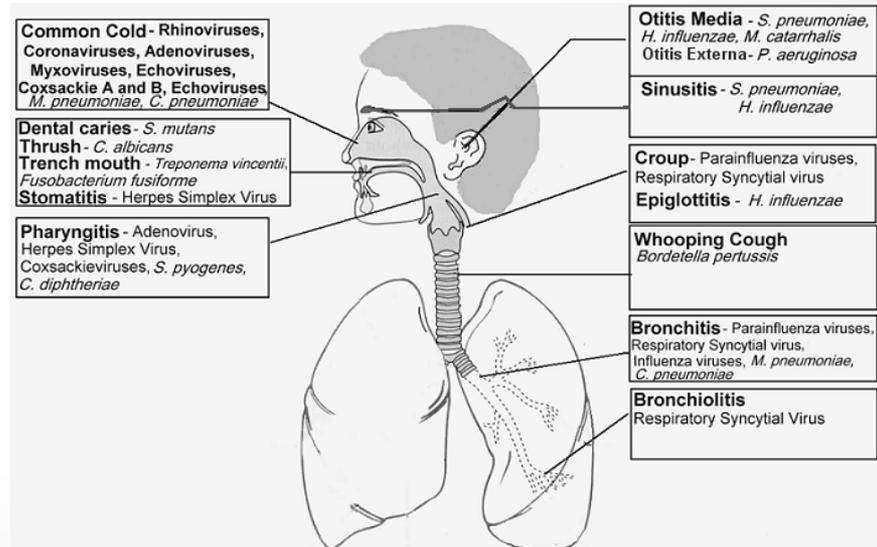
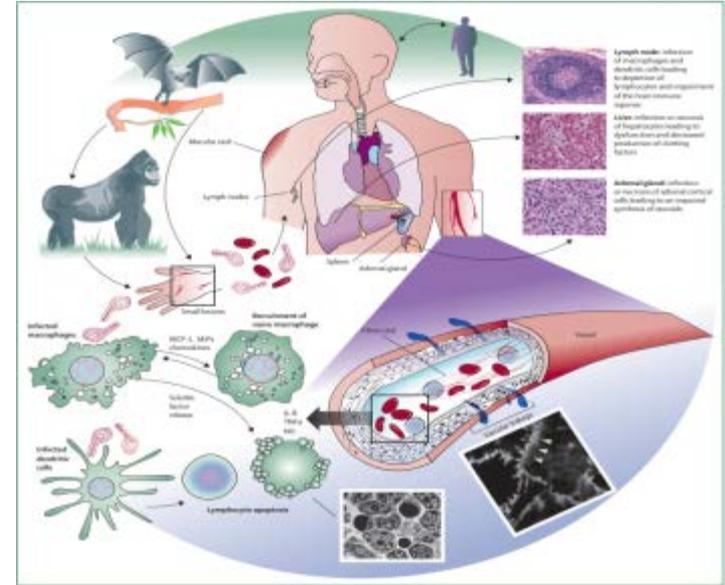


