



Post Tuberculosis Lung Disease: Epigenetics of Persistent Lung Damage Despite Successful RHZE

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New Directions in TB

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Andrew R. DiNardo, MD, PhD has the following disclosures to make:


- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity



Epigenetics of persistent lung damage despite successful RHZE

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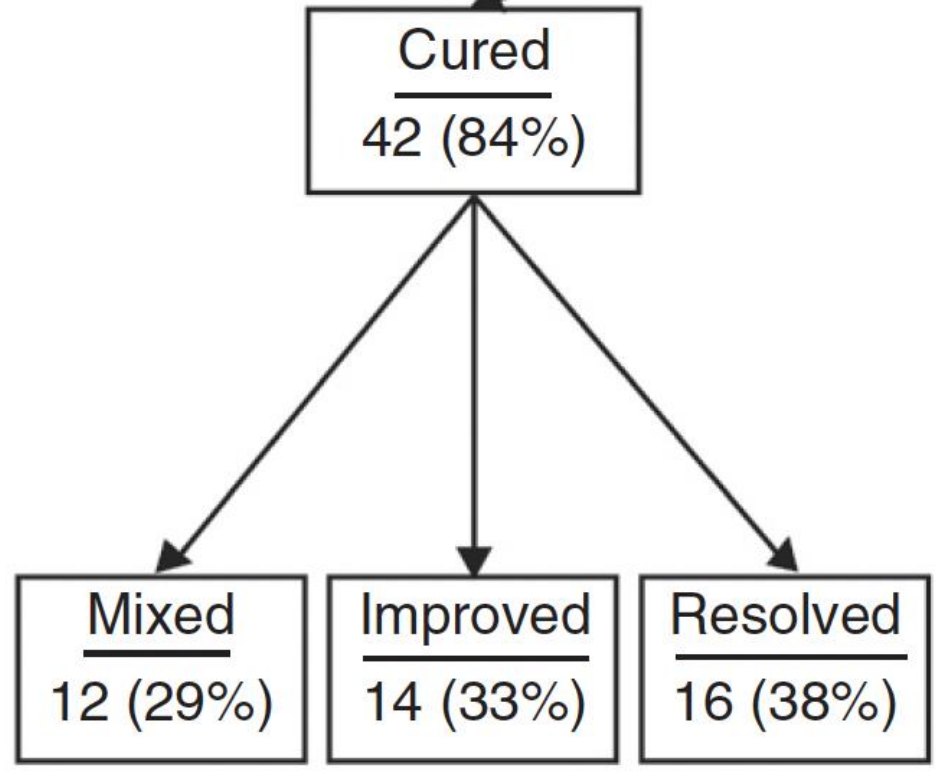


Even with "cure," some TB patients have worsening lung function despite successful RHZE Abxs

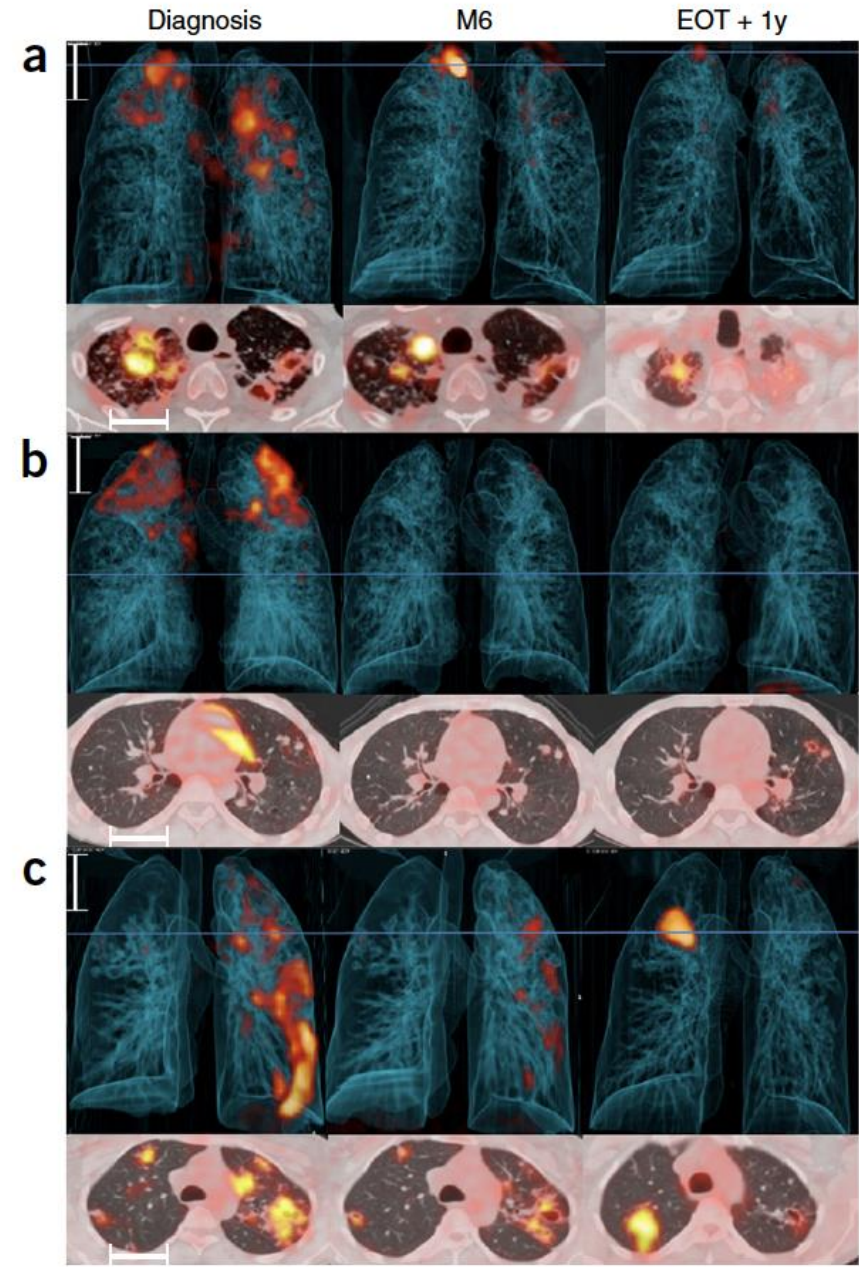
Why?

Persisting positron emission tomography lesion activity and *Mycobacterium tuberculosis* mRNA after tuberculosis cure

Stephanus T Malherbe^{1,2}, Shubhada Shenai³, Katharina Ronacher^{1,2}, Andre G Loxton^{1,2}, Gregory Dolganov⁴, Magdalena Kriel^{1,2}, Tran Van⁴, Ray Y Chen⁵, James Warwick^{6,7}, Laura E Via^{5,8}, Taeksun Song⁹, Myungsun Lee⁹, Gary Schoolnik⁴, Gerard Tromp^{1,2}, David Alland³, Clifton E Barry III^{1,2,5,8}, Jill Winter¹⁰, Gerhard Walzl^{1,2}, the Catalysis TB-Biomarker Consortium¹⁵

