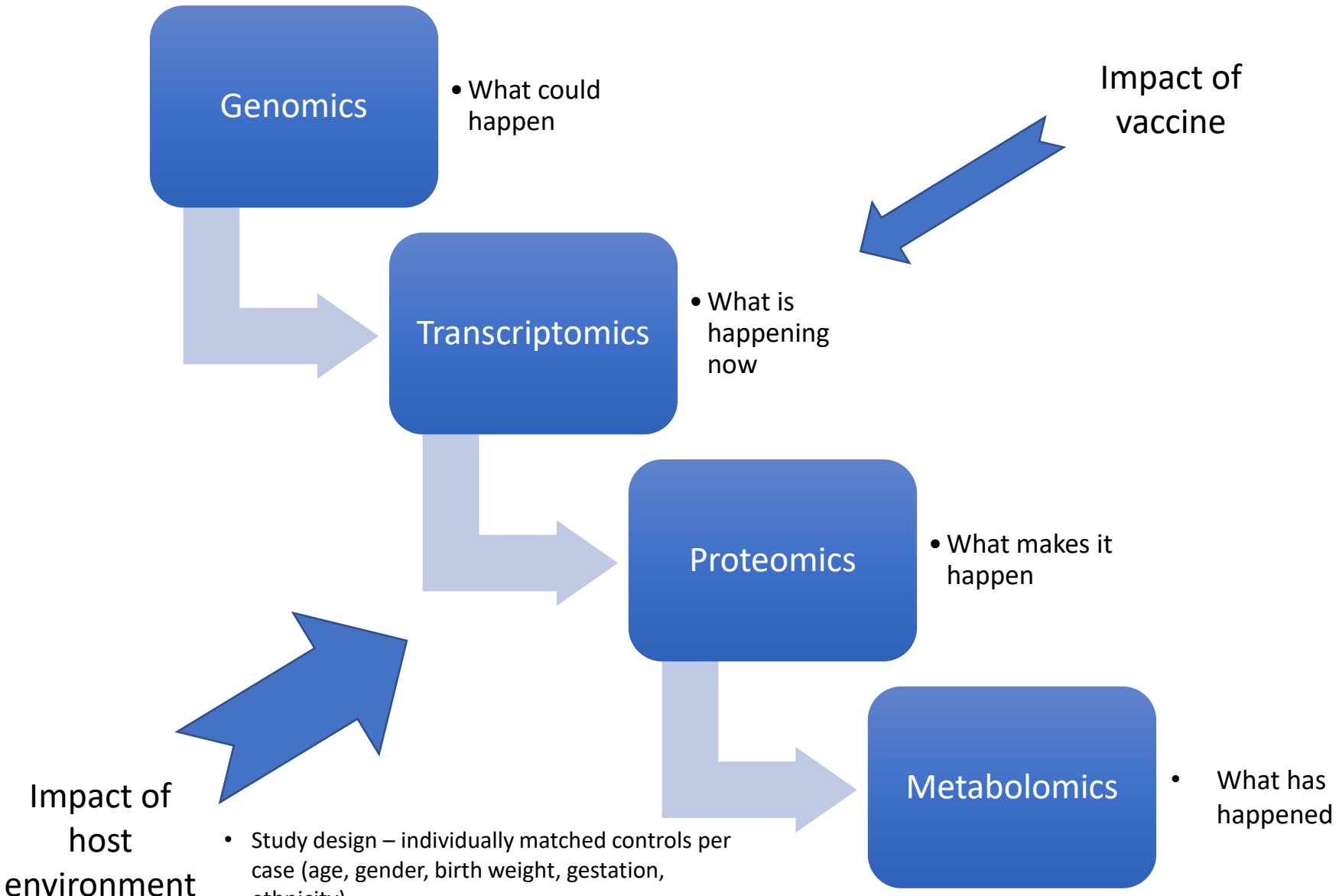
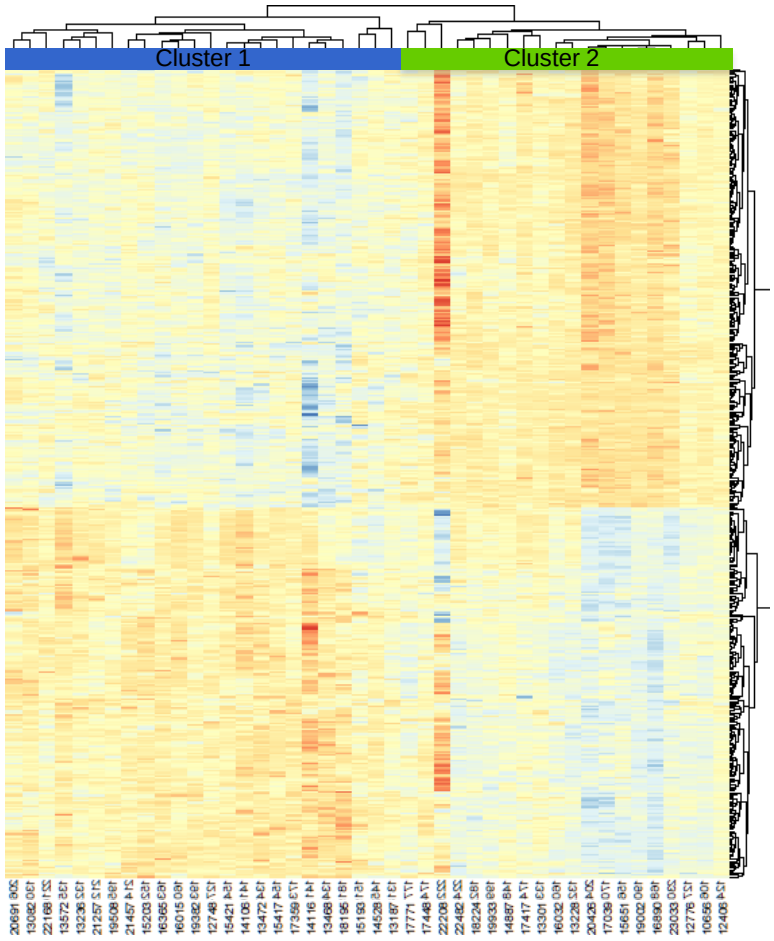
Impact of MTB infection
Transcriptomics
• What is happening now
Proteomics
• What makes it happen
Metabolomics
• What has happened
Impact of host environment


