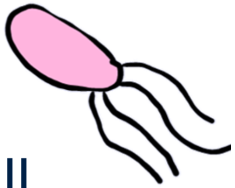
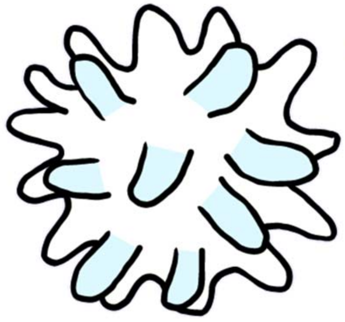
oxford vaccine group
www.ovg.ox.ac.uk

UNIVERSITY OF OXFORD

Integration of Transcriptomic and Genomic Data Reveals Important Aspects of the Early Host Response to *Salmonella* Typhi Infection





Amber J Barton, Daniel O'Connor, Jennifer Hill,
Christoph J Blohmke, Andrew J Pollard

UKCRC Registered Clinical Trials Units
NHS National Institute for Health Research
Oxford Biomedical Research Centre

oxford vaccine group
www.ovg.ox.ac.uk

Why use a human challenge model to investigate the early response?

UNIVERSITY OF OXFORD

Advantages over field studies

- Pre-symptomatic
- Control over dose, strain, time
- Allows comparison to those exposed who do not develop disease

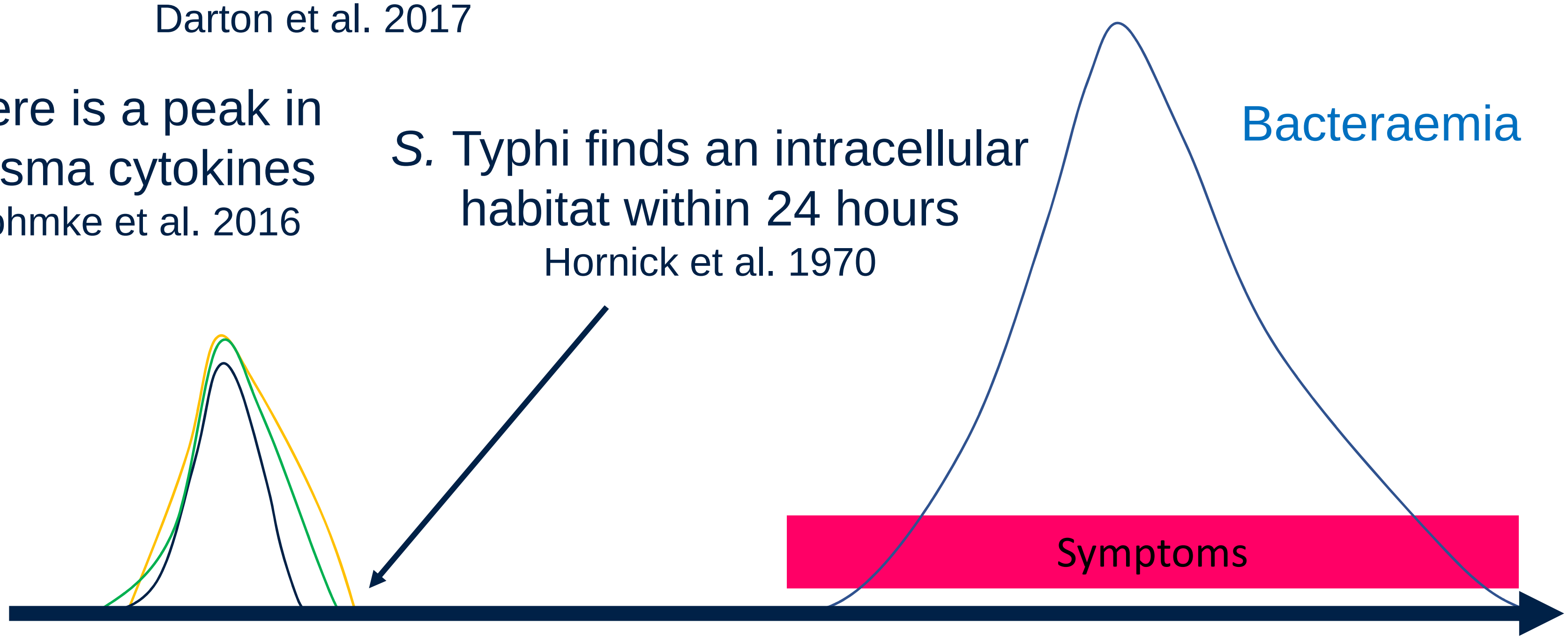
Advantages over mouse models

- *S.* Typhi rather than *S.* Typhimurium
- Biological variation in the host

oxford vaccine group
www.ovg.ox.ac.uk

UNIVERSITY OF OXFORD

What have human challenge models taught us so far?