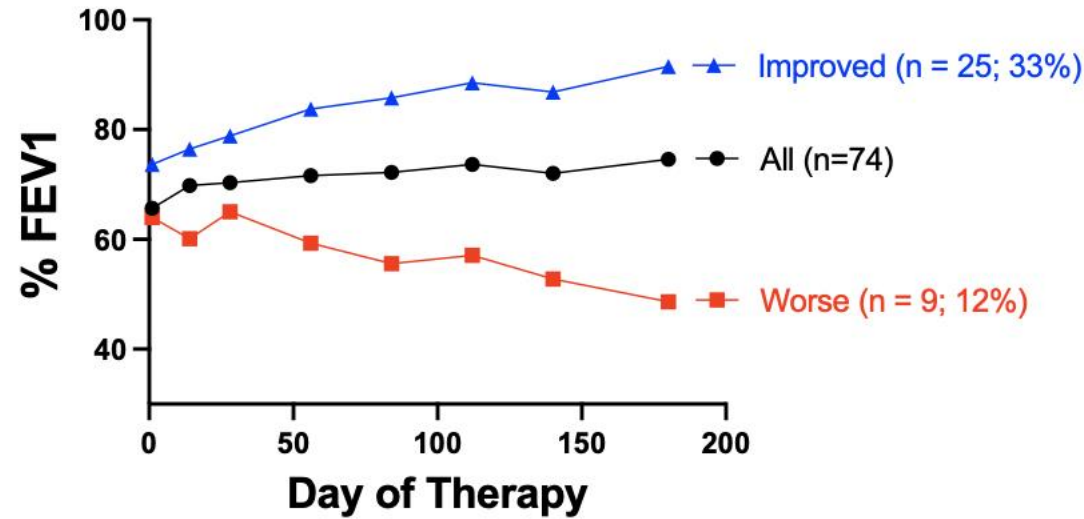
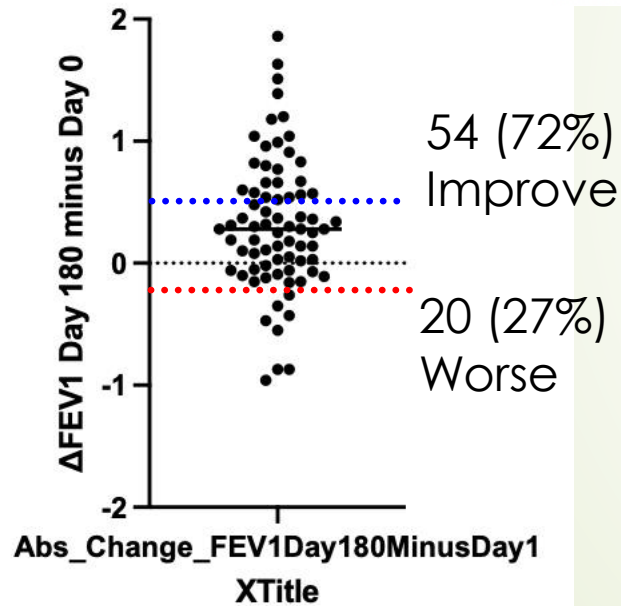
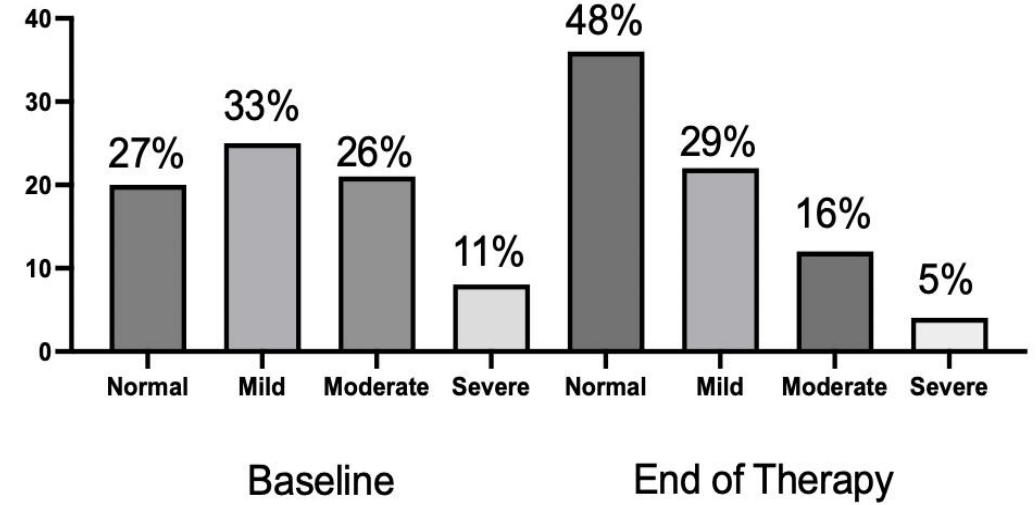
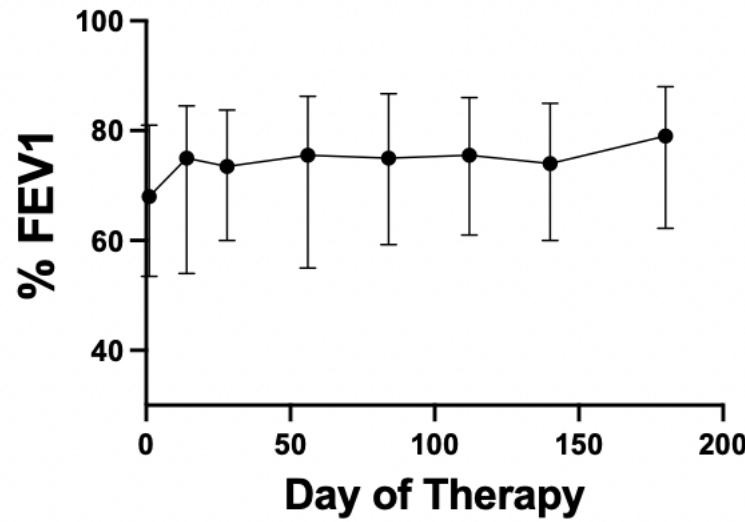
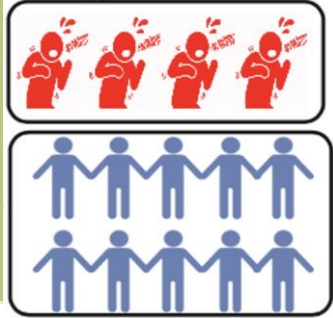