Genetic Diversity in Ebola Response

Martin T. Ferris
UNC-Chapel Hill
3/19/2015

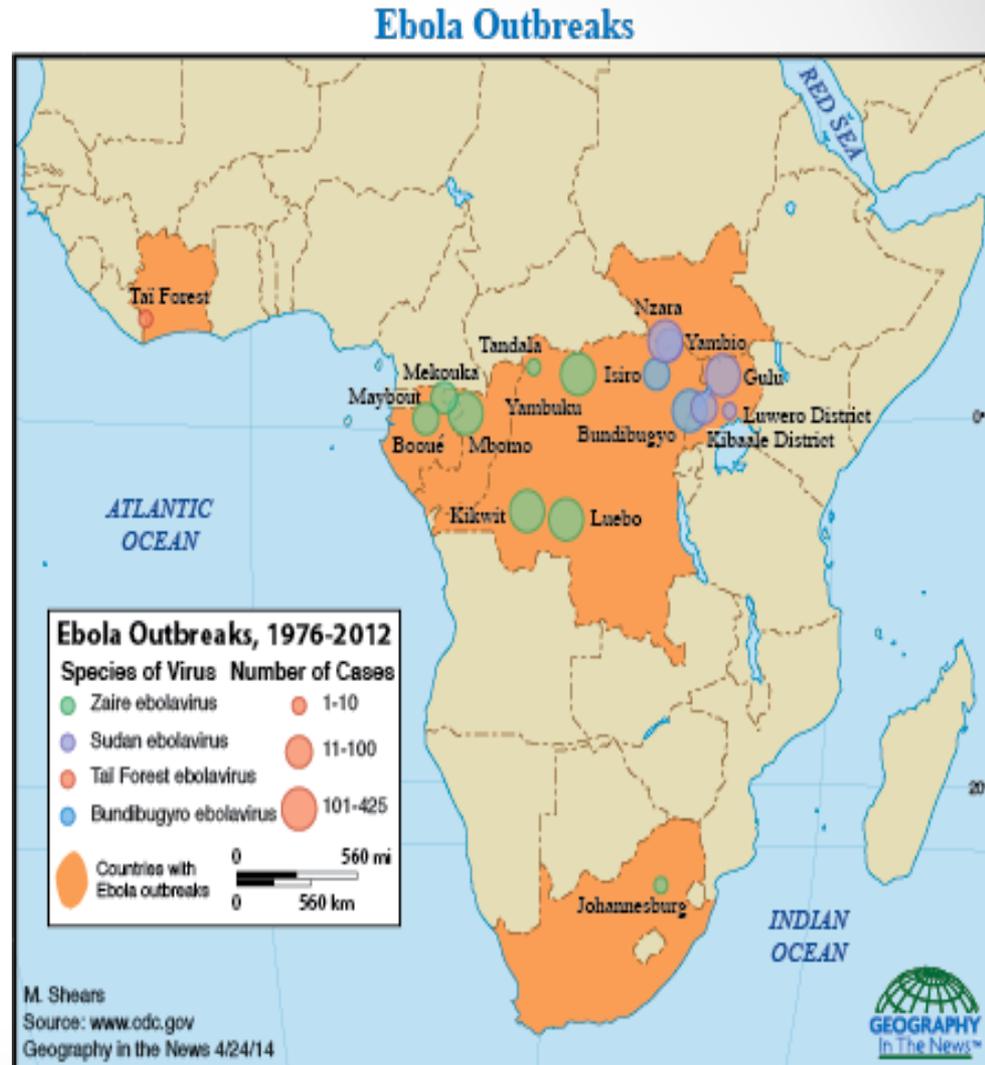
Acute viral pathogens

- Annual disease burdens worldwide
 - 10^8 - 10^9 cases/year (flu)
 - Less than 1,000 (MERS, Ebola)
- Often emerging from animal reservoirs
- Increased severity in susceptible sub-populations
- Many have immune-pathologic features



Ebola virus

- 1st described emergence in 1976
- Regular outbreaks of small → moderate cases
- Small animal reservoir
 - Originally thought of as primate
 - Evidence for bats
- Severe disease
 - Fever
 - Organ failure
 - Hemorrhage (~20-50% of ID'd cases)
 - 25-100% mortality (large outbreaks show this is close to 50-90%)



Emergent disease models

- New pathogens require new models of disease
- Lab mouse has been used for a long time
 - Often a poor model for some diseases
 - Adaptation of pathogens to mouse
 - Changes disease
 - Variable success