Genomics
• What could happen
Impact of vaccine
Transcriptomics
• What is happening now
Proteomics
• What makes it happen
Metabolomics
• What has happened
Impact of host environment
• Study design – individually matched controls per case (age, gender, birth weight, gestation, ethnicity)
• Normalize eg. Deconvolution
• Discovery

Monocyte frequency and phenotype variable in South African infants



Fletcher *et al. BMC Medicine* (2016) 14:76
DOI 10.1186/s12916-016-0617-3

BMC Medicine

World TB Day

RESEARCH ARTICLE Open Access

Human newborn bacille Calmette–Guérin vaccination and risk of tuberculosis disease: a case-control study

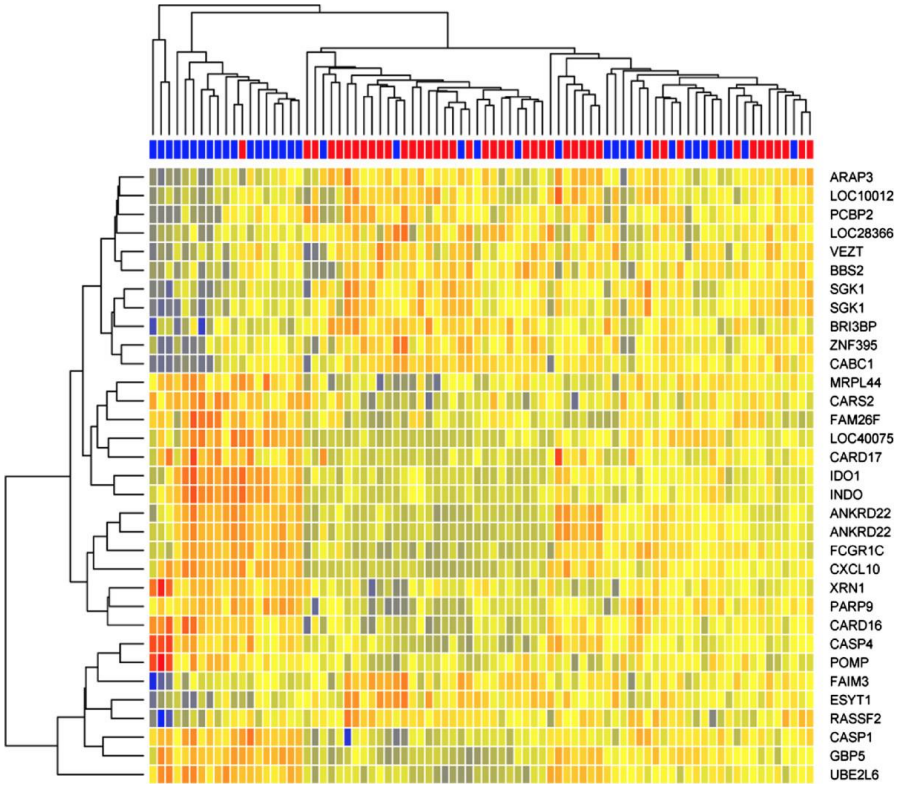
Helen A. Fletcher[1†], Ali Filali-Mouhim[2†], Elisa Nemes[3†], Anthony Hawkridge[3], Alana Keyser[3], Samuel Njikan[3], Mark Hatherill[3], Thomas J. Scriba[3], Brian Abel[3], Benjamin M. Kagina[3], Ashley Veldsman[3], Nancy Marín Agudelo[4], Gilla Kaplan[5], Gregory D. Hussey[3], Rafick-Pierre Sekaly[2], Willem A. Hanekom[3*] and the BCG study team

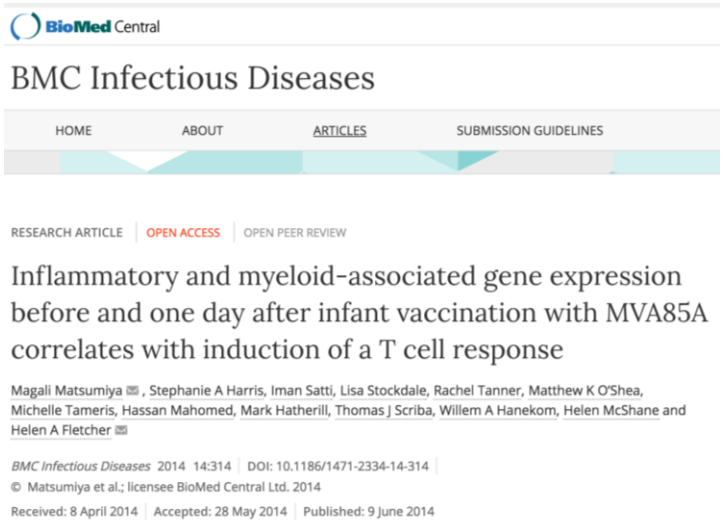
Differences in;

- CD4+ Th1 response
- Monocyte frequency
- Lymphocyte frequency
- Monocyte phenotype (M1/M2)

Both responders and non-responders 1 day post MVA85A vaccination

MVA85A (blue) or Candin (red)





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Inflammatory and myeloid-associated gene expression before and one day after infant vaccination with MVA85A correlates with induction of a T cell response

Magali Matsumiya, Stephanie A Harris, Iman Satti, Lisa Stockdale, Rachel Tanner, Matthew K O'Shea, Michelle Tameris, Hassan Mahomed, Mark Hatherill, Thomas J Scriba, Willem A Hanekom, Helen McShane and Helen A Fletcher

