

New approaches to mouse models

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Relevant inbred resistant and susceptible mouse models of TB

50-100cfu (aerosol)

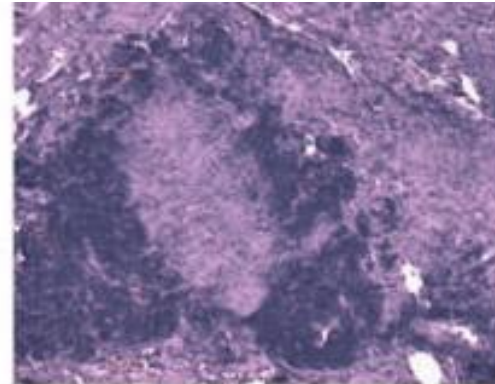


C57BL/6-resistant



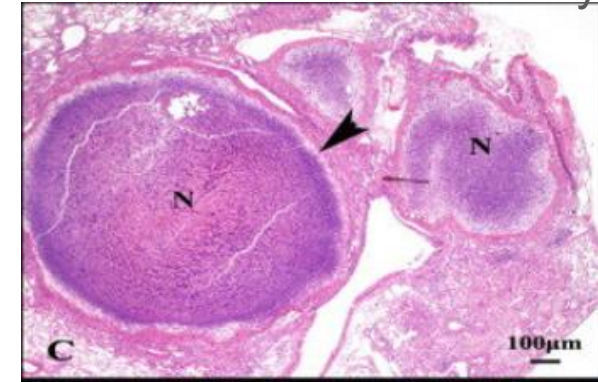
C3HeB/FeJ- susceptible

Non-necrotic



Granulomas

Necrotic and often cavitory

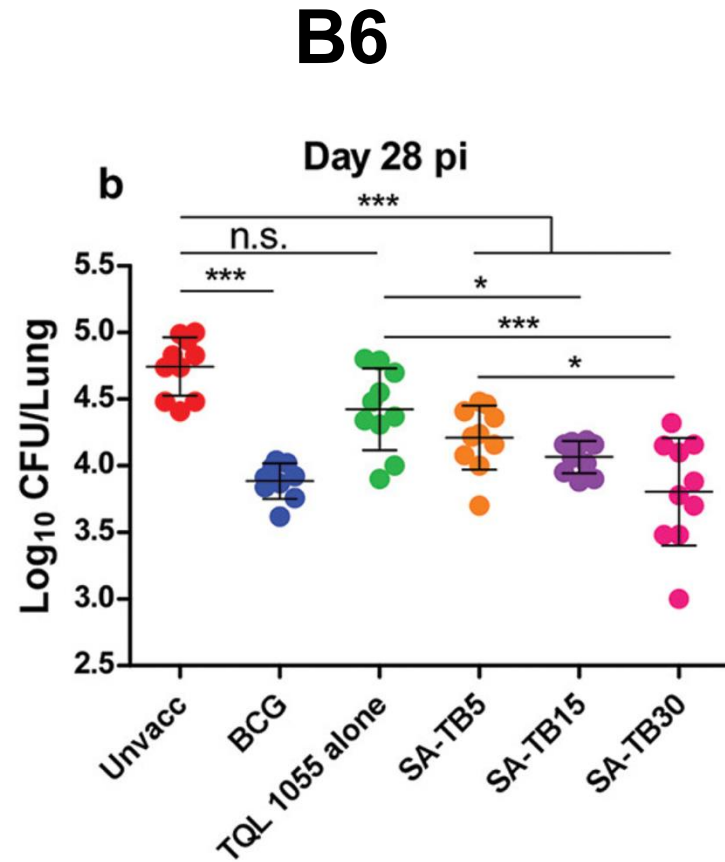


Tractable

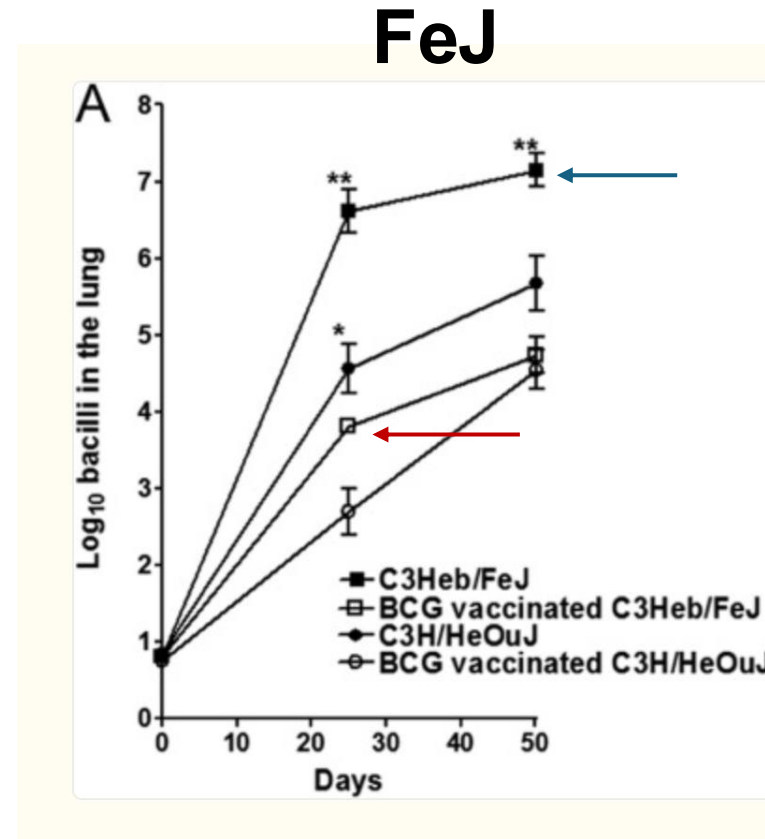
Extremely tractable for vaccine studies - gene knock out mice, adoptive transfer tools, tetramers etc

Not very tractable - gene knock out mice rare or have to be created.