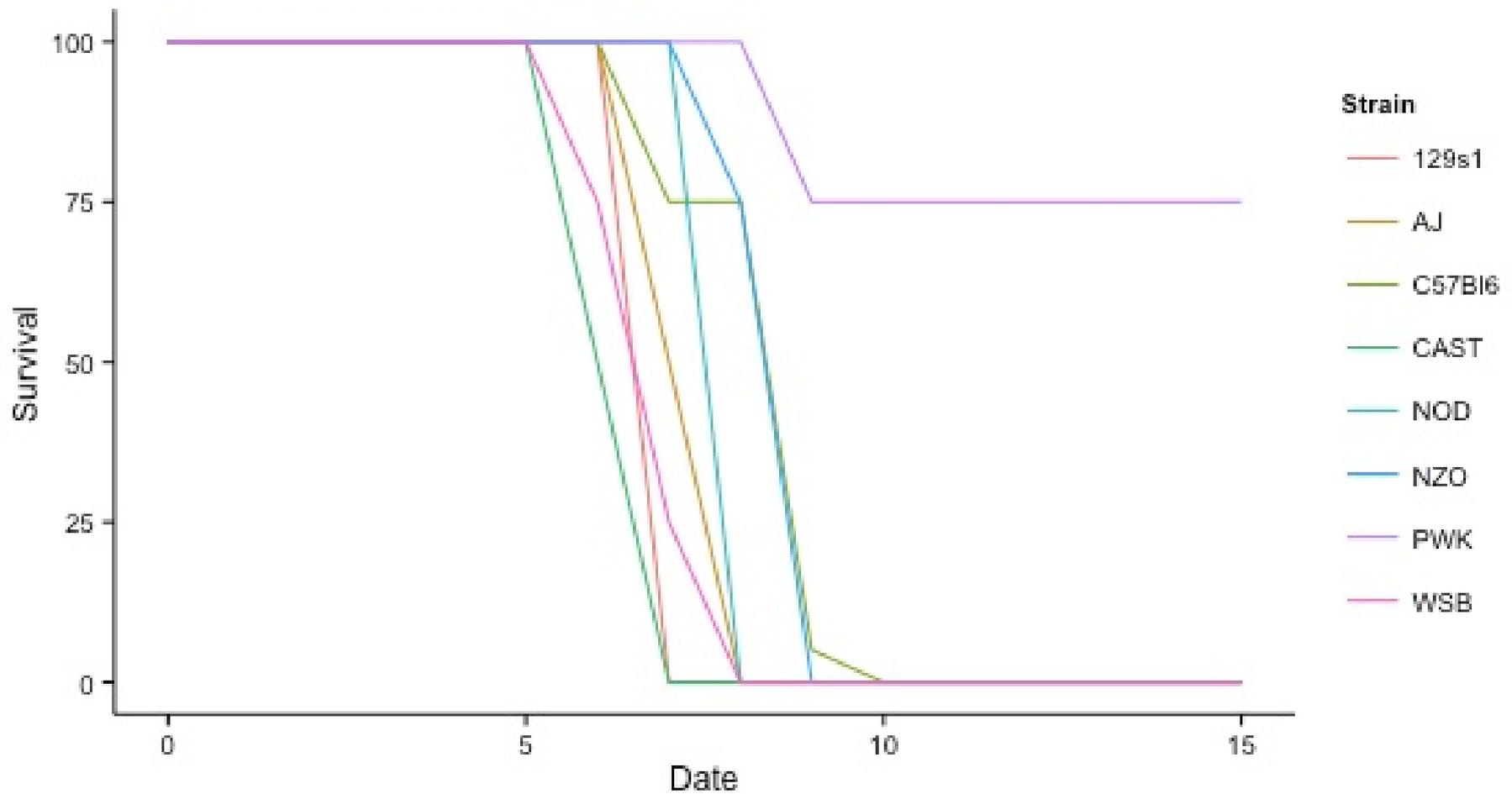
Animal models of EVD



EVD	Hemorrhage	Ease of Use	Reagents	Genetics
++	++	-	~	-
+	+	+/~	---	-
+	-	+	+++	+++