BMC Infectious Diseases 2014 14:314 | DOI: 10.1186/1471-2334-14-314

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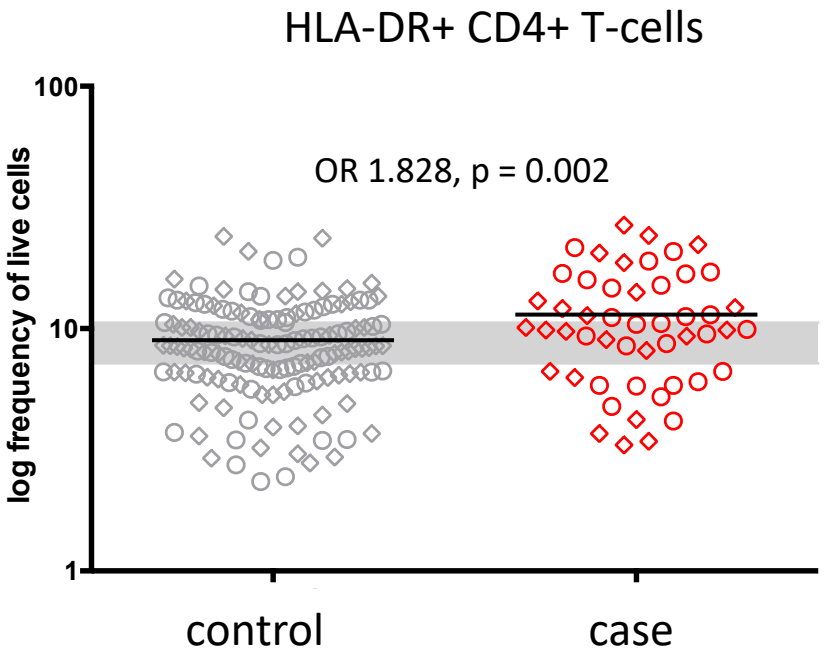
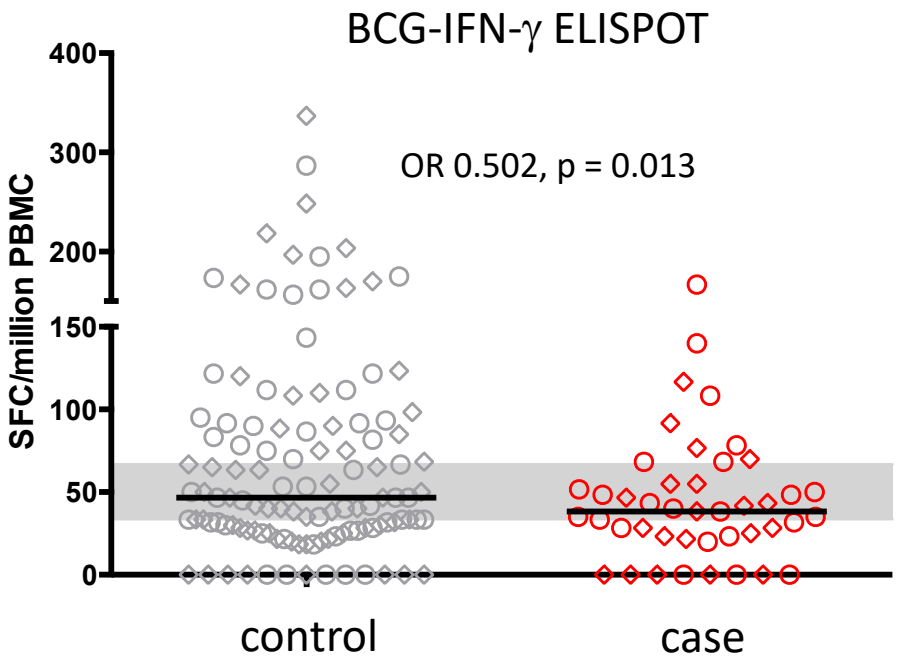
Received: 8 April 2014 | Accepted: 28 May 2014 | Published: 9 June 2014