Heterogenous inflammatory response despite cure



Cohort: micro+ pulm

n= 74



>10% FEV1 gain
And pFEV1 >70% EOT

>10% FEV1 loss
And pFEV1 <70% EOT



Compare DNA methylation changes

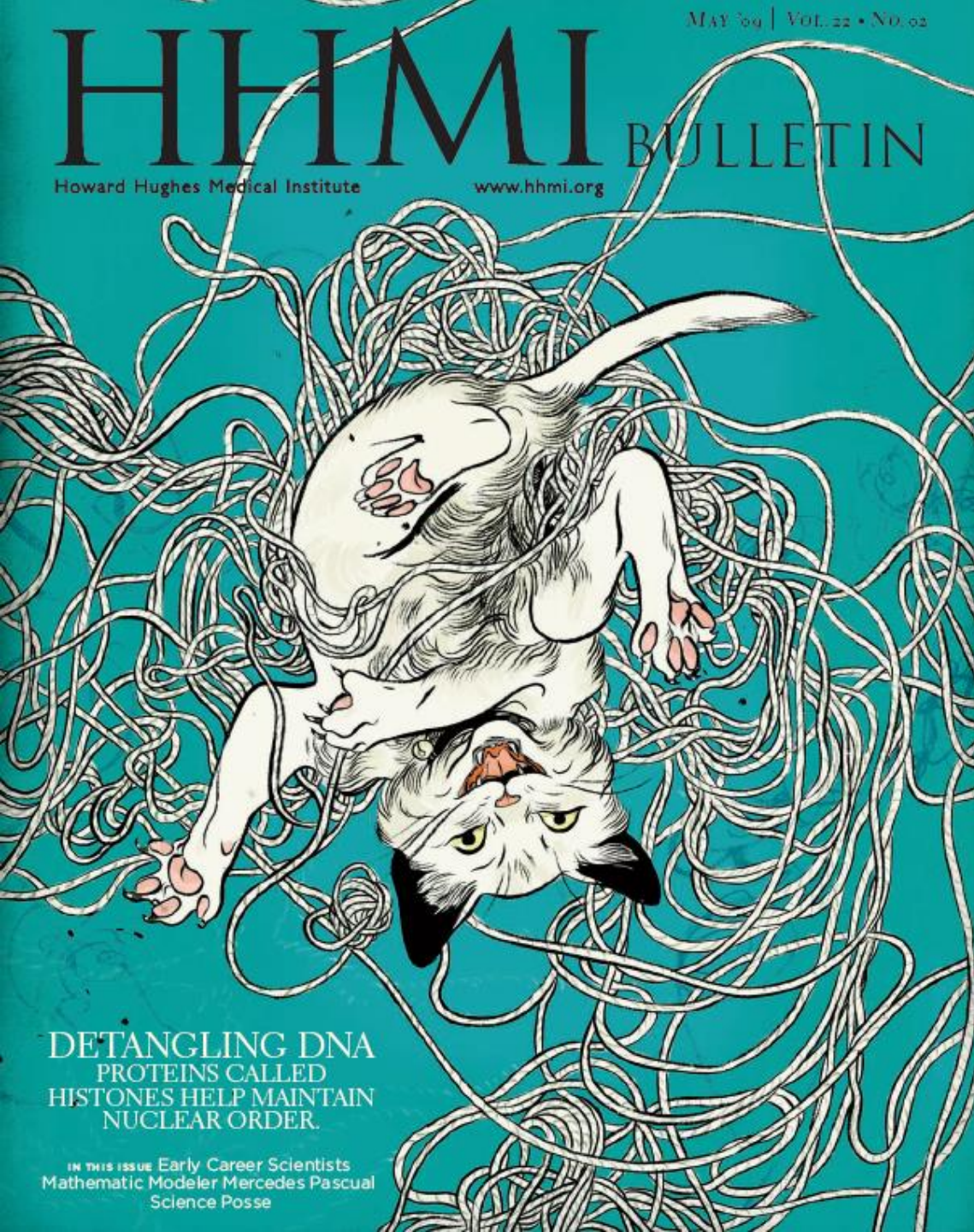


Why do some people improve lung fxn while others worsen?

What is the DNAm status of those who improve compare to those who worsen?

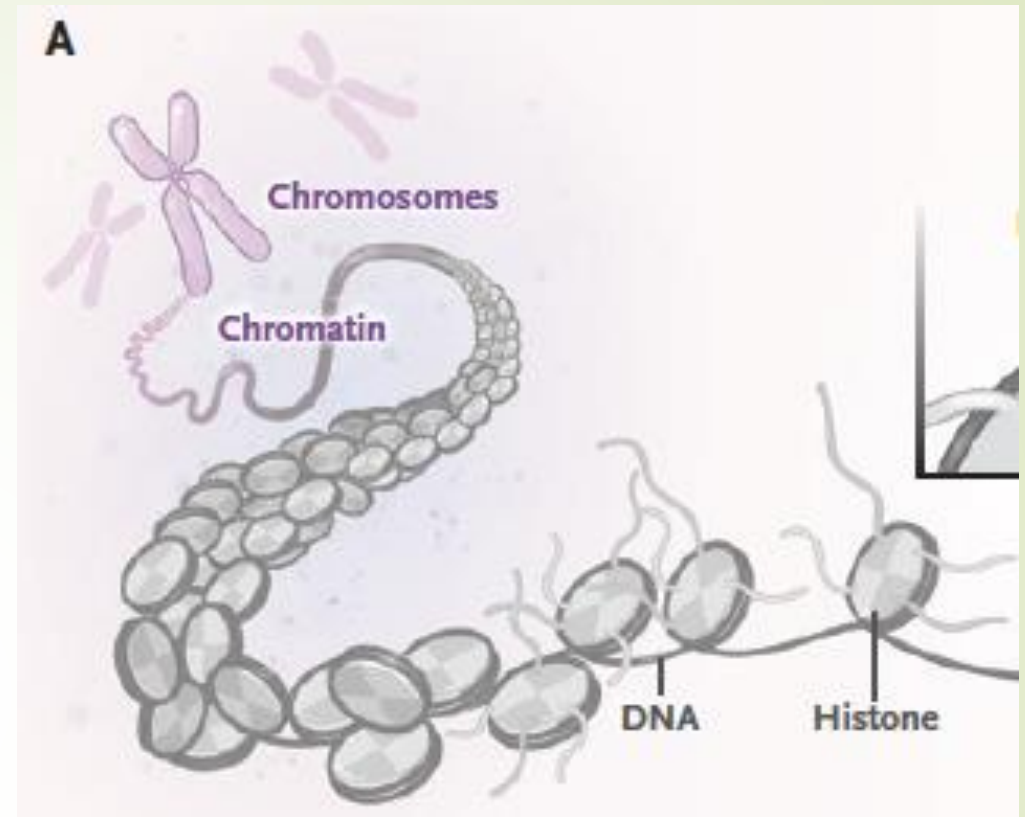


What is DNA methylation and epigenetics?



DETANGLING DNA
PROTEINS CALLED
HISTONES HELP MAINTAIN
NUCLEAR ORDER.

IN THIS ISSUE Early Career Scientists
Mathematic Modeler Mercedes Pascual
Science Posse

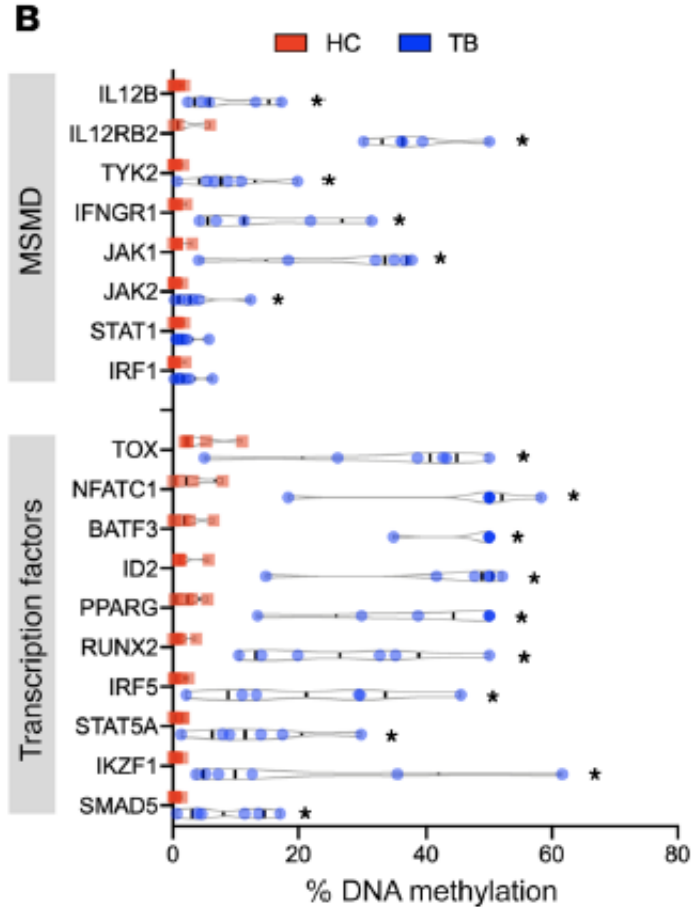
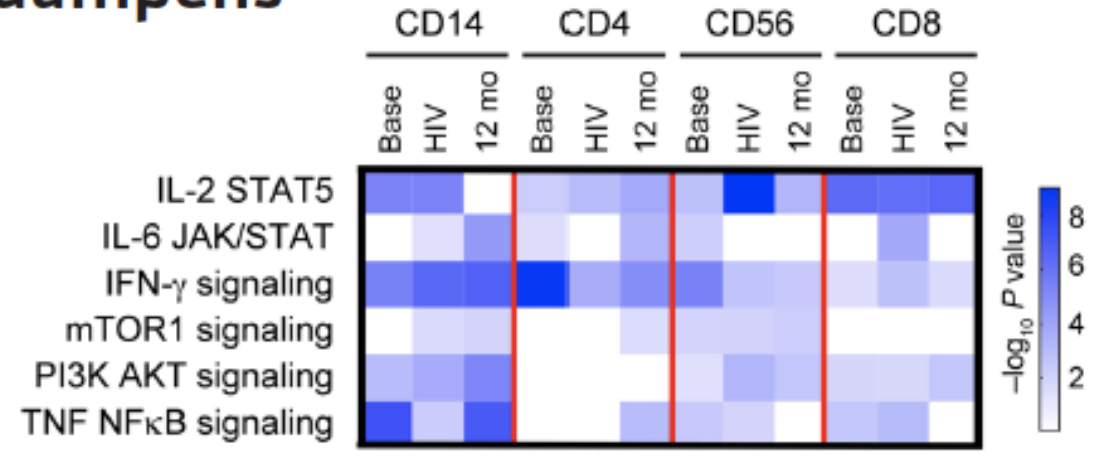
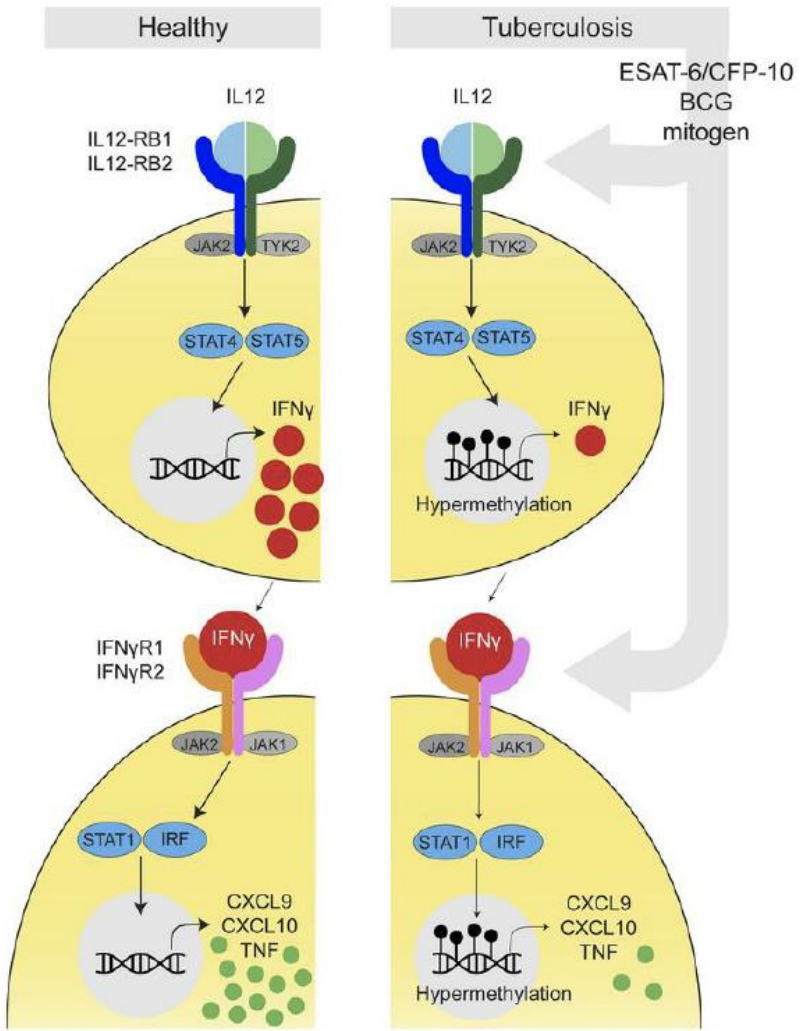