Vaccine induced immunity in B6 and FeJ

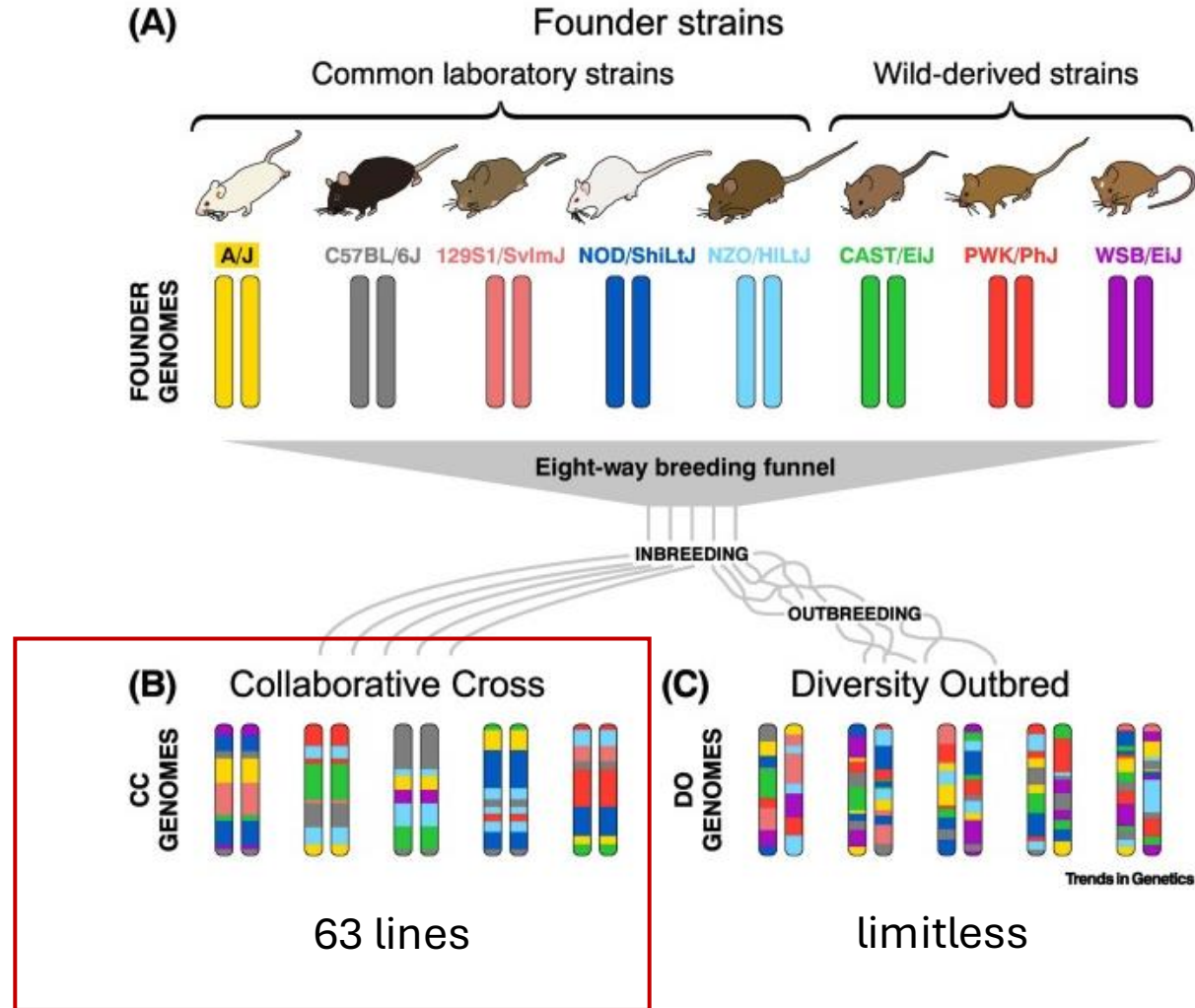


Ahmed et al, 2023

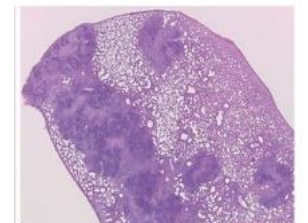
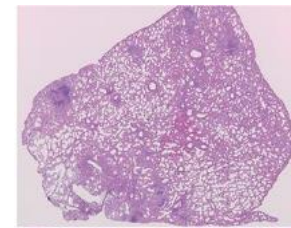
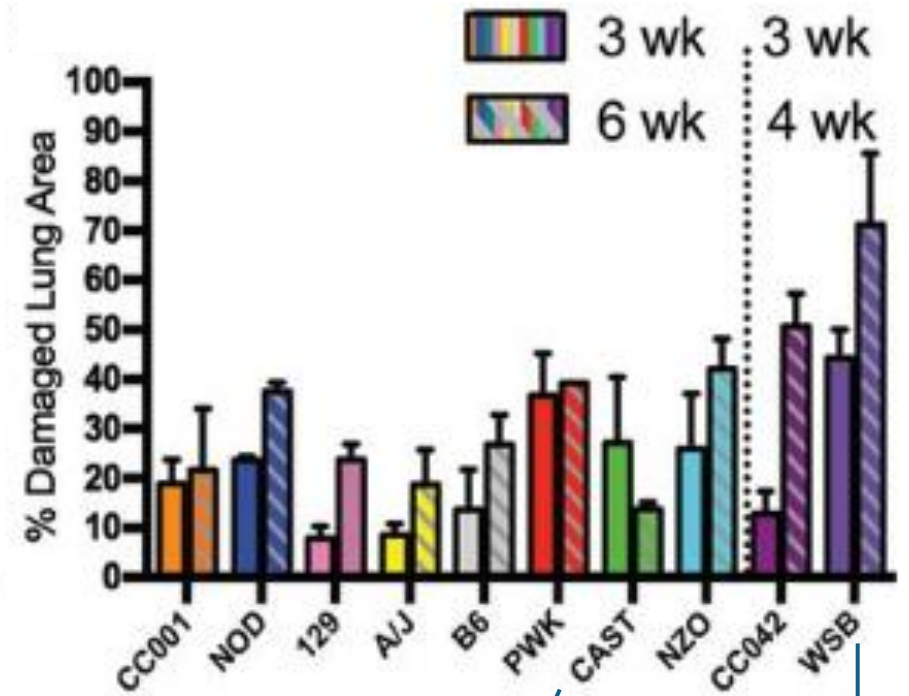
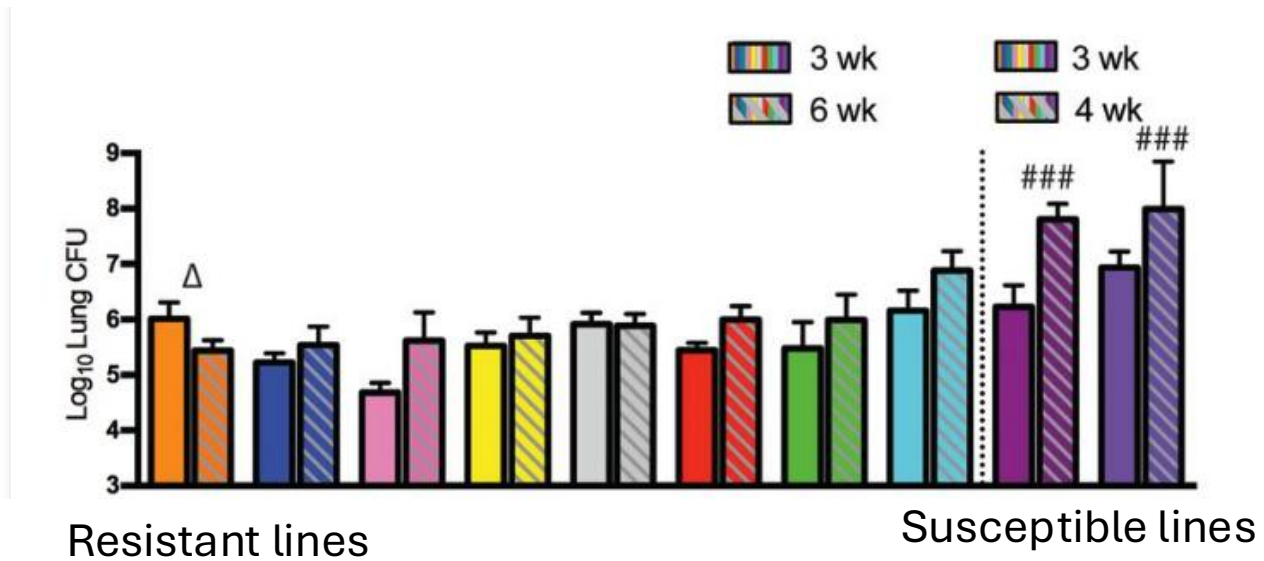