Whole blood from infant heel-stick

T-cell activation is a correlate of risk in BCG-vaccinated infants





Result significant if Conditional Logistic Regression P<0.05 and FDR<2
Shaded bar indicates medium third of immune response level

BCG Antigen specific IFN-g positive T cells (CD4+ polyfunctional) in peripheral blood associated with reduced risk of disease in BCG vaccinated infants

Fletcher HA *et al* Nature Communications, 2016

Matsumiya et al. BMC Infectious Diseases 2014, 14:314
http://www.biomedcentral.com/1471-2334/14/314

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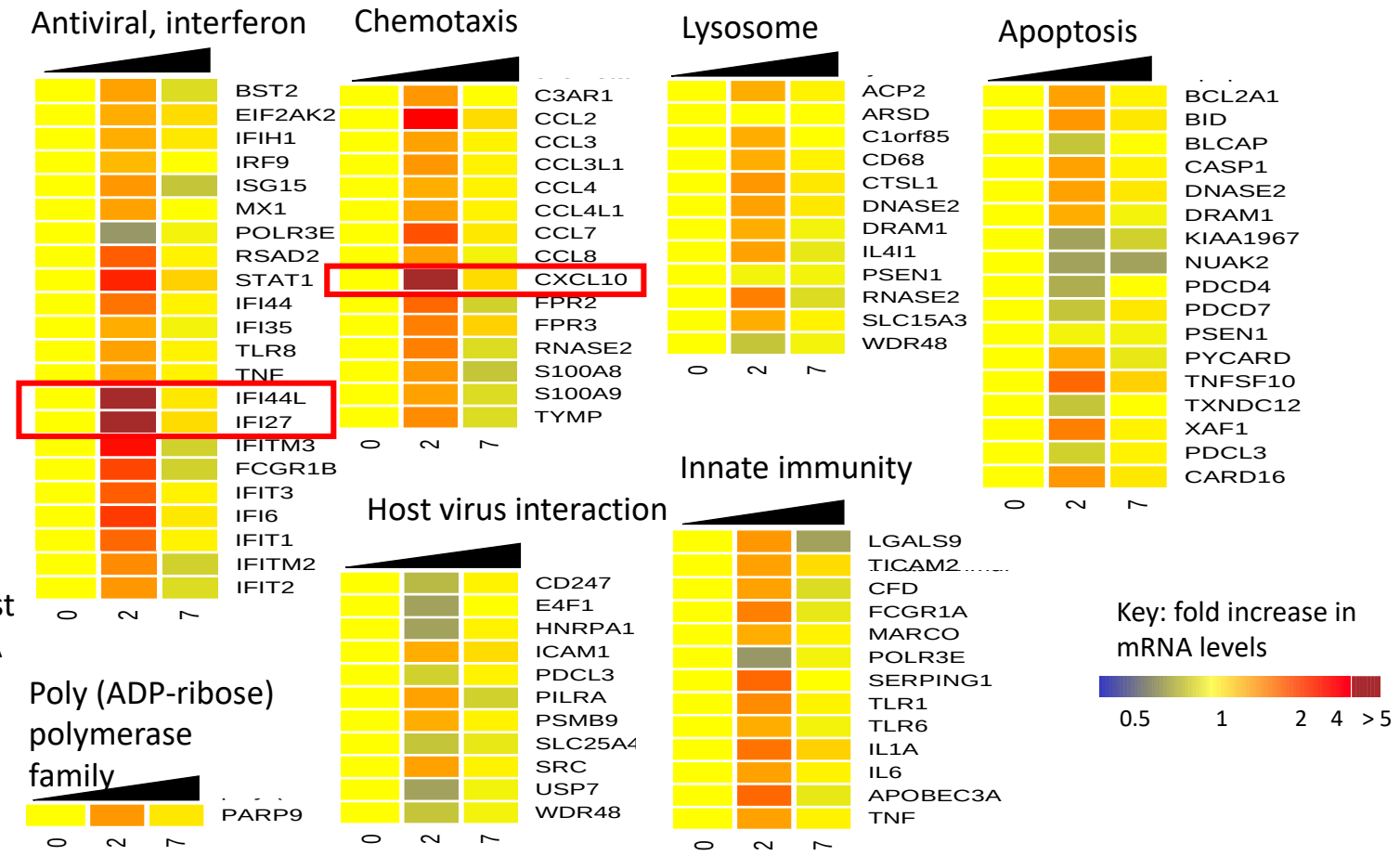
Inflammatory and myeloid-associated gene expression before and one day after infant vaccination with MVA85A correlates with induction of a T cell response