Every cell contains 2 meters of DNA...

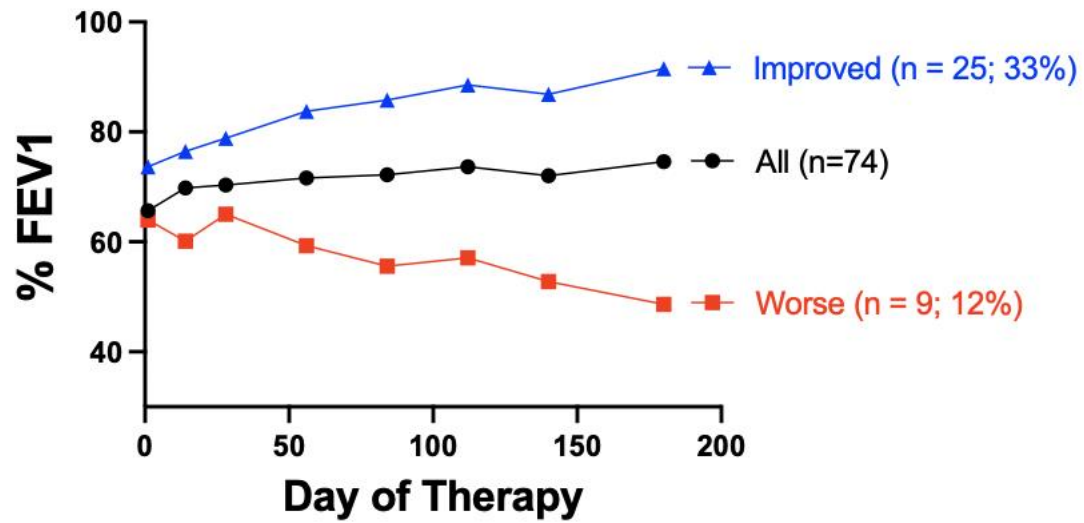
How that “ball of yarn” is coiled determines accessibility

DNA methylation: “hides” genes inside the ball of yarn, thereby silencing the genes

DNA hypermethylation during tuberculosis dampens host immune responsiveness

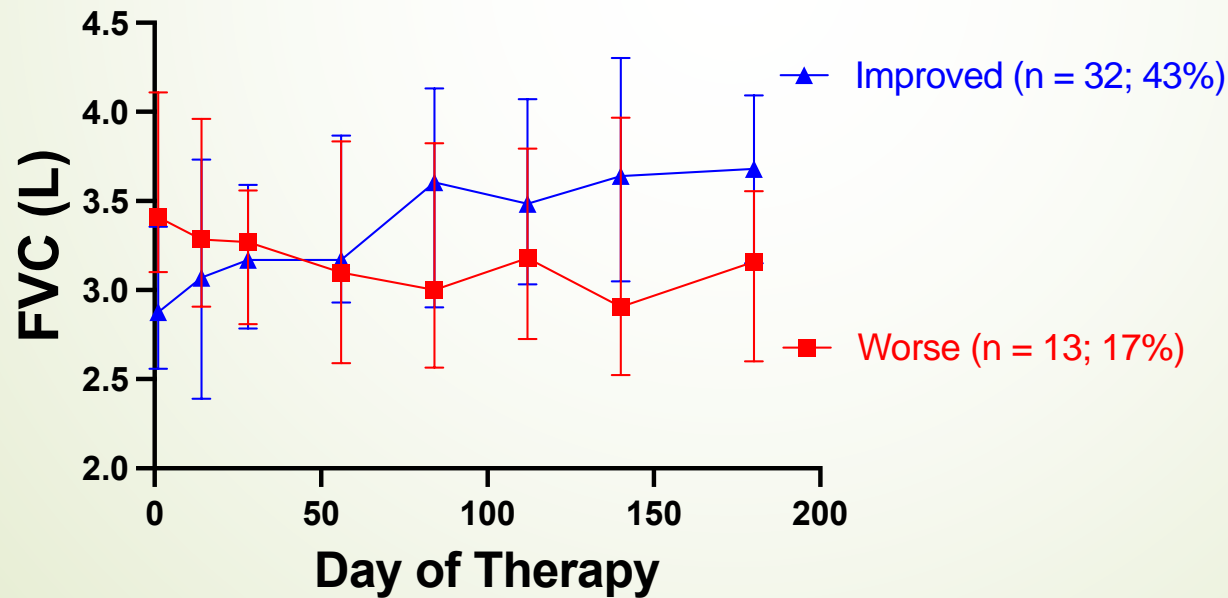


What are the clinical effects of persistent post-TB DNA methylation perturbations?