Henao-Tamayo M et al, 2014

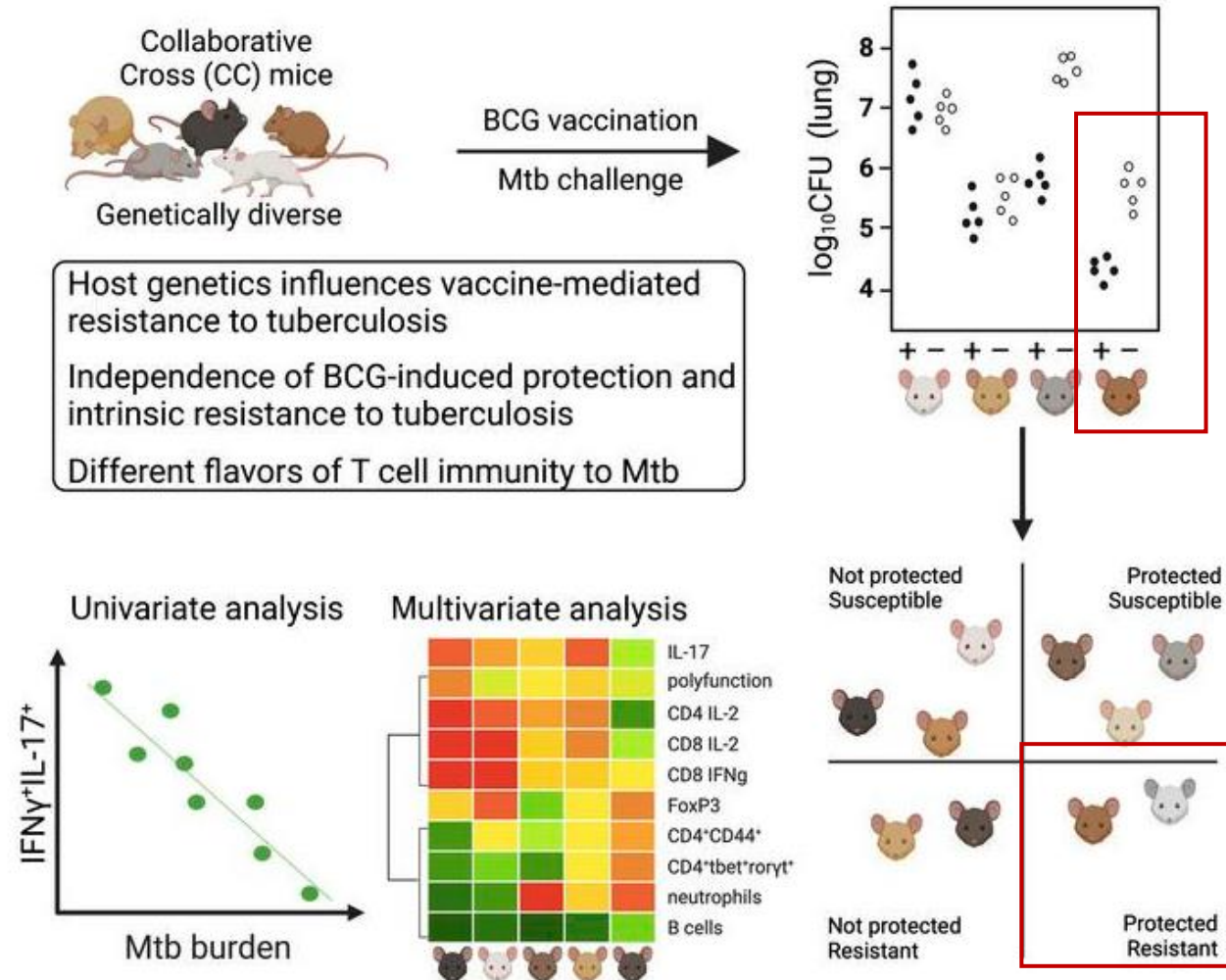
Collaborative Cross model of TB



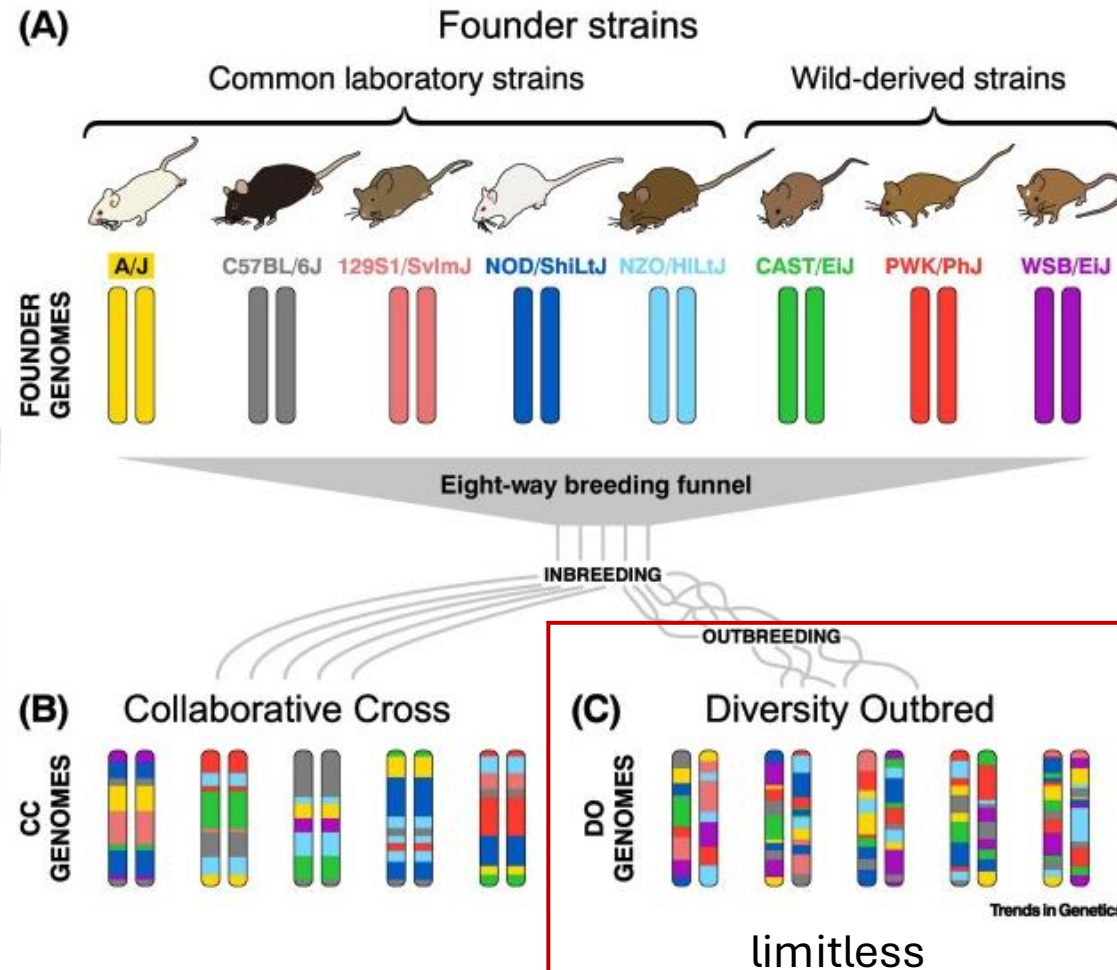