Magali Matsumiya[1*], Stephanie A Harris[1], Iman Satti[1], Lisa Stockdale[1], Rachel Tanner[1], Matthew K O'Shea[1], Michelle Tameris[2], Hassan Mahomed[3,4], Mark Hatherill[2], Thomas J Scriba[2], Willem A Hanekom[2], Helen McShane[2] and Helen A Fletcher[1,5*]

Does MVA85A drive Type I/II IFN and T cell activation?



Omics methods low input and high output

Challenges

- Small sample size - poor statistical Power
- Sensitive to type I error (false positive)
- Heterogeneity – clinical samples

Solutions

- False discovery rate (FDR) - if too stringent type 2 error
- Larger sample sizes – reduced costs
- Normalisation

- Study design - case definition, matched controls
- When is heterogeneity noise and when is it telling you something important?

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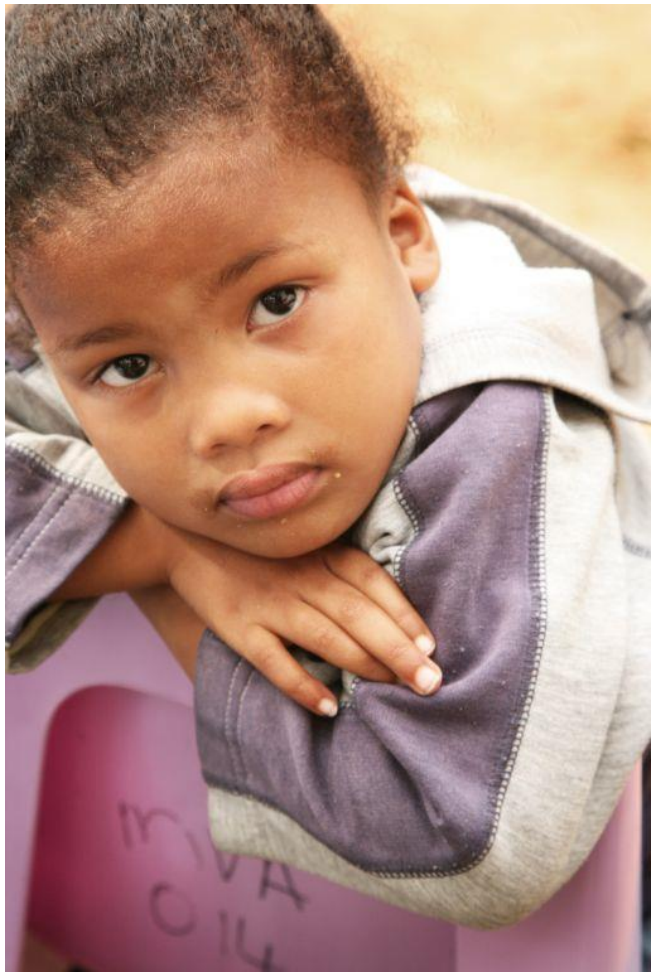

MVA85A Study team
All the mothers and babies

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Lisa Stockdale
Satria Prabowo

SATVI
Elisa Nemes
Michele Tameris
Mark Hatherill
Tom Scriba
Greg Hussey
Adam Penn-Nicholson
Hassan Mahomed
Willem Hanekom