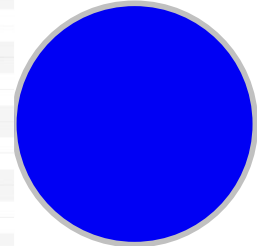
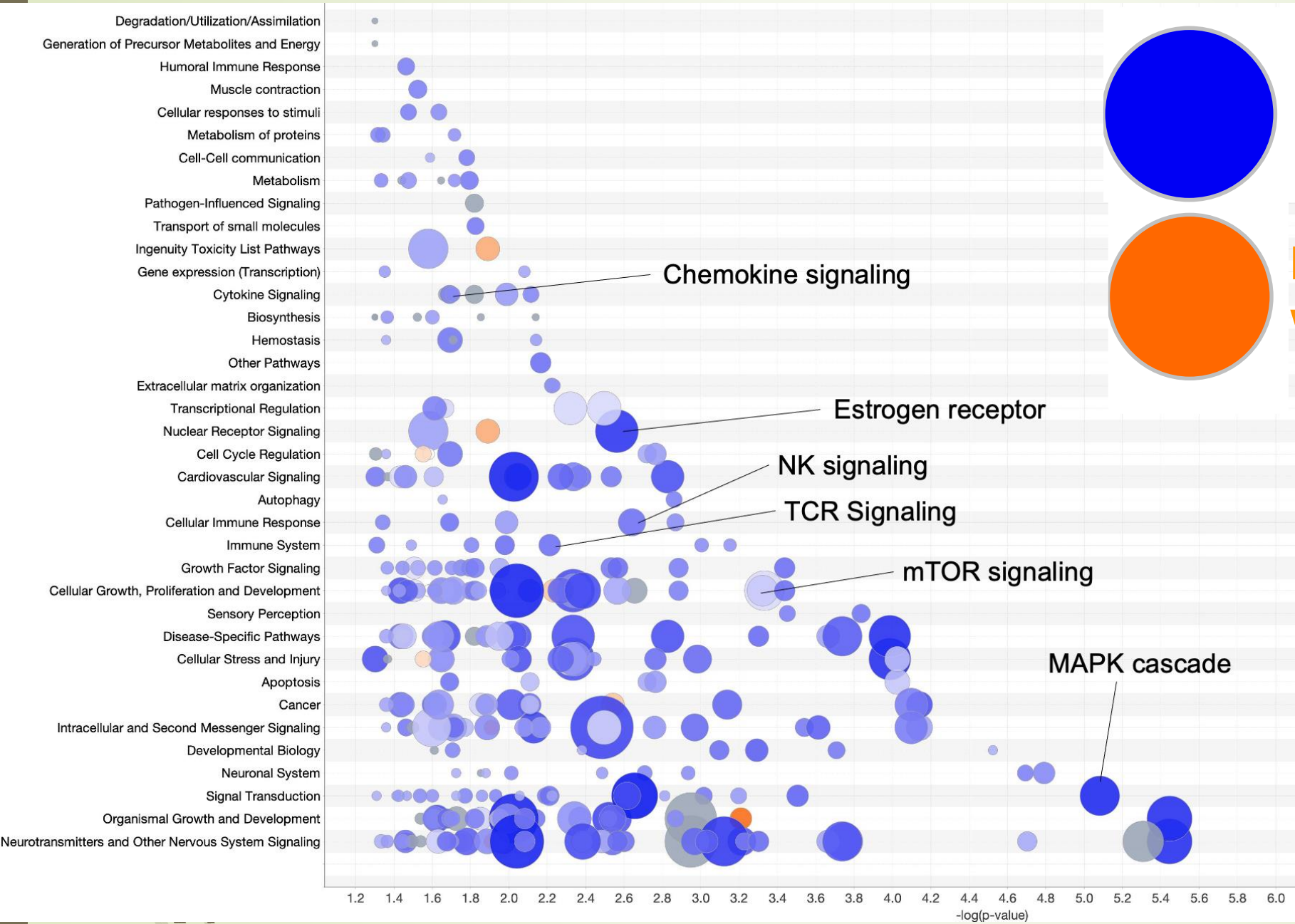
Can epigenetics tell us why some people improve and others worsen?

FVC_overtime_by ClassChange_Worse vs better

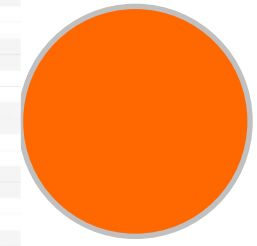


*10% cut-off threshold

Improving FEV1 assoc. DNA hyper-methylation

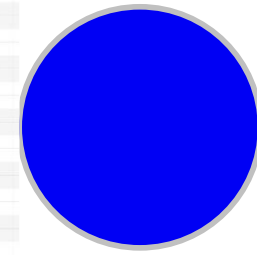
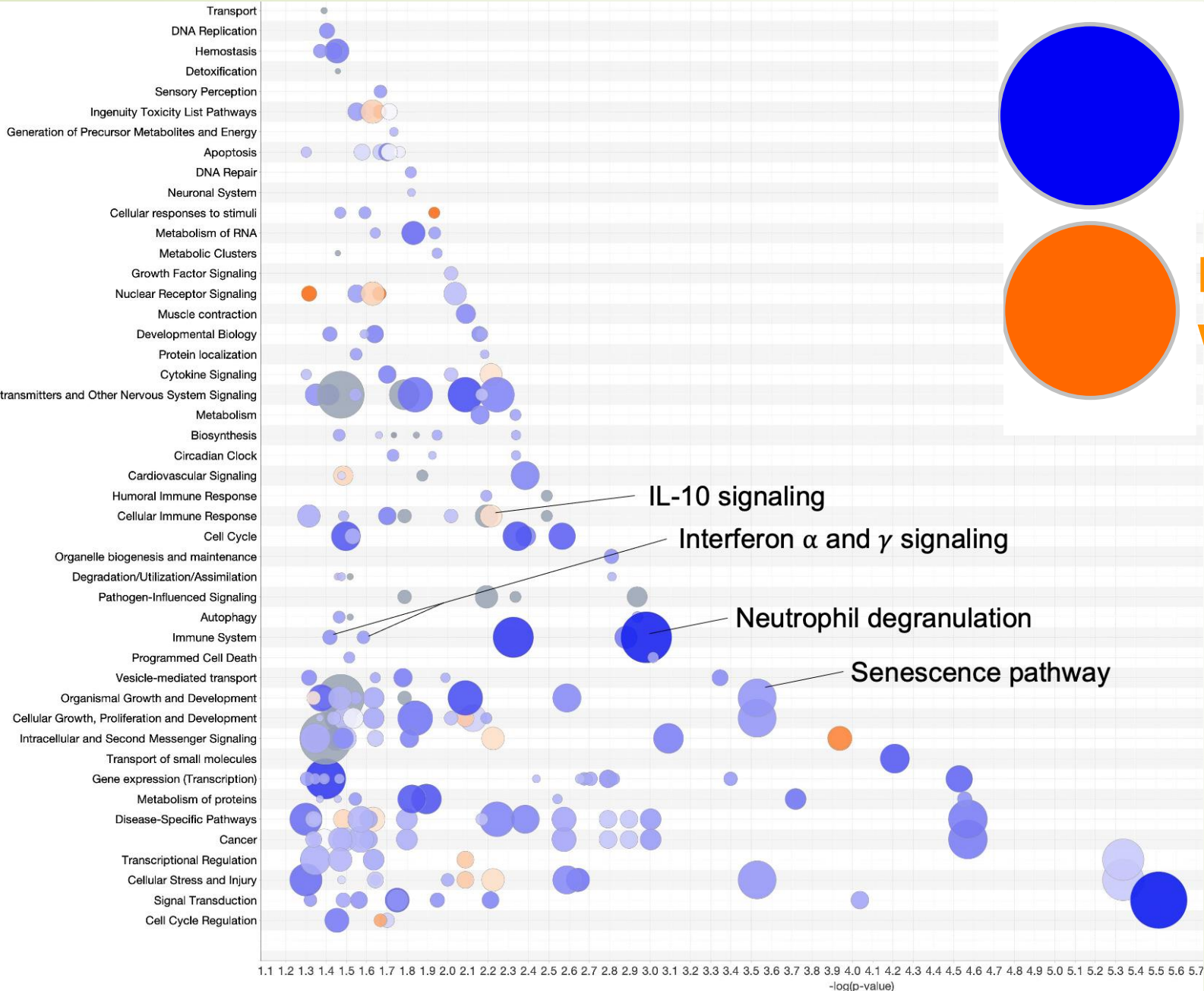