S. Typhi DNA can be detected in the blood
Darton et al. 2017

There is a peak in plasma cytokines
Blohmke et al. 2016

S. Typhi finds an intracellular habitat within 24 hours
Hornick et al. 1970

Bacteraemia

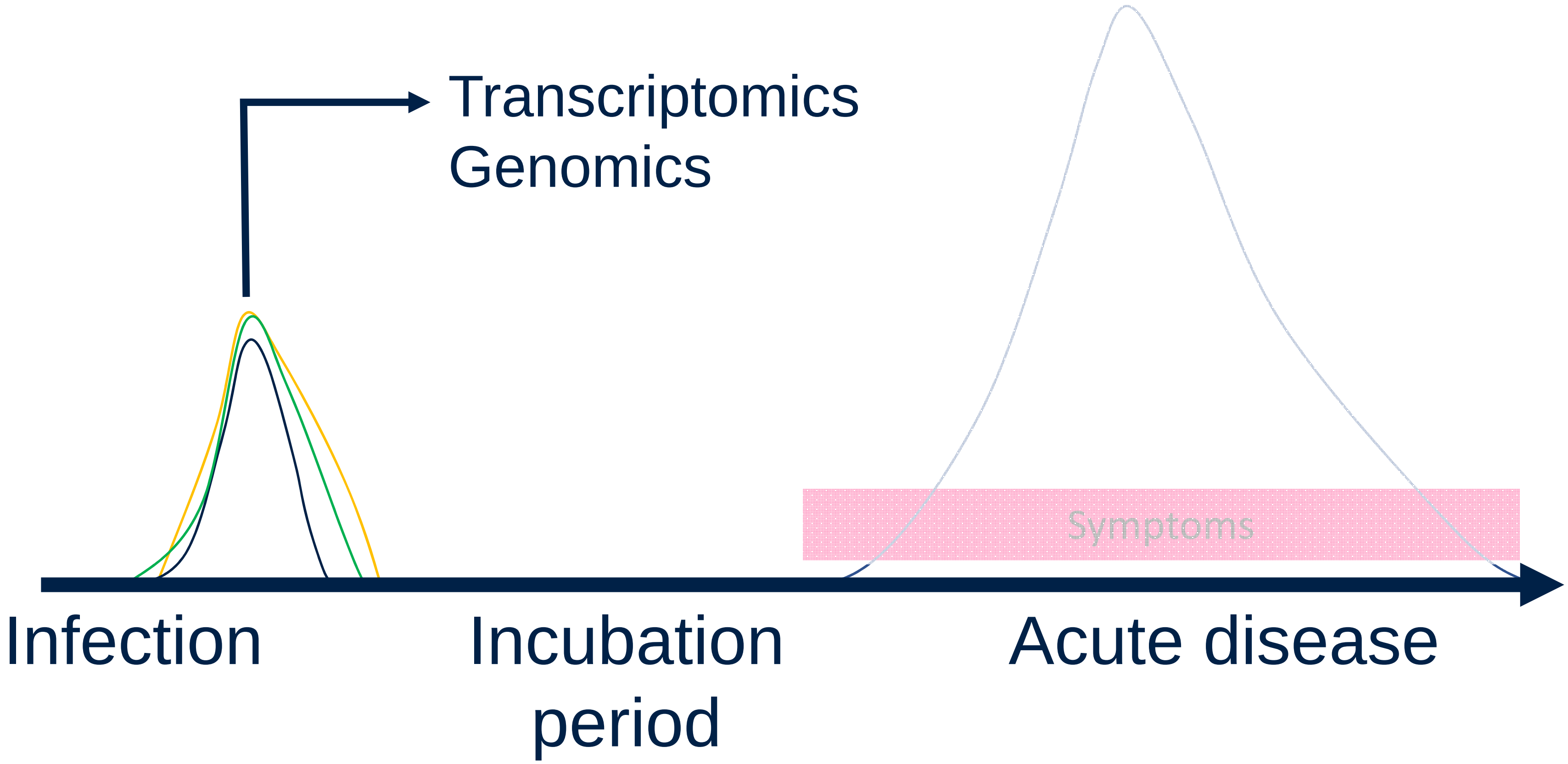
Symptoms

Infection

Incubation period

Acute disease

What have human challenge models taught us so far?



Transcriptomics
Genomics

Infection

Incubation period

Acute disease

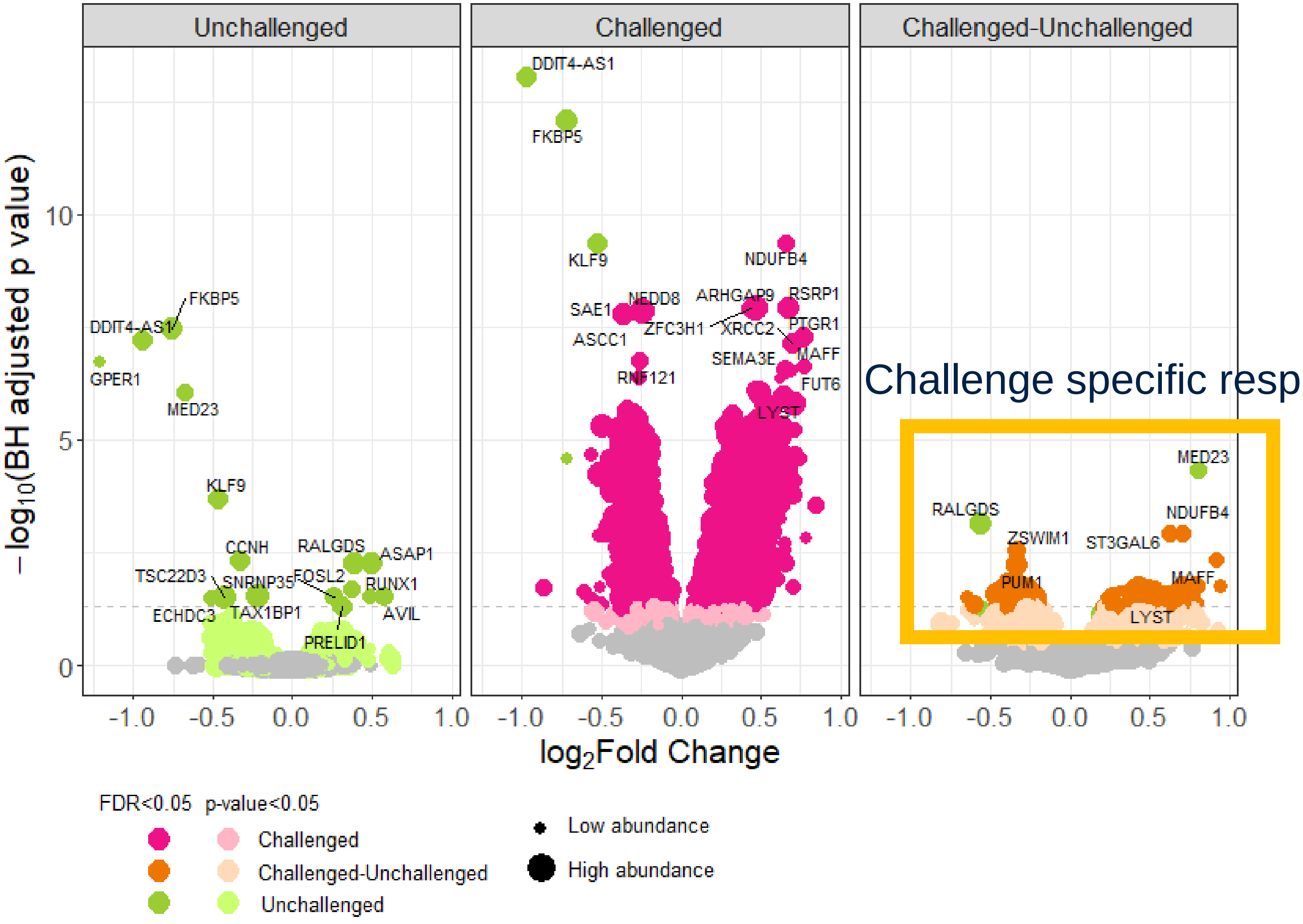
Cohorts

	Discovery			**Validation**	
Cohorts	Typhoid dose escalation study	Typhoid oral vaccine trial (placebo group)	Circadian rhythms study	Paratyphoid dose de-escalation study	Typhoid Vi vaccine trial
Baseline & 12 hour transcriptomics	Microarray	Microarray	Microarray	RNA-seq	RNA-seq
24 hour transcriptomics	Microarray				
Genotyping	Microarray	Microarray			