Emergent disease models

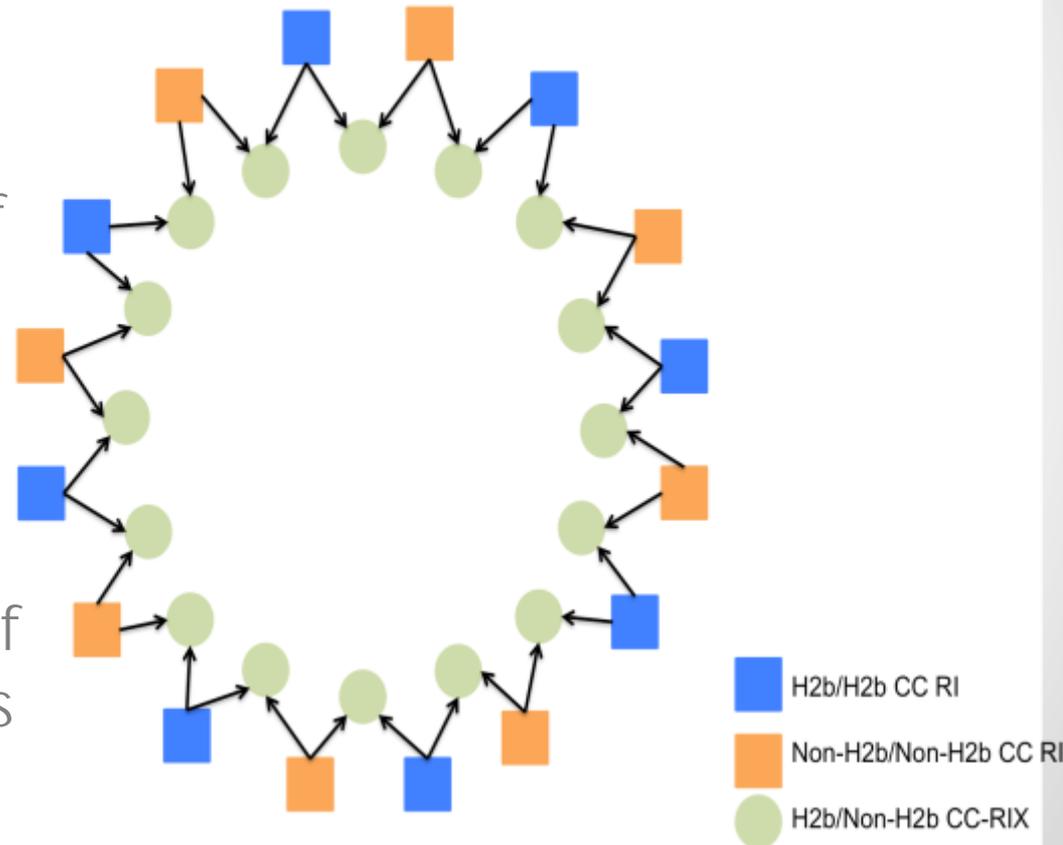
- New pathogens require new models of disease
- Lab mouse has been used for a long time
 - All mice are not (genetically) created equal
 - Why not change the mouse to see if we change the disease?