Hypermethylated in improved FEV1

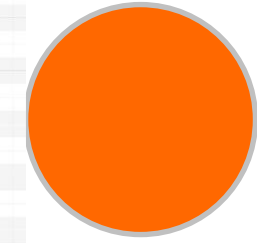


Hypomethylated in worsening FEV1

Improving FVC assoc. DNA hyper-methylation



Hypermethylated in improved FEV1



Hypomethylated in worsened FEV1



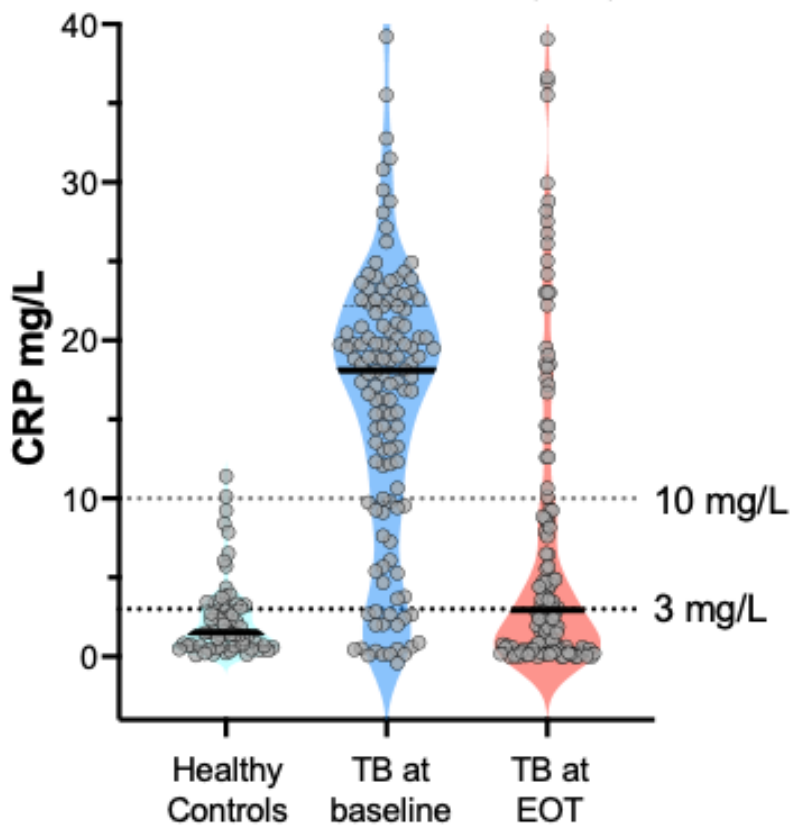
DNA hyper-methylation is associated with improving lung function

DNA hyper-methylation suppresses gene expression, resulting in gene silencing

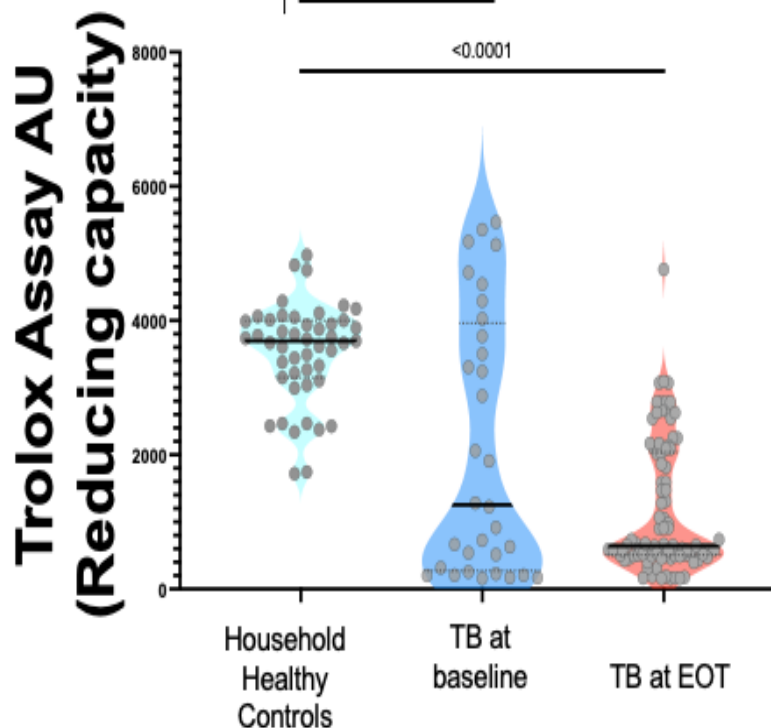
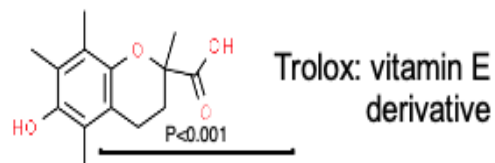


~50% TB survivors remain inflammatory

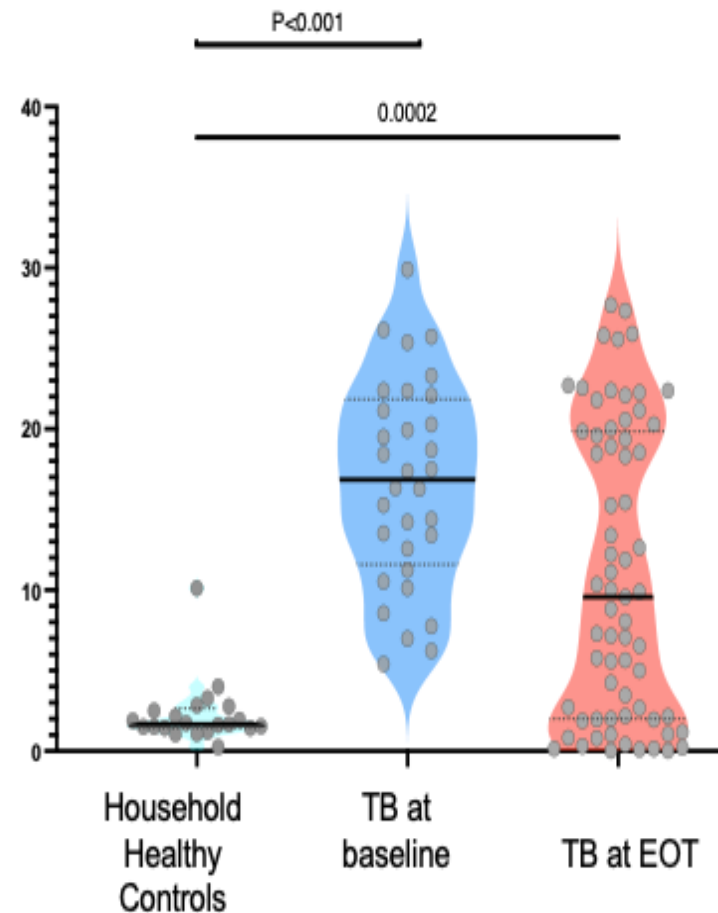
Measure levels of inflammatory marker:
C-reactive protein (CRP)