Resistant and susceptible *Mtb* disease phenotypes in CC lines



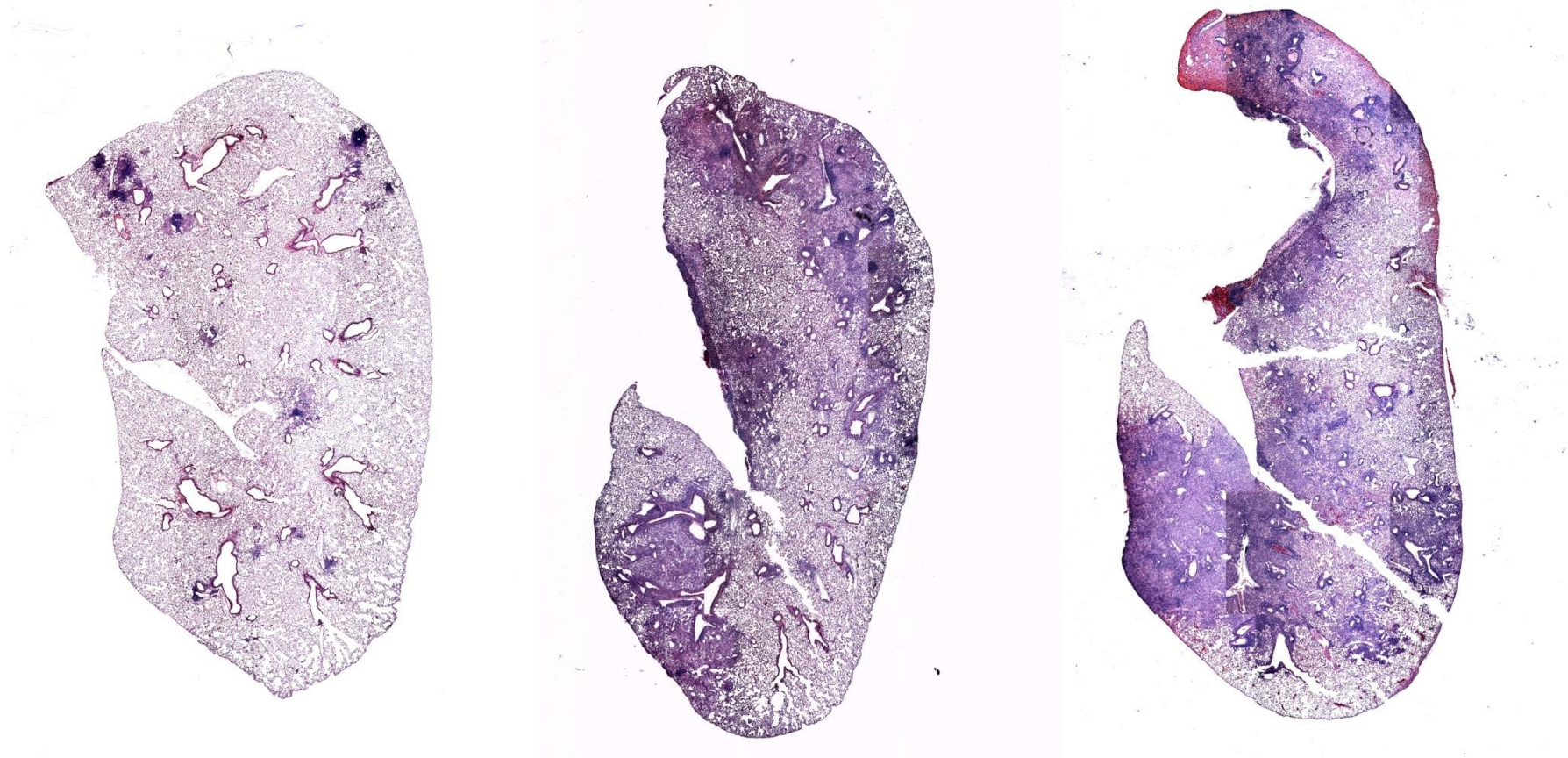
CC model of vaccination and *Mtb* challenge