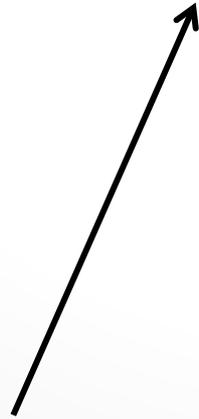
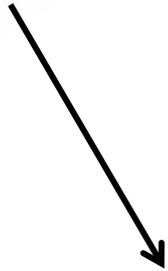
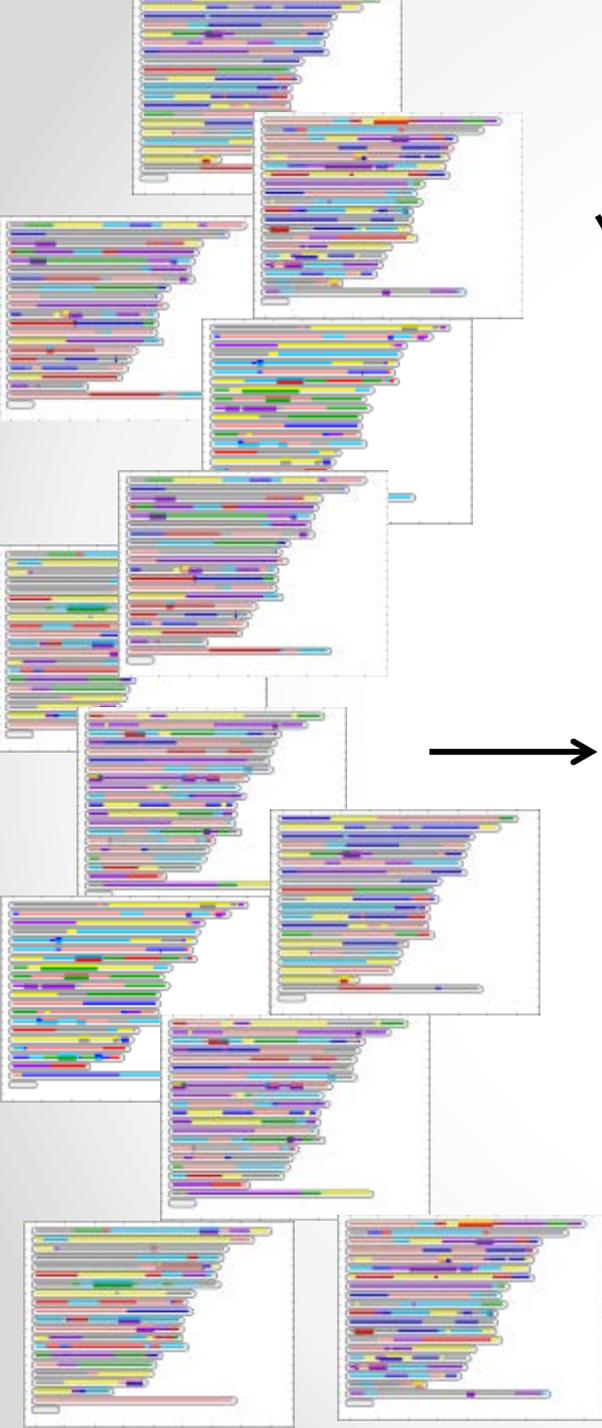


NO founders show evidence of hepatic involvement or hemorrhage

CC-RIX (F1s between CC lines)

- Alternate experimental design
- Critical for utilization of genotype specific reagents or gene specific inclusion
- Allow for assessment of parent of origin effects