Reducing Capacity



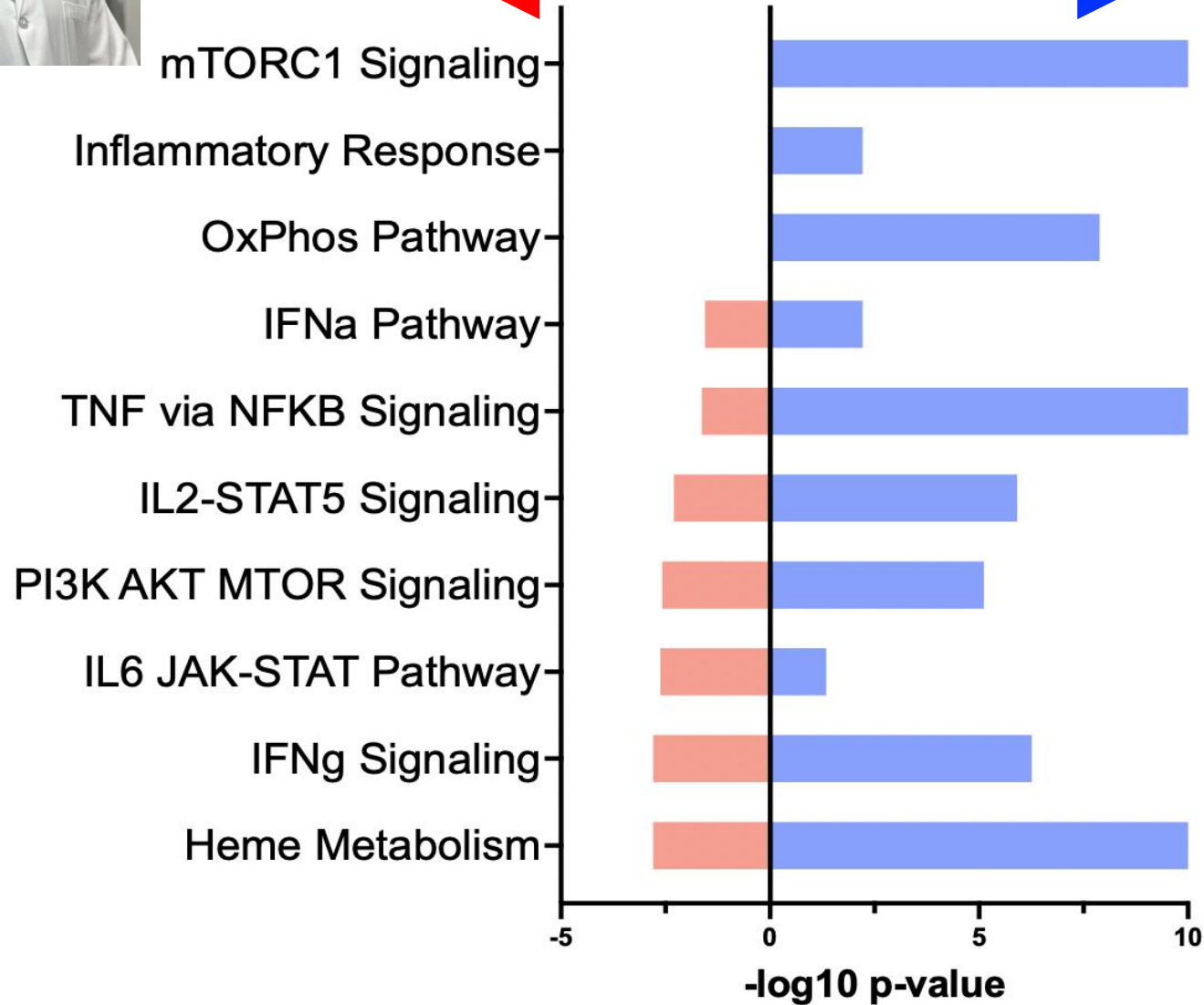
Lipid peroxidation
HNE-LDL



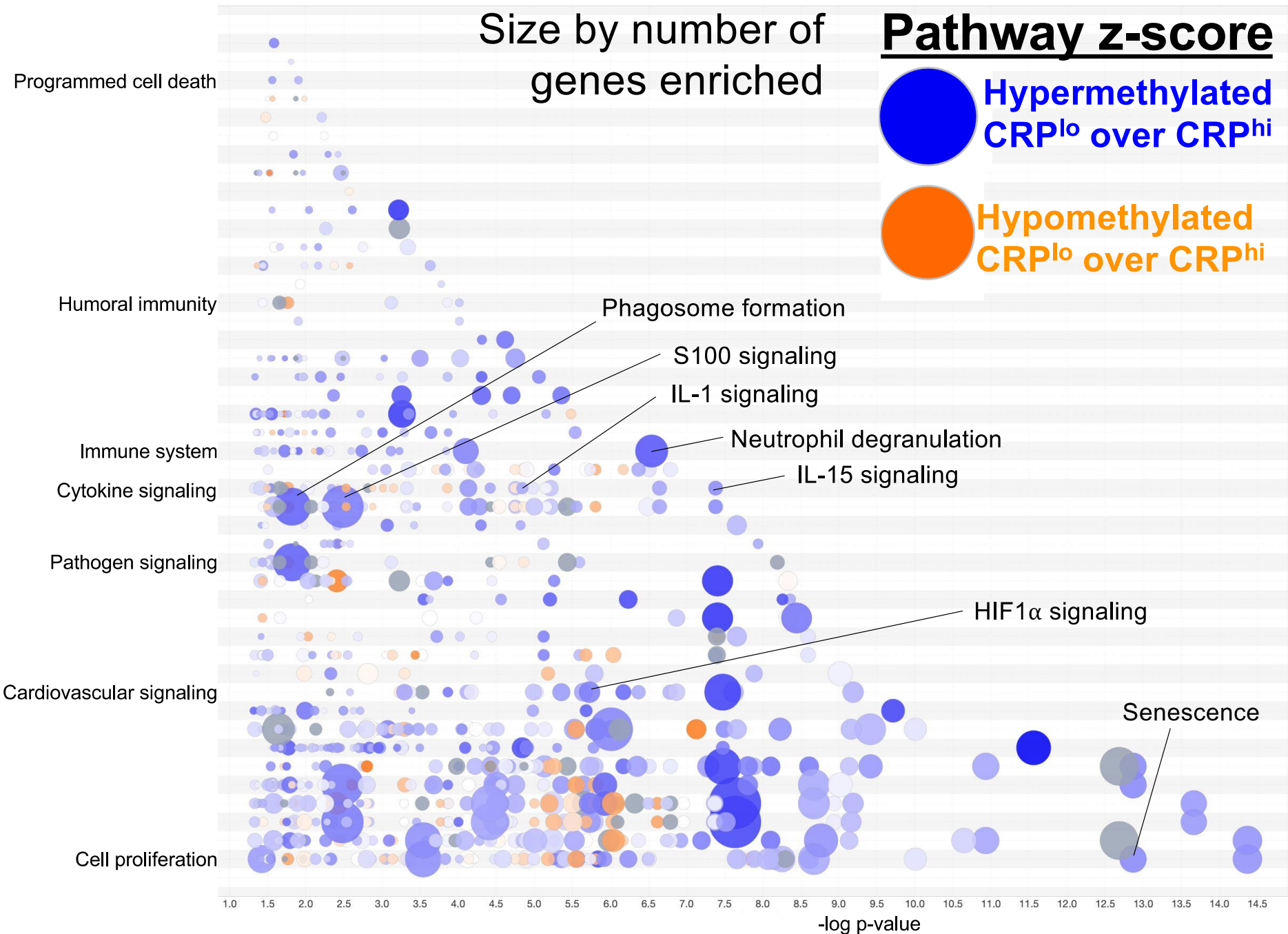


**Hypo Methylated
in CRP^{hi} over CRP^{lo}**

**Hyper Methylated
in CRP^{lo} over CRP^{hi}**



TB survivors that
normalize
inflammation
have
DNA hyper-
methylation



TB survivors that normalize inflammation (CRP) have increased DNA hypermethylation