oxford vaccine group
www.ovg.ox.ac.uk

The human blood transcriptome is perturbed 12 hours post-challenge

UNIVERSITY OF
OXFORD



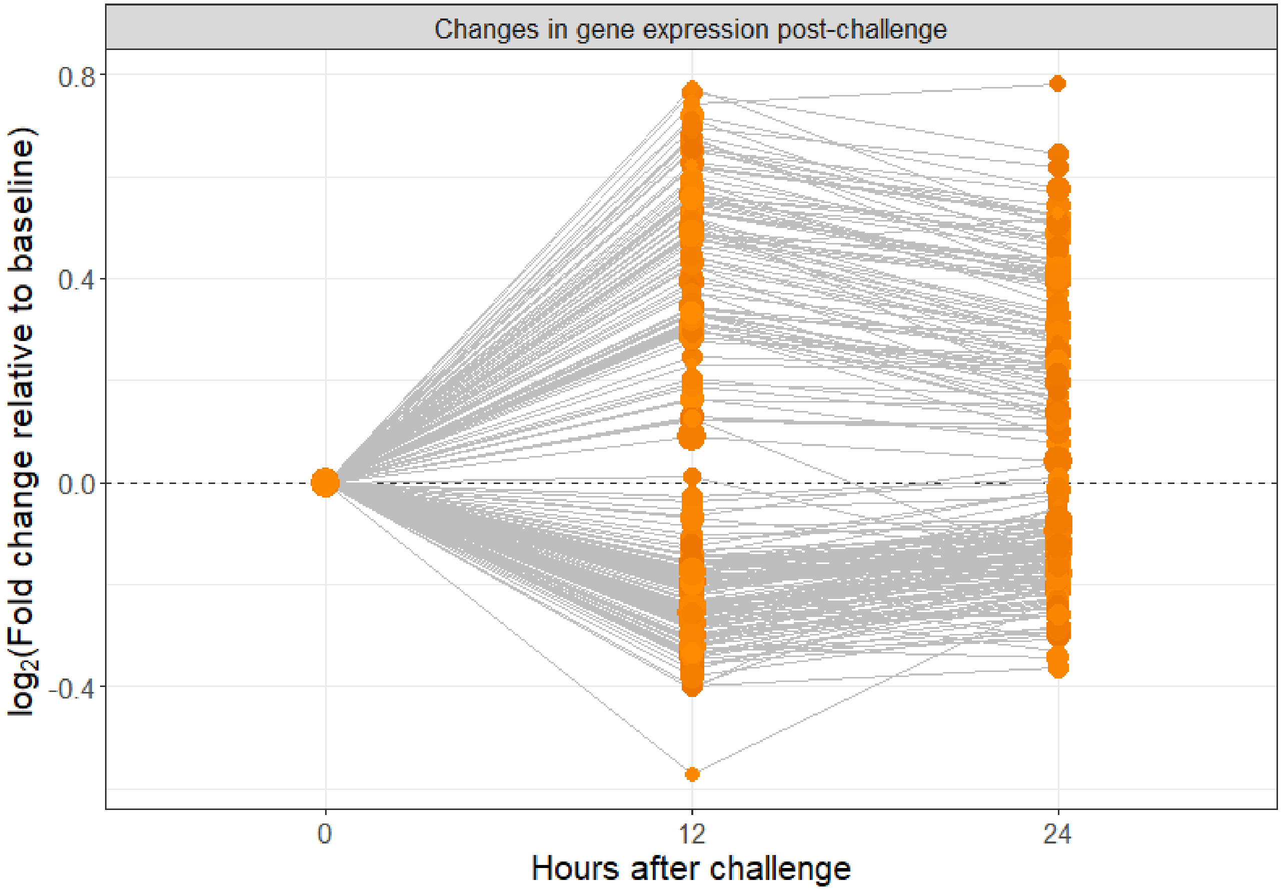
Challenge specific response

Top 10 Challenge-specific genes

HGNC Symbol	Function	Log_2Fold Change		FDR adjusted p-value
		Challenged	Unchallenged	
Upregulated				
MED23	Required for SP1 activation	0.12	-0.68	0.00005
ST3GAL6	Sialyltransferase involved in formation of selectin ligands and CD15	0.38	-0.25	0.001
NDUFB4	Subunit of NADH:ubiquinone oxidoreductase	0.65	-0.05	0.001
MAFF	Basic leucine zipper transcription factor involved in stress response	0.78	-0.14	0.005
PTGR1	Inactivation of chemotactic factor leukotriene B4	0.78	-0.02	0.02
Downregulated				
RALGDS	Guanine nucleotide dissociation stimulator	-0.18	0.39	0.0007
ZSWIM1	Unknown	-0.16	0.18	0.003
PUM1	Translational regulator	-0.21	0.13	0.006
TRAF3IP2	NF-kB activator	-0.29	0.11	0.01
ALKBH5	RNA demethylase	-0.24	0.08	0.02

www.ovg.ox.ac.uk

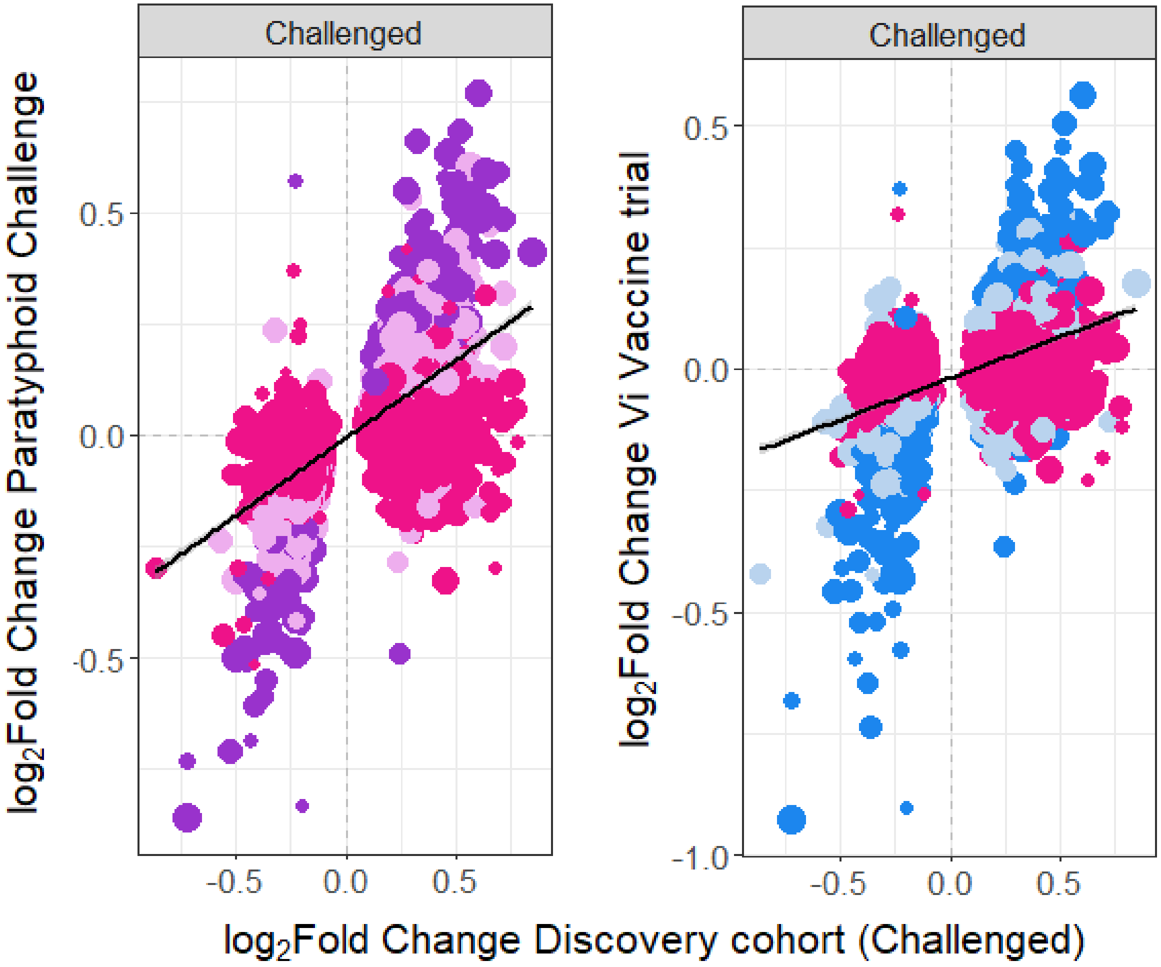
After 24 hours gene expression is on its way back to baseline



oxford vaccine group
www.ovg.ox.ac.uk

Changes in gene expression were validated by RNA-sequencing in two independent cohorts