~20-25 animals/RIX

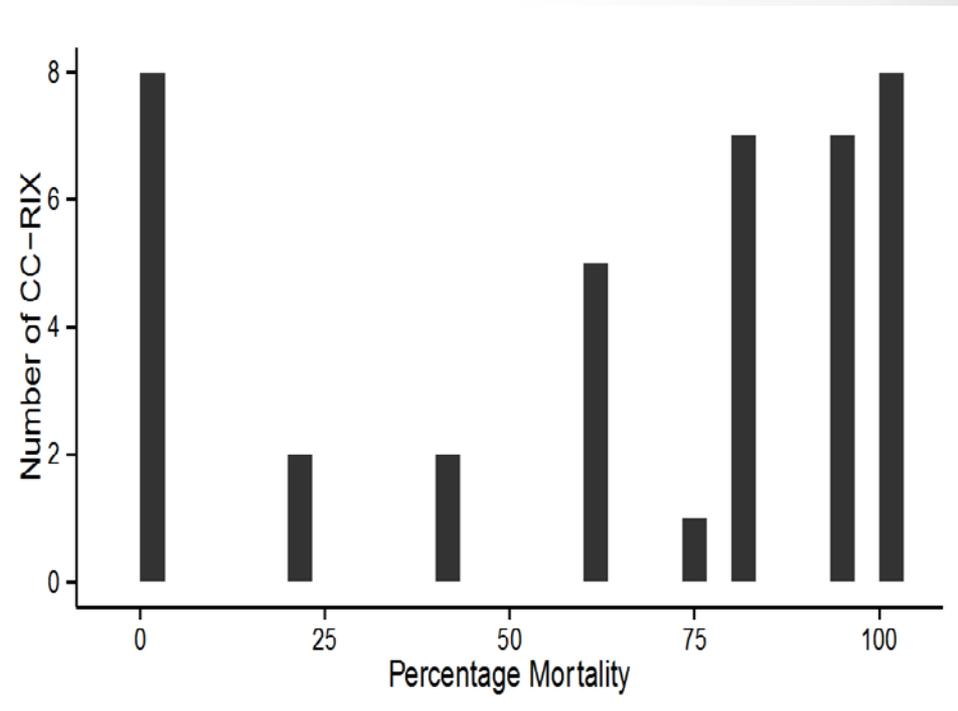
10^2 FFU of ZEBOV-MA

Tissue harvest at specified timepoints

~10-15 animals for survival analysis

Range of overall mortalities

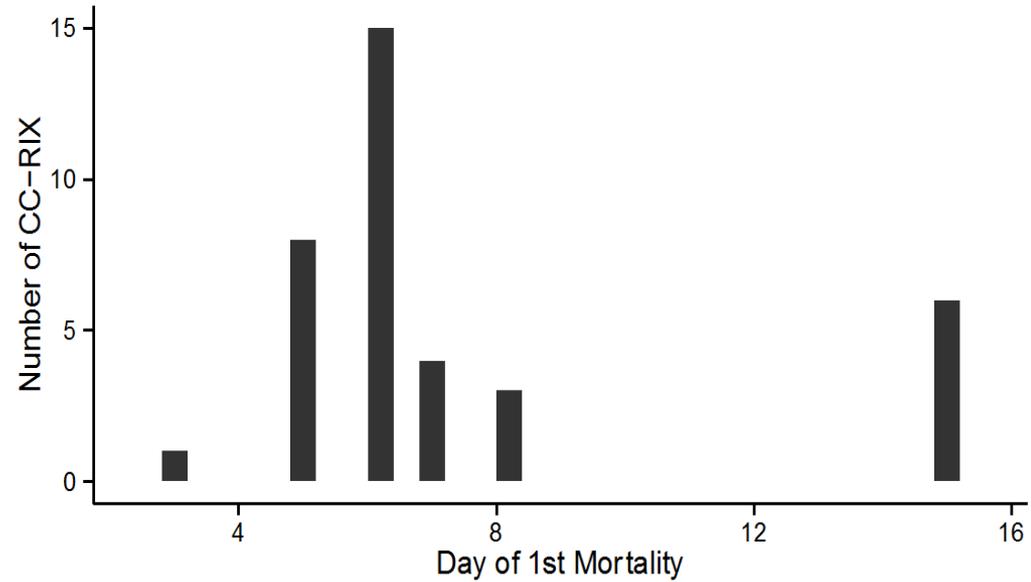
Larger fraction of resistant RIXes



Range of overall mortalities