Using the diversity outbred mouse model to study TB disease heterogeneity in mice

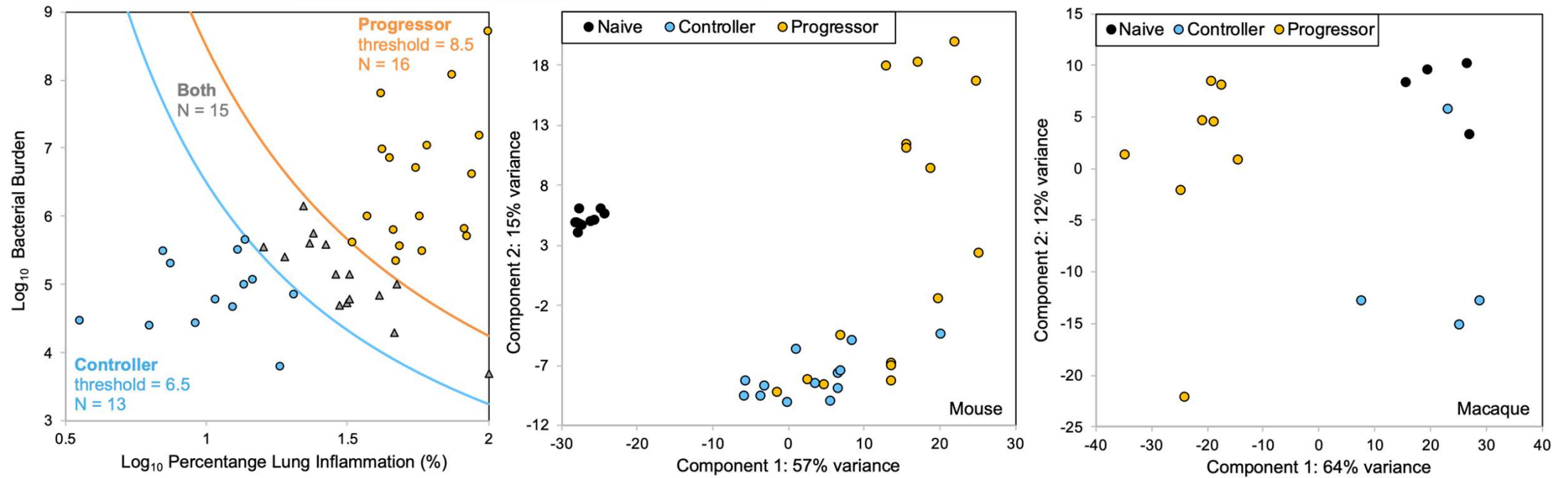


Diversity outbred mice display a spectrum of TB disease outcomes

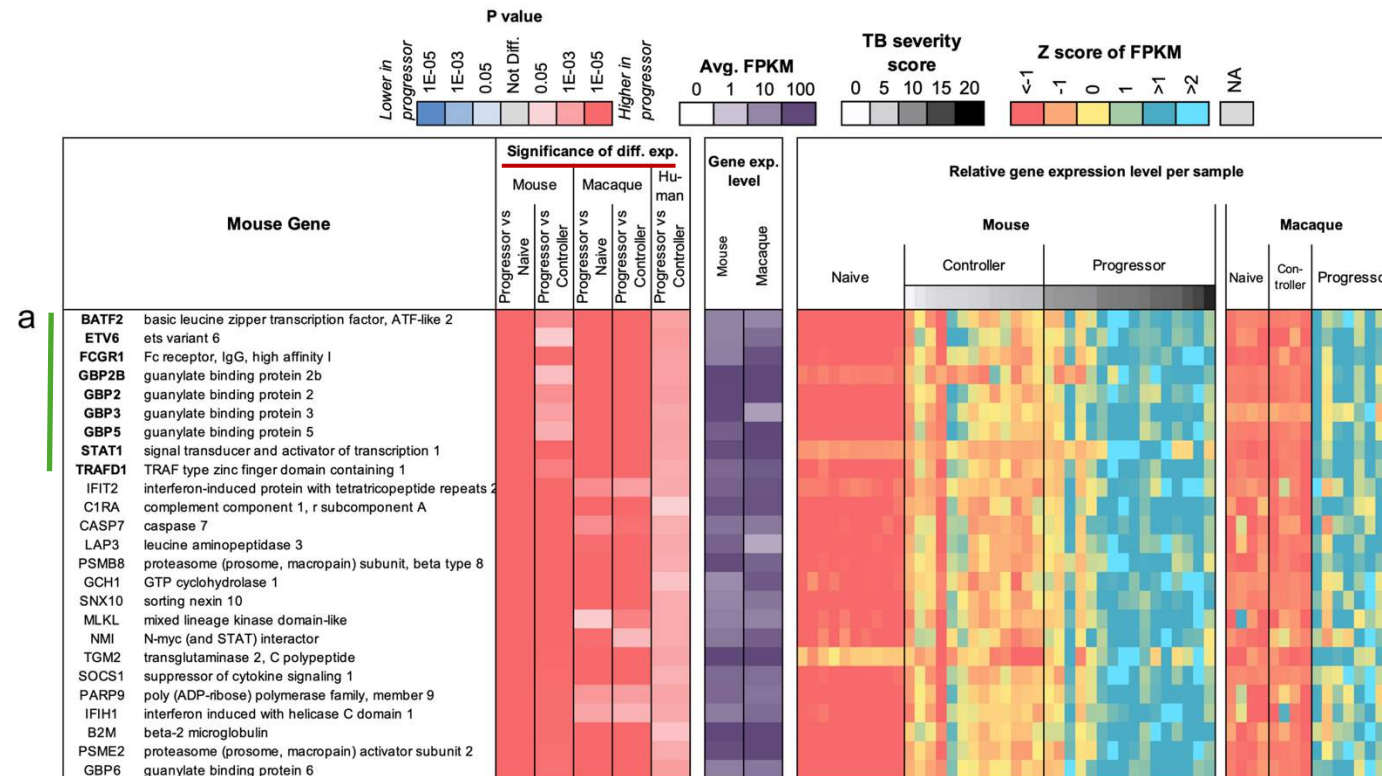


Gopal *et al*, American Journal of Respiratory and Critical Care Medicine, 2013