UNIVERSITY OF
OXFORD



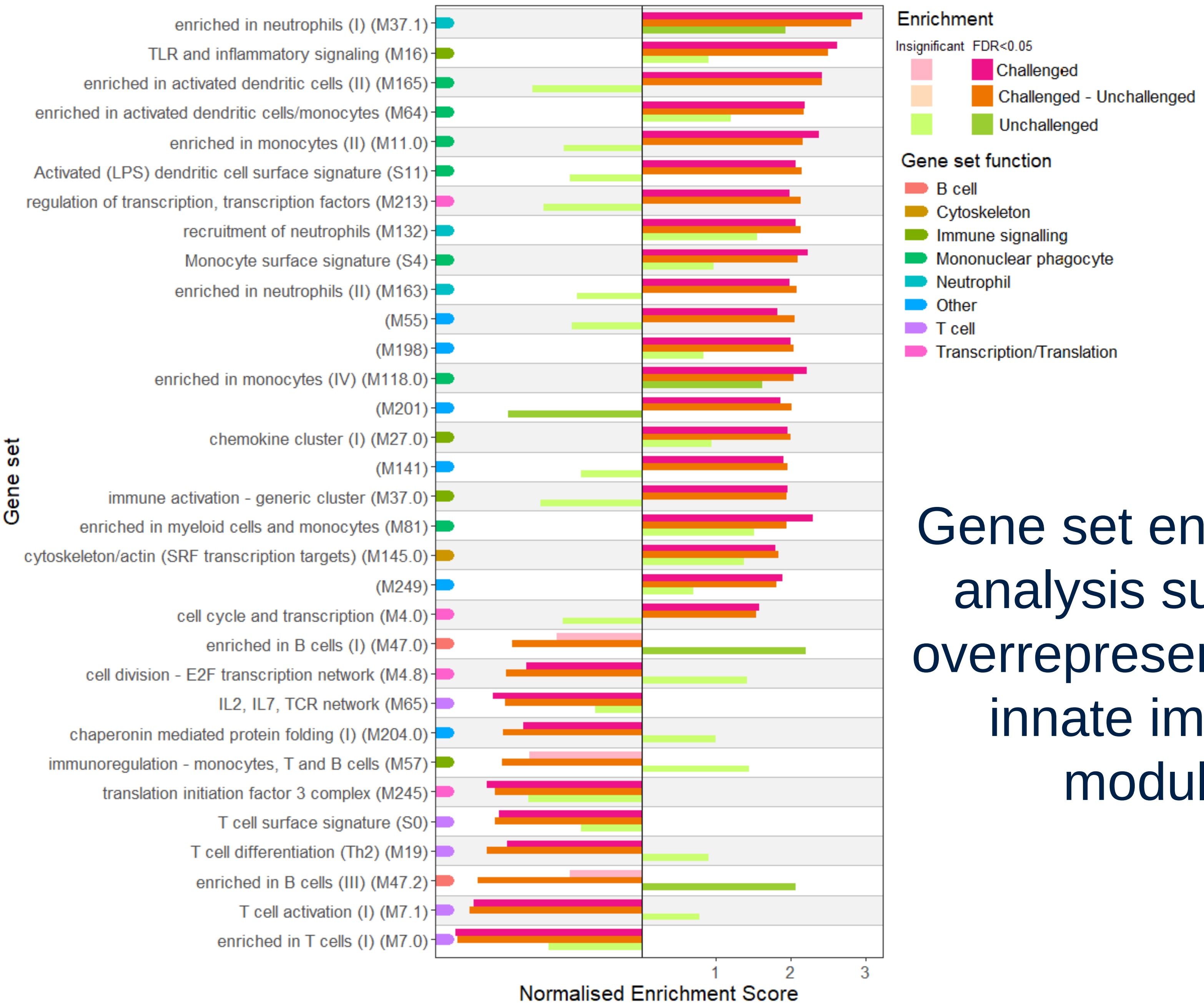
- ● Low abundance
- ● High abundance

FDR<0.05	p-value<0.05		
●	●	Paratyphoid challenge	Differentially expressed in both discovery and validation cohort
●	●	Vi Vaccine Trial	

● Differentially expressed (FDR < 0.05) in discovery cohort only

Cohort	Cut-off	Statistic	Challenged
Paratyphoid challenge	None	R	0.65
		p-value	0.00
		Same direction	85%
	FDR<0.05	R	0.91
		p-value	0.00
		Same direction	99%
Vi vaccine trial	None	R	0.47
		p-value	0.00
		Same direction	71%
	FDR<0.05	R	0.85
		p-value	0.00
		Same direction	97%

UNIVERSITY OF OXFORD



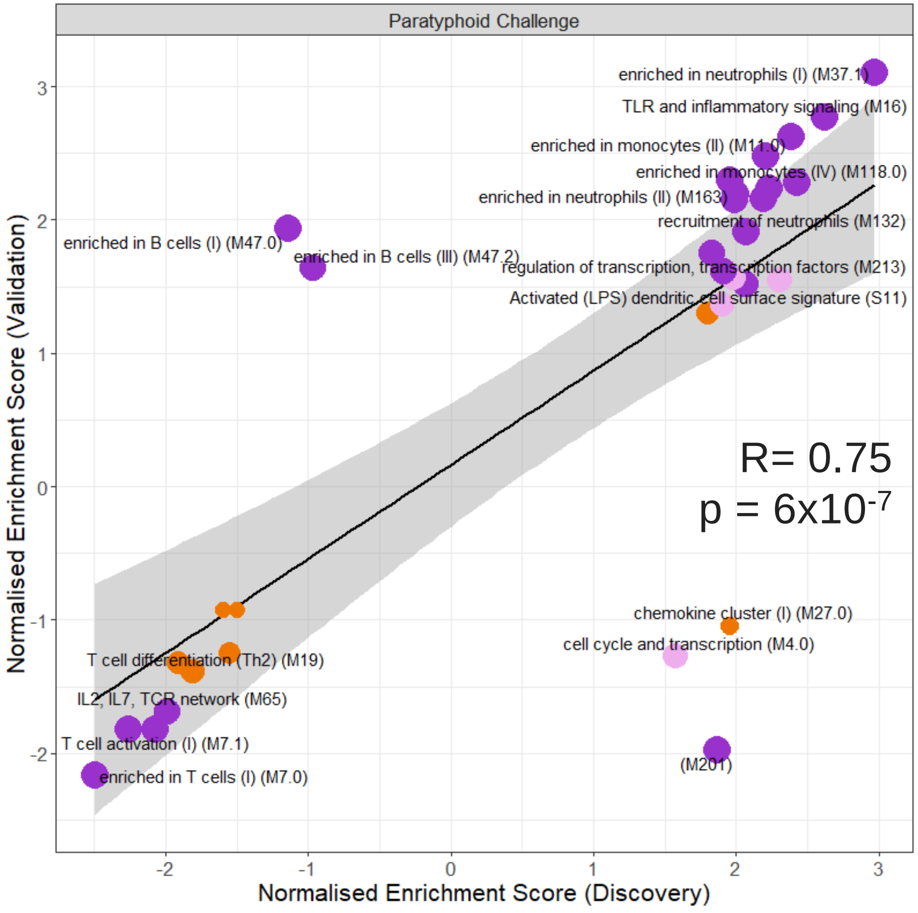
Gene set enrichment analysis suggests overrepresentation of innate immune modules