Larger fraction of resistant RIXes

Earlier disease onset in RIXes v. Founders

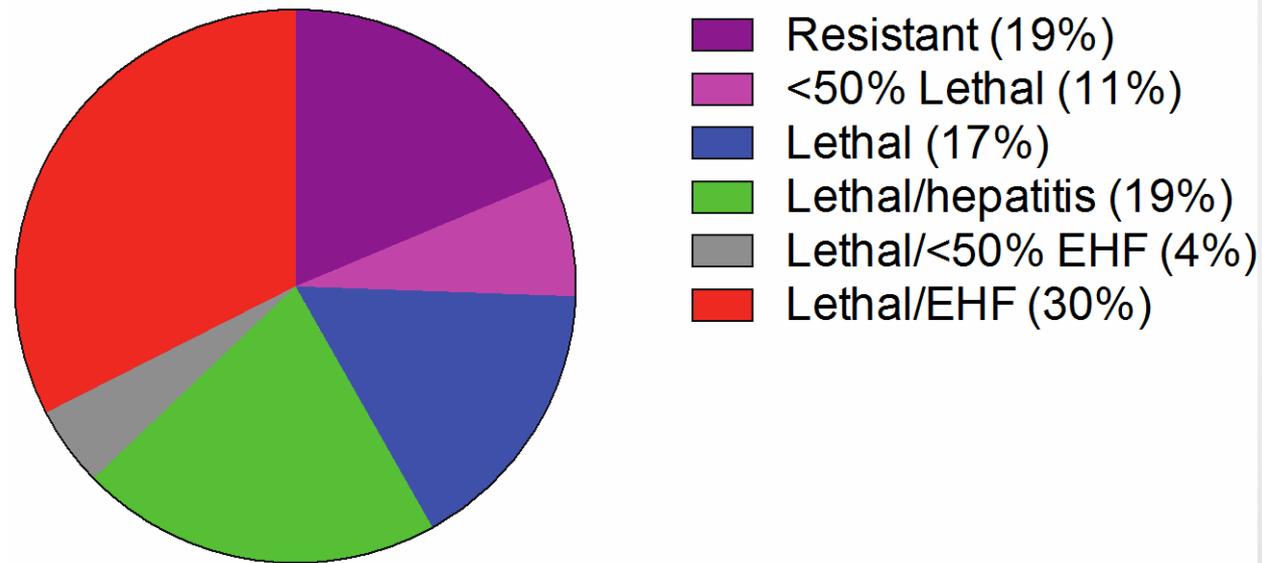


Range of overall mortalities

Larger fraction of resistant RIXes

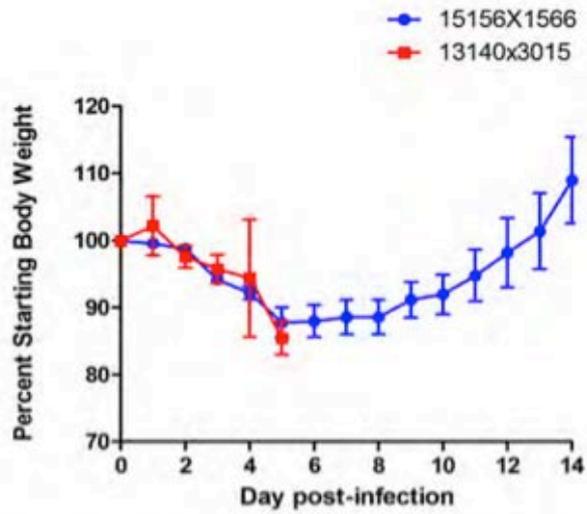
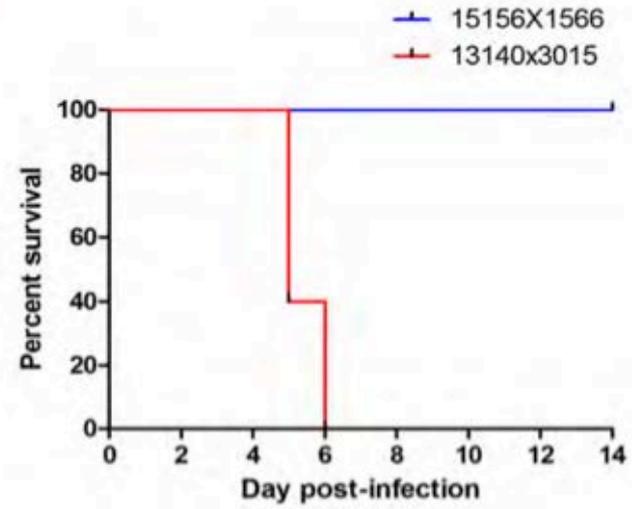
Earlier disease onset in RIXes v. Founders