DNA Methylation pathway z-score



MDMΦ
Fast MtB
killing
capacity

Resolving
CRP
Eswatini

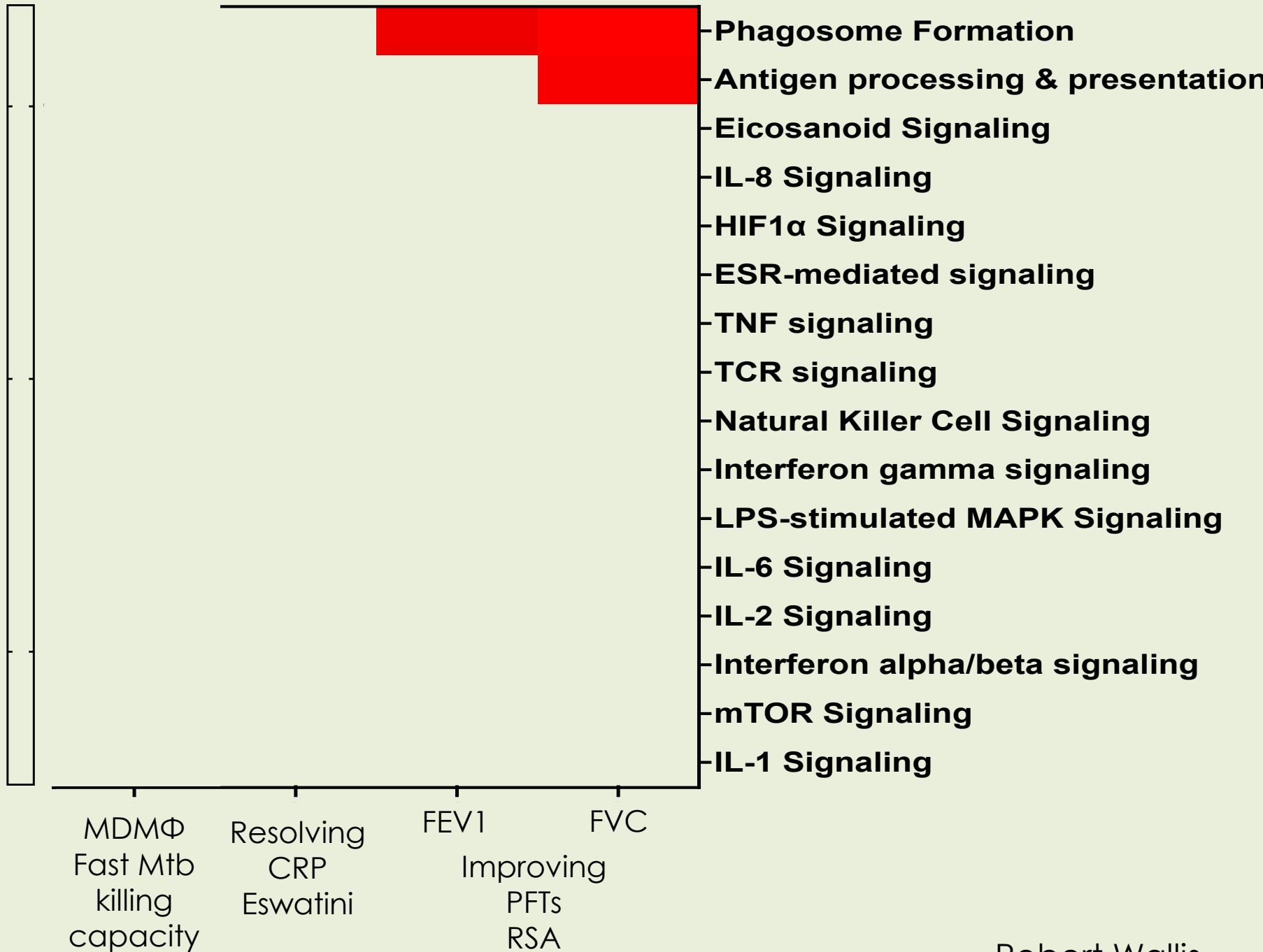
FEV1
Improving
PFTs
RSA

FVC

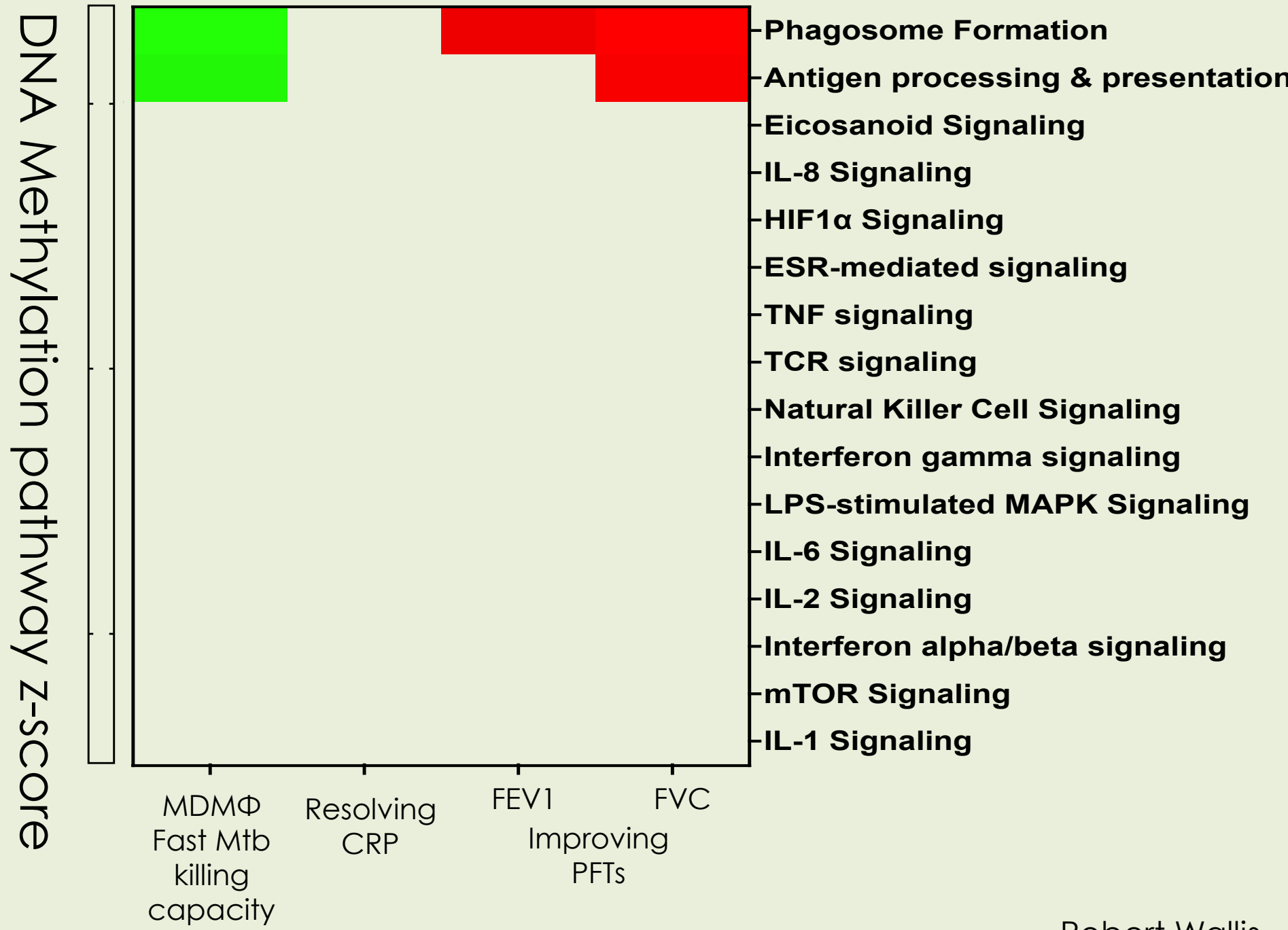
- Phagosome Formation
- Antigen processing & presentation
- Eicosanoid Signaling
- IL-8 Signaling
- HIF1α Signaling
- ESR-mediated signaling
- TNF signaling
- TCR signaling
- Natural Killer Cell Signaling
- Interferon gamma signaling
- LPS-stimulated MAPK Signaling
- IL-6 Signaling
- IL-2 Signaling
- Interferon alpha/beta signaling
- mTOR Signaling
- IL-1 Signaling

Similar DNAm landscape in resolving CRP and improving lung function

DNA Methylation pathway z-score



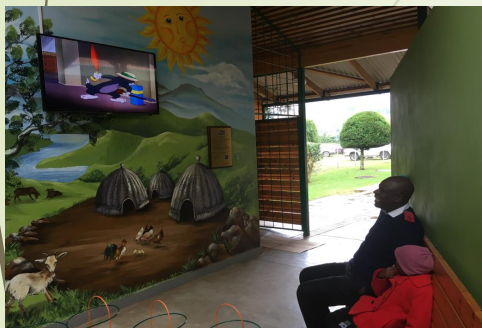
DNAm landscape that correlates with resolving inflammation is contradictory to *Mtb* killing capacity



Summary

- 10-20% TB pts have worsening lung FXN despite successful Abxs.
- DNA methylation silences genes
- DNA methylation correlates with improving lung function
- Resolution of inflammation is associated with DNA hyper-methylation and contradictory to Mtb killing capacity
- Is there an epigenetic trade off?

Thank you



Methodist

Edward Graviss
Ngan Ha

Rice

Isaac Hilton
Rosa Selenia



Eswatini

Gugu Maphalala
Ntombi Ginindza
Sindi Dlamini
Precious Dlamini
Welile
Sikhondze
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Thank you...