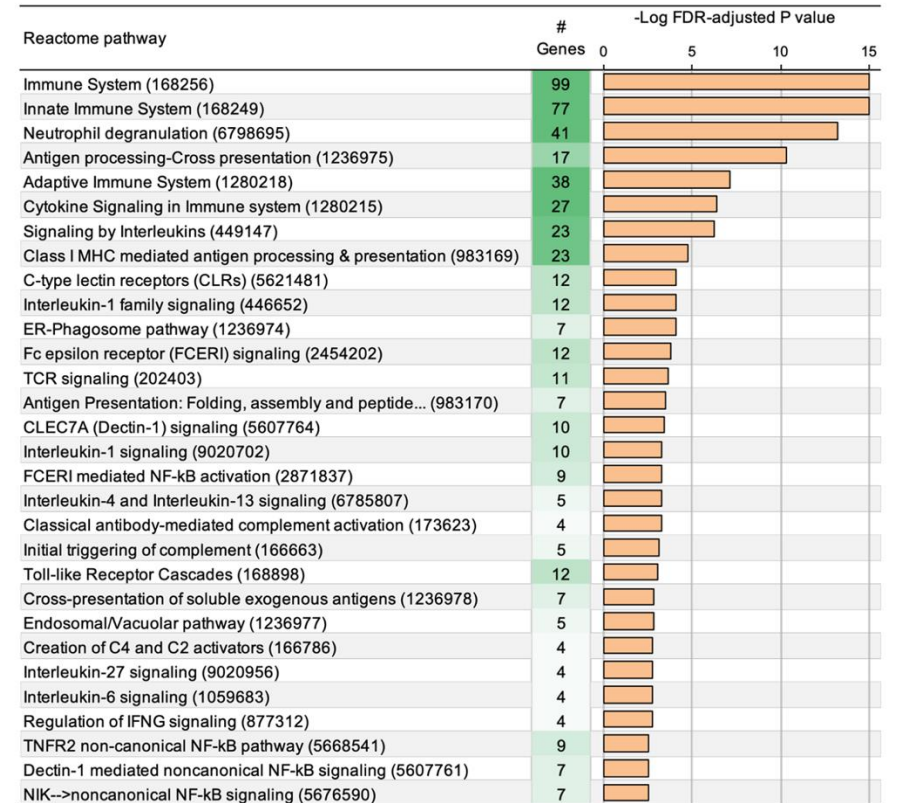
Diversity outbred mice display a spectrum of TB disease outcomes



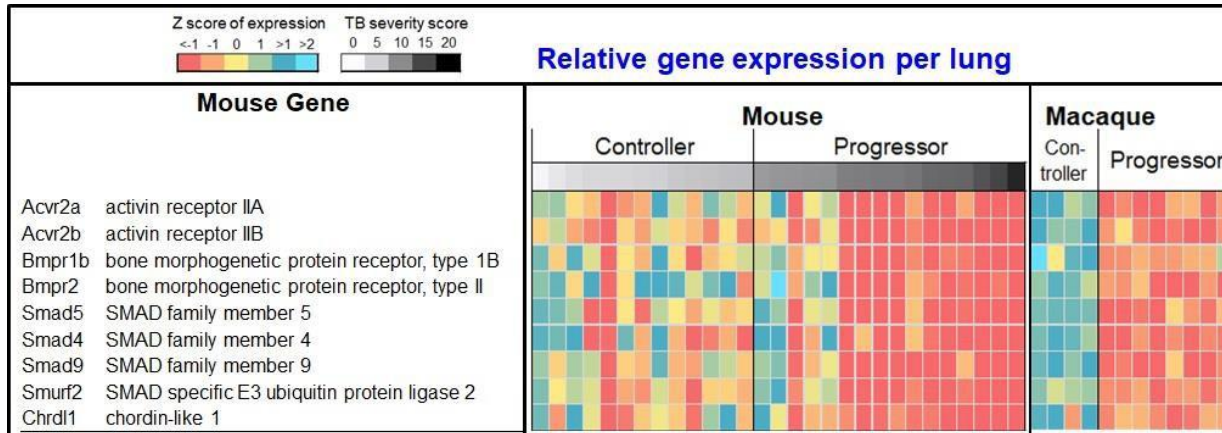
Progressor DO mice (and macaques) show a type I IFN/neutrophil lung transcriptional signature