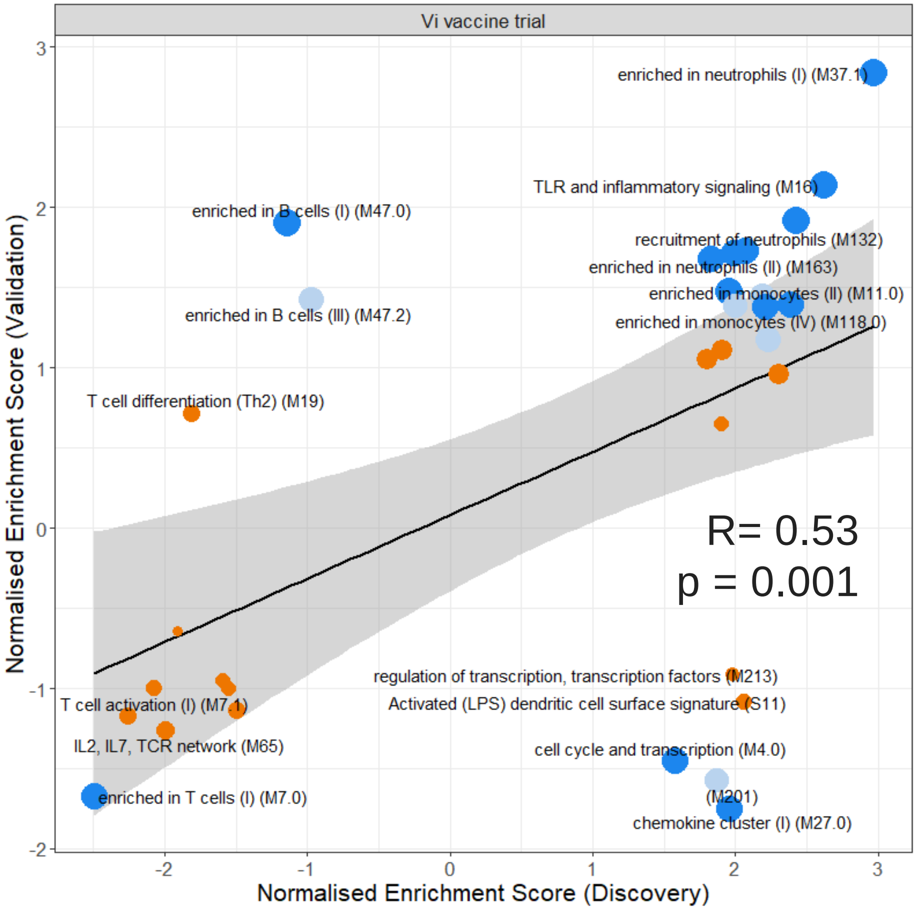
oxford vaccine group

www.ovg.ox.ac.uk

Gene set enrichment analysis suggests overrepresentation of innate immune modules