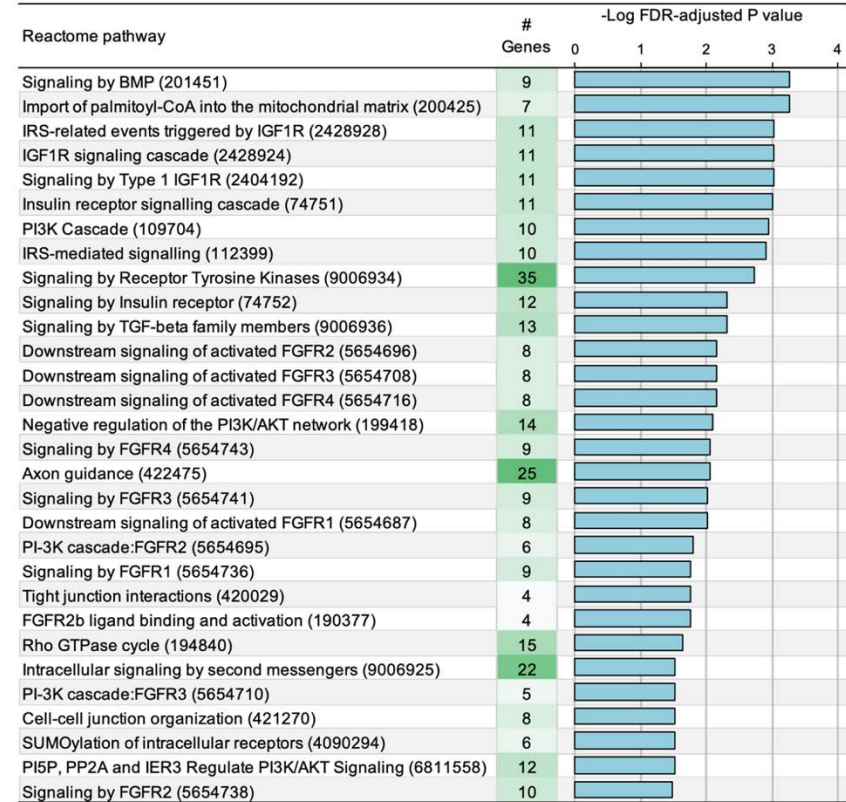
257 genes higher in Progressor vs both Naive and Controller (both species) and positive human spline**



Controller DO mice (and macaques) express transcriptional signatures associated with lung repair



777 genes higher in Controller vs Progressor, in both mouse and macaque*

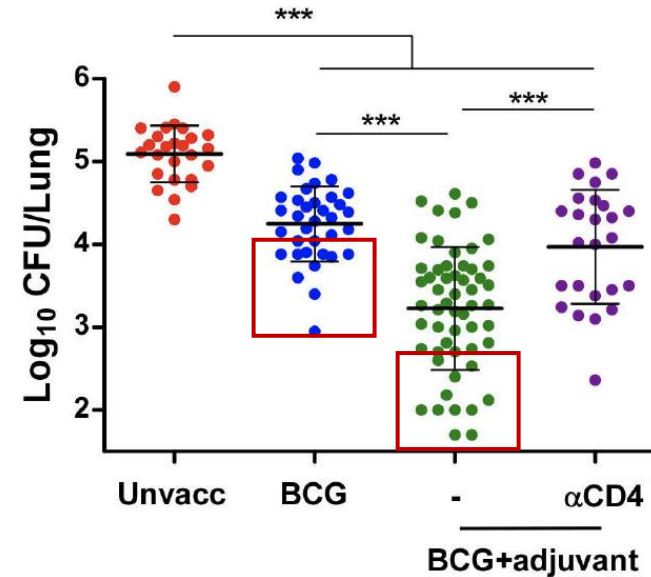
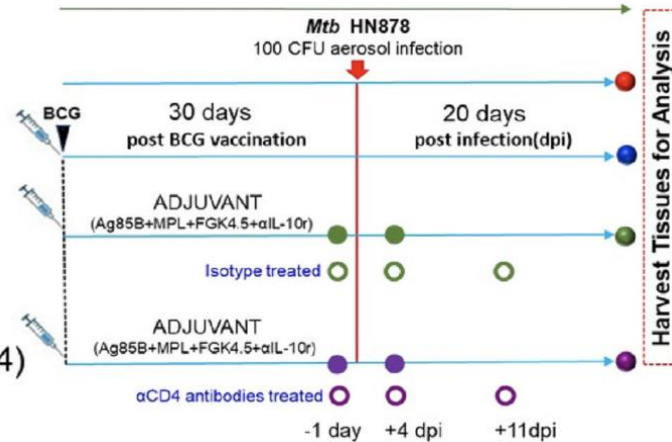


DO mouse model of vaccination

DO mice



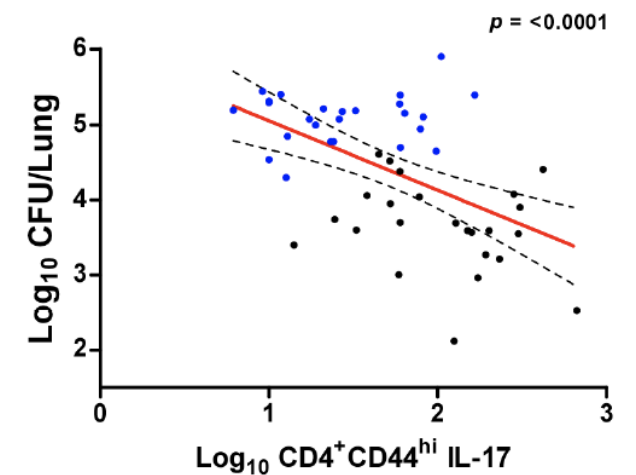
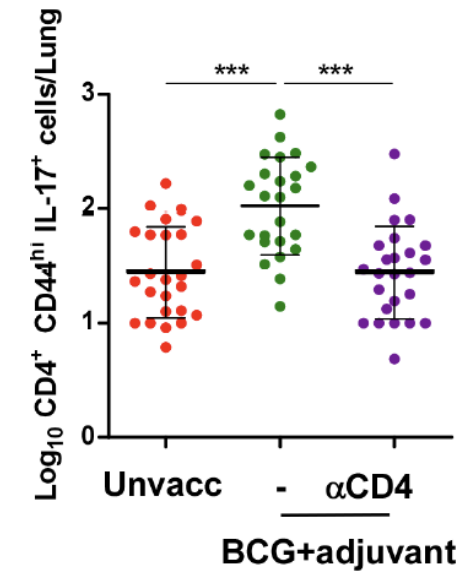
- Uninfected
- Unvaccinated
- BCG
- BCG+adjuvant
- BCG+adjuvant +CD4 depletion (α CD4)



Vaccine-induced protection in resistant DO mice are associated with Th17 responses and pathways associated with B cells

Gene name	Log ₂ Fold Change	Std. Error	FDR-adjusted P value	Average expression (FPKM)		Z-score of gene expression (Log FPKM)					
				BCG	BCG + Adjuvant	Uninfected	Unvaccinated	BCG	BCG + Adjuvant	BCG + Adjuvant + CD4 depletion	
J chain	2.11	0.38	1.8E-06	17.3	75.2						
Fls2g2d	1.49	0.38	1.3E-03	1.00	2.83						
S100a4	1.33	0.29	7.7E-05	2.16	5.48						
Lama1	1.33	0.31	3.6E-04	0.20	0.51						
Mzb1	1.28	0.29	2.7E-04	0.43	1.05						
Hbb-bt	1.23	0.23	2.5E-06	327.0	768.3						
Slc4a1	1.18	0.29	6.6E-04	0.48	1.10						
Marco	1.15	0.35	8.9E-03	13.3	29.6						
C1p	1.08	0.33	8.0E-03	0.78	1.68						
Der13	0.98	0.19	5.3E-06	1.01	2.00						
Rpl35a	0.98	0.15	8.2E-09	20.5	40.8						
Slc13a4	0.94	0.28	8.1E-03	1.02	1.97						
Konip2	0.90	0.25	2.9E-03	0.29	0.55						
Eaf2	0.87	0.26	8.9E-03	0.15	0.28						
Gm5148	0.83	0.14	2.8E-07	1.15	2.06						
H2-Oa	0.79	0.19	4.8E-04	4.88	8.45						
Pou2af1	0.77	0.21	2.7E-03	3.60	6.18						
Cacna1h	0.76	0.23	7.8E-03	0.18	0.31						
Hbb-bs	0.75	0.23	7.6E-03	2766.4	4673.8						
Sspo	0.72	0.15	4.4E-05	0.24	0.39						

Z score of expression (Log FPKM) <-1 -0.5 0 0.5 >1 >2



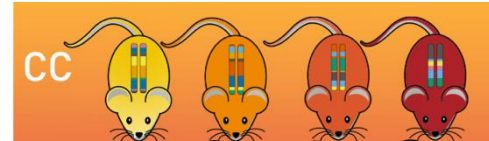
TB vaccine studies in mice – which is the right model?



- Screening new TB vaccines (Mtb control, inflammation)
- Mechanistic studies



- Mtb control
- Effect on TB disease (Granulomas)

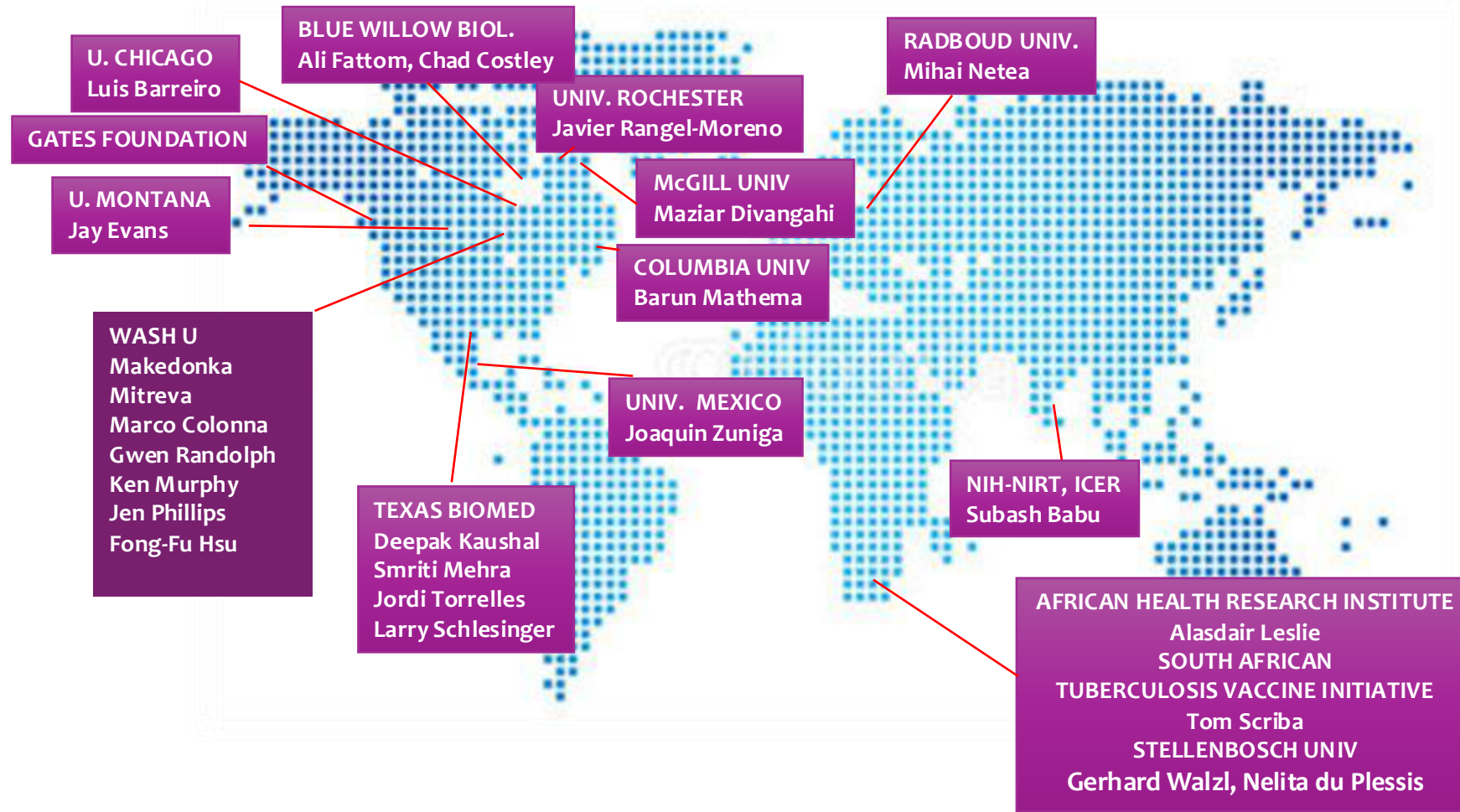


- Host Genetics
- Correlates of vaccine-protection
- Screening new vaccines (pick CC lines)



- Correlates of vaccine-protection
- Screening new vaccines
- Host Genetics

THE PARTNERSHIPS:



R01HL105427



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R01 AI155024
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