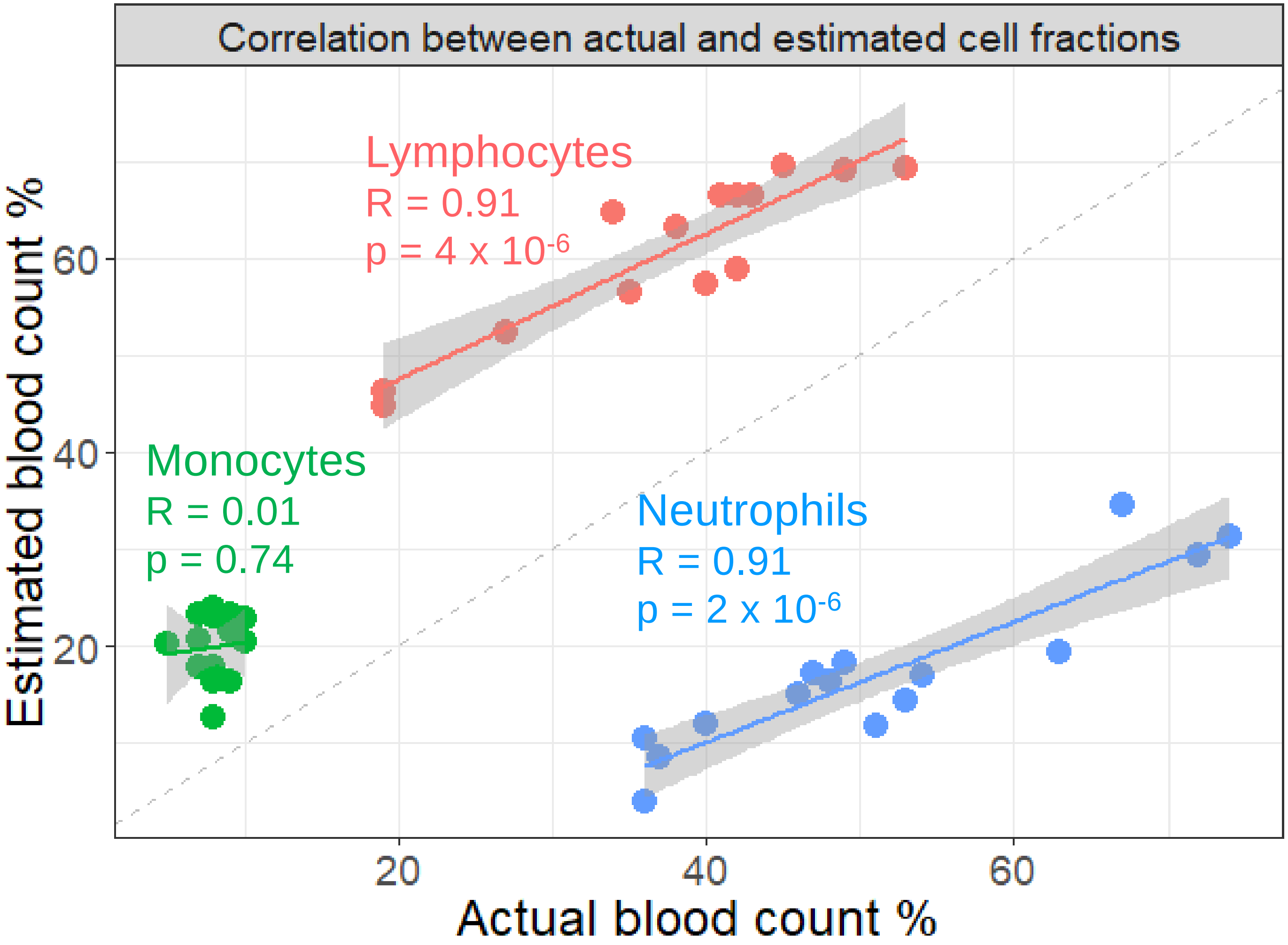
UNIVERSITY OF OXFORD





www.ovg.ox.ac.uk

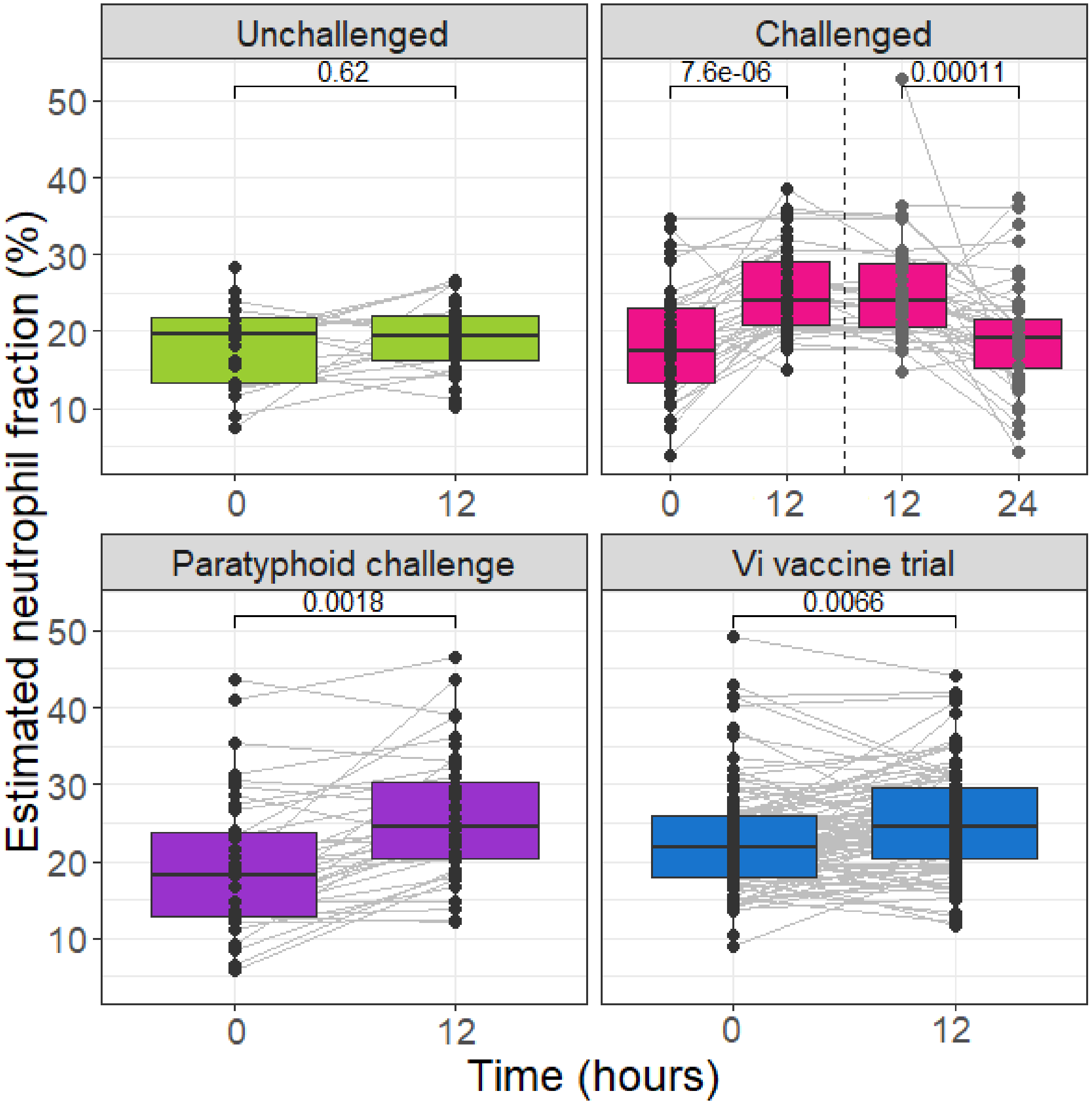
CIBERSORT-estimated immune cell fractions correlate well with differential blood counts



www.ovg.ox.ac.uk

Estimated neutrophil counts are raised 12 hours post-challenge

UNIVERSITY OF OXFORD



www.ovg.ox.ac.uk

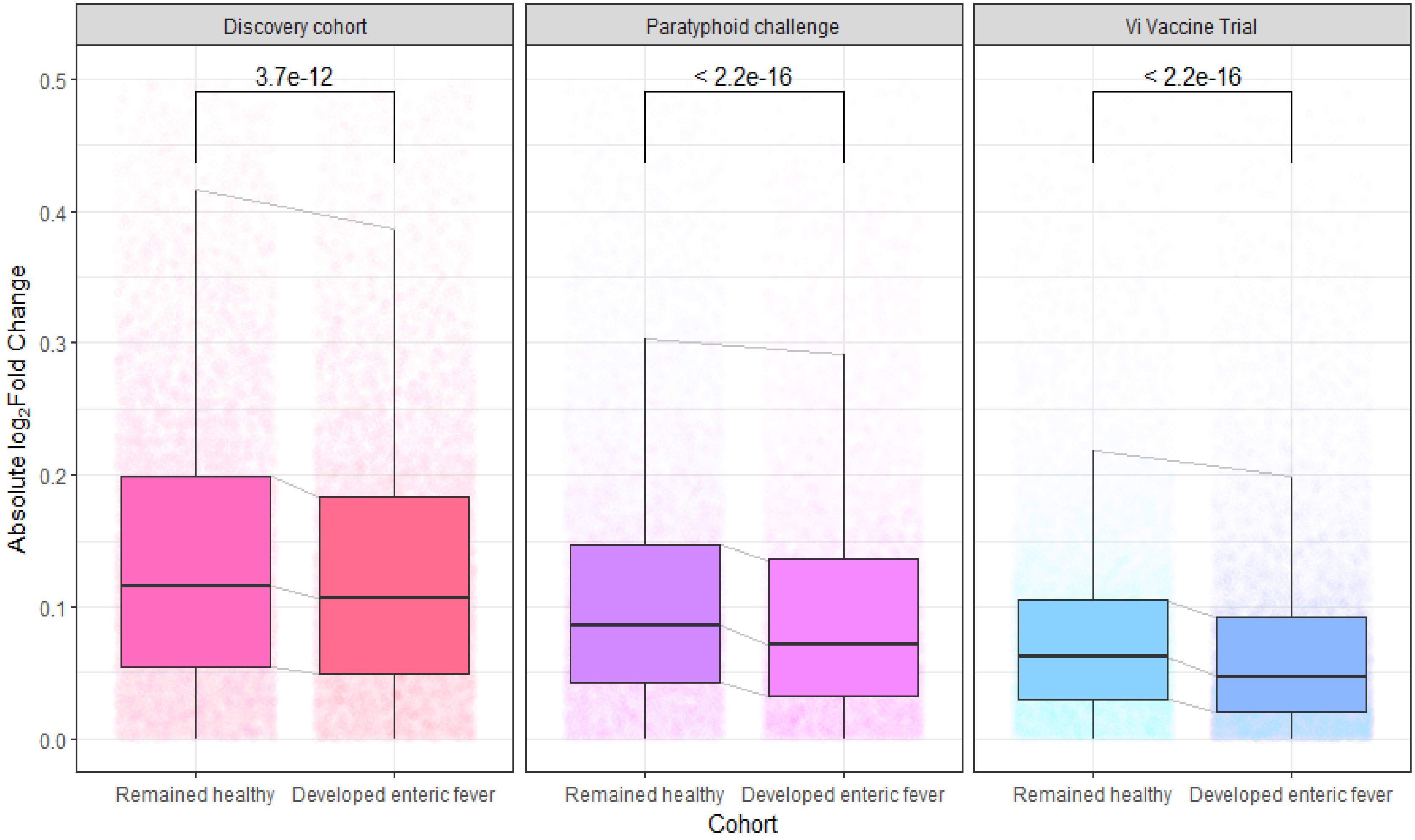
Responses are very similar between those who do and do not go on to develop enteric fever

oxford vaccine group

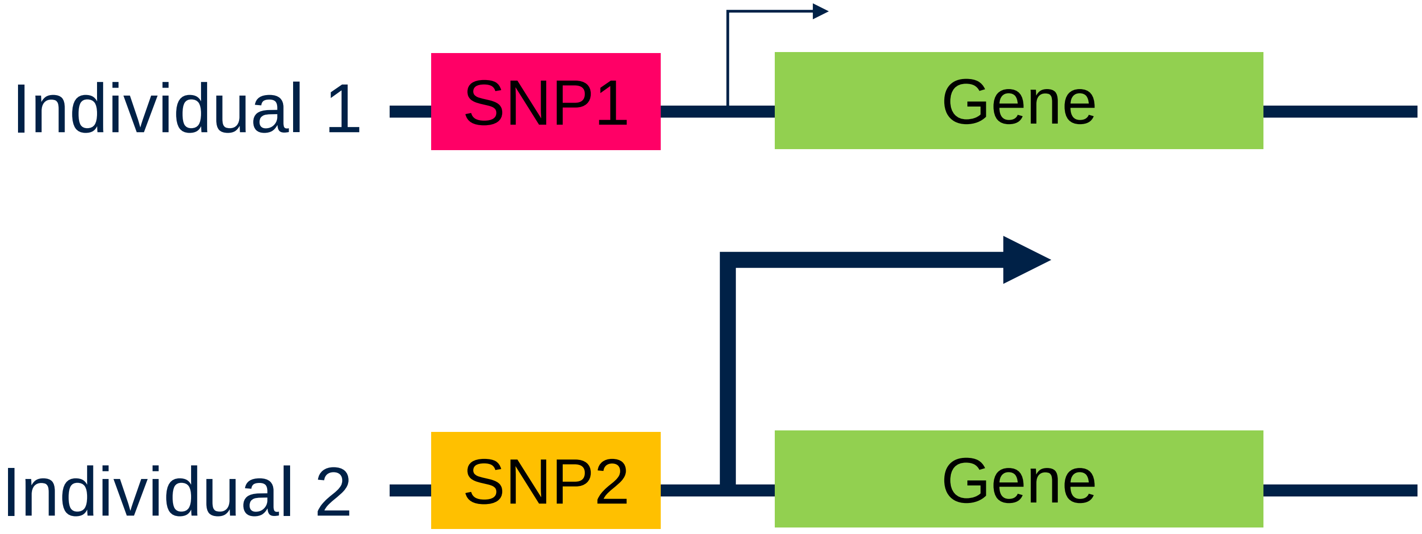
www.ovg.ox.ac.uk

Those who do not develop enteric fever have greater transcriptome perturbation

UNIVERSITY OF OXFORD



Does genetic variation affect how we respond to *S.* Typhi?



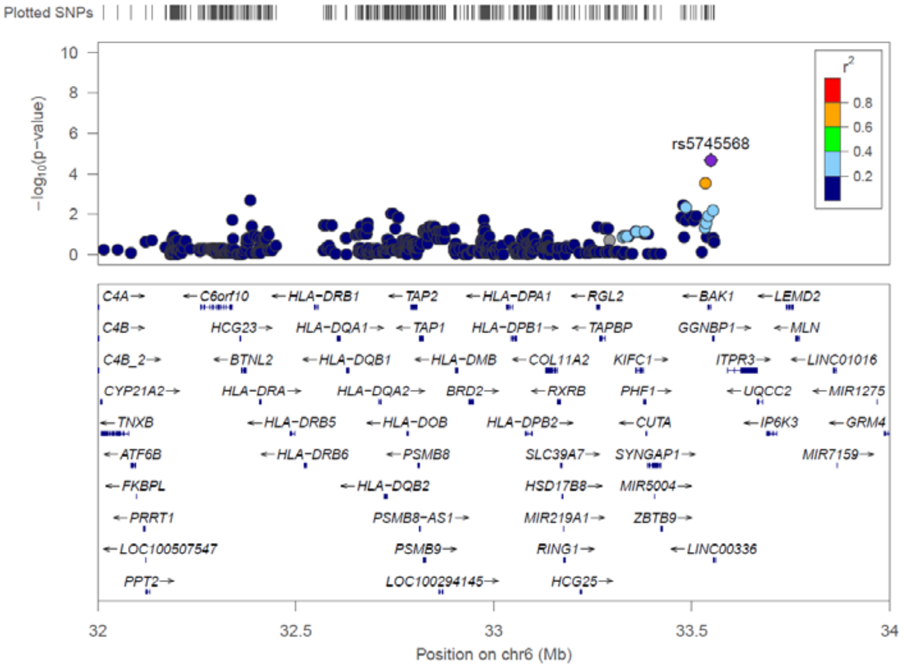
cis-eQTLs

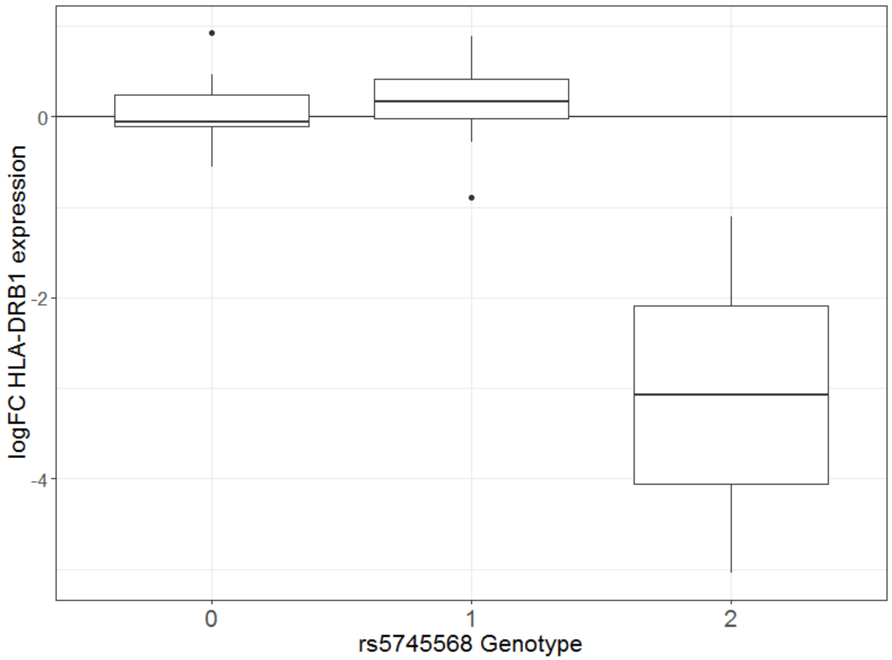
oxford vaccine group

www.ovg.ox.ac.uk

The most significant eQTLs for early changes in expression after typhoid challenge are in the HLA region

UNIVERSITY OF OXFORD



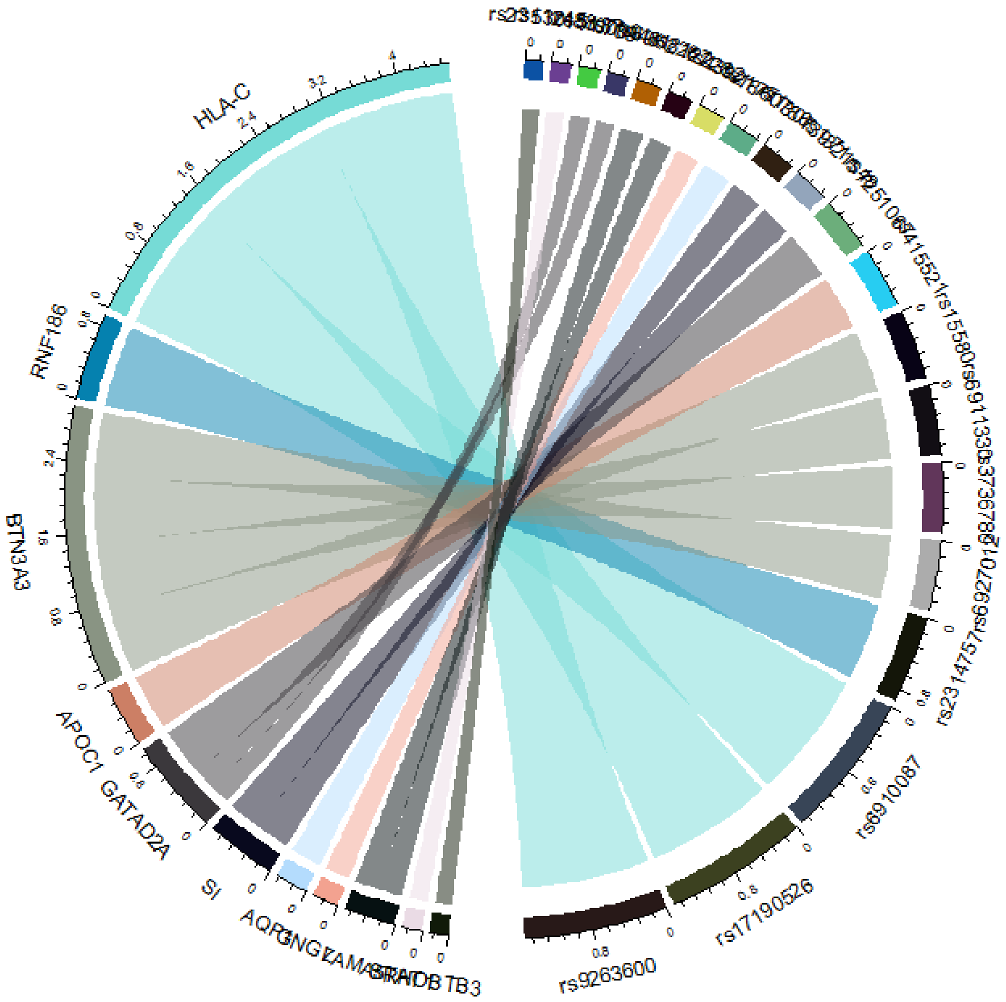


HLA-DRB1

www.ovg.ox.ac.uk

The most significant eQTLs for early changes in expression after typhoid challenge are in the HLA region

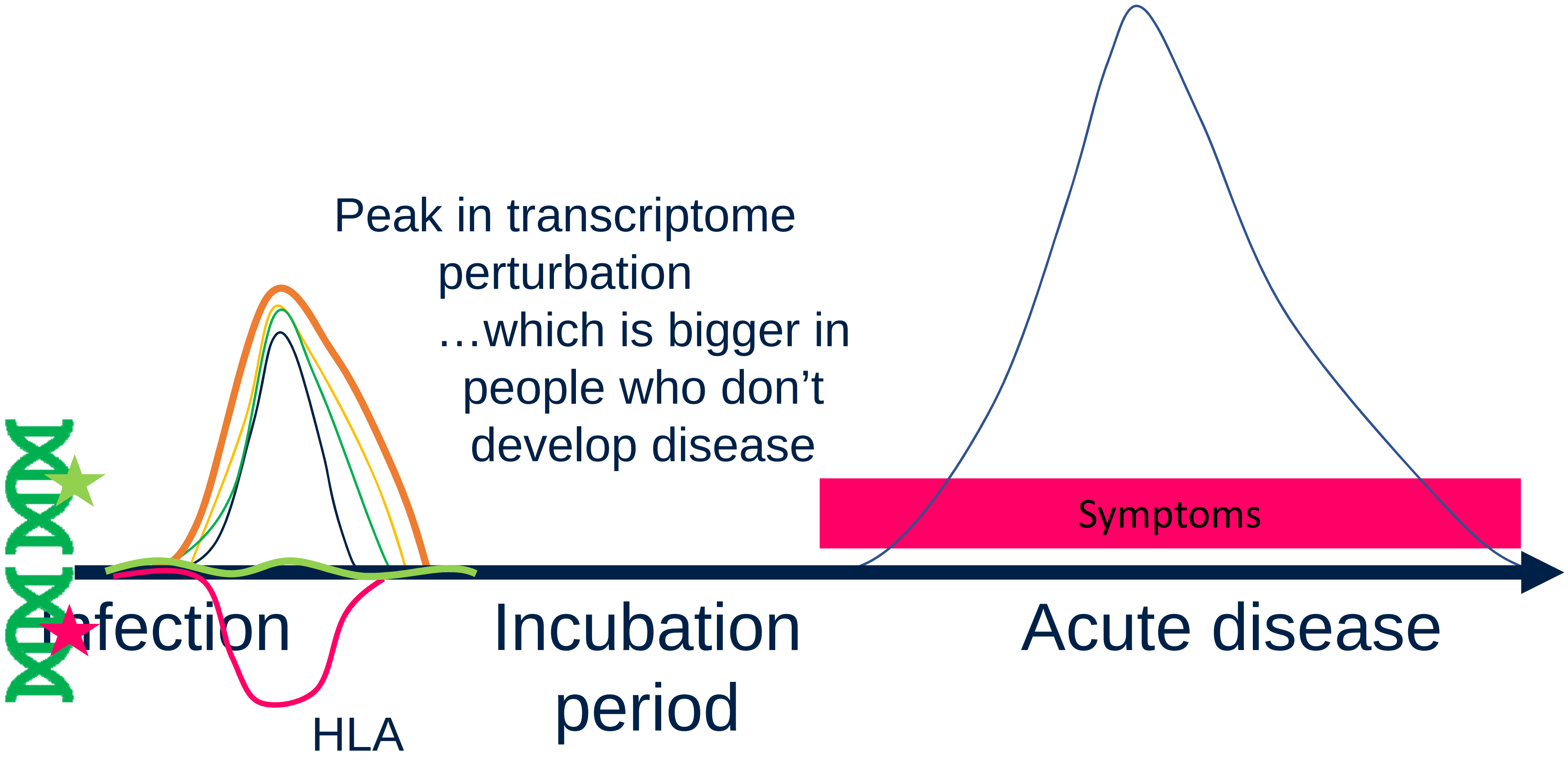
Genes



SNPs

Wider = smaller
p-value

Summary



Peak in transcriptome perturbation …which is bigger in people who don’t develop disease

oxford vaccine group

www.ovg.ox.ac.uk

Thank you!

UNIVERSITY OF OXFORD

OVG Enteric team

Andy Pollard
Jenny Hill
Christoph Blohmke
Malick Gibani
Helena Thomaides-Brears
Lizzy Jones
Celina Jin

OVG Bioinformatics team

Daniel O’Connor
Irina Mohorianu