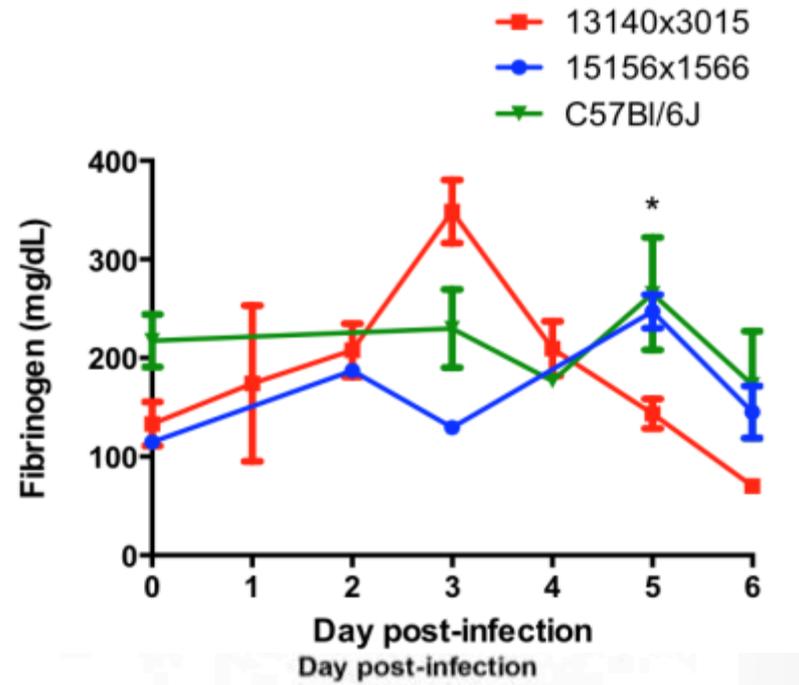
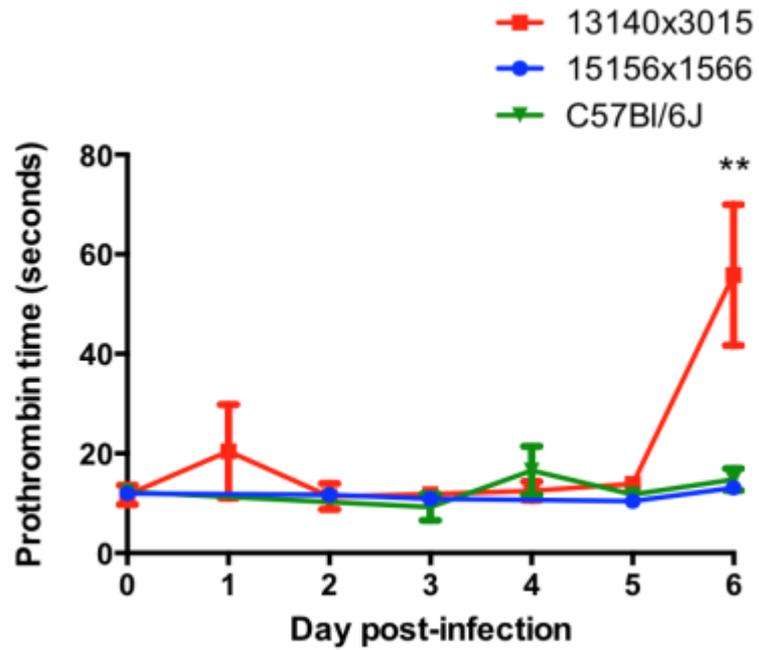
Outlier responses exist



Emergent phenotypes

Hepatitis, Splenomegaly, Hemorrhage

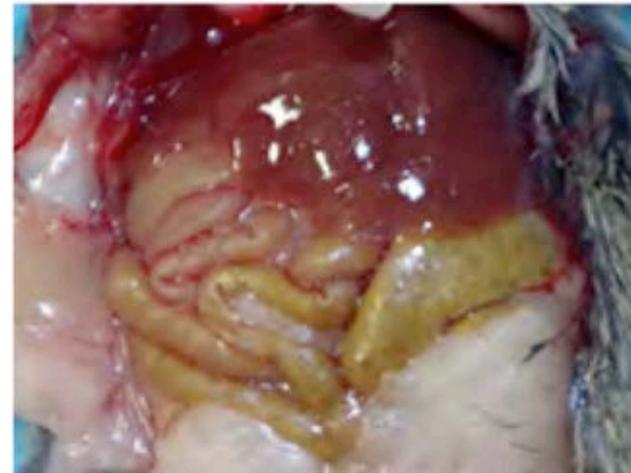
a**b****c****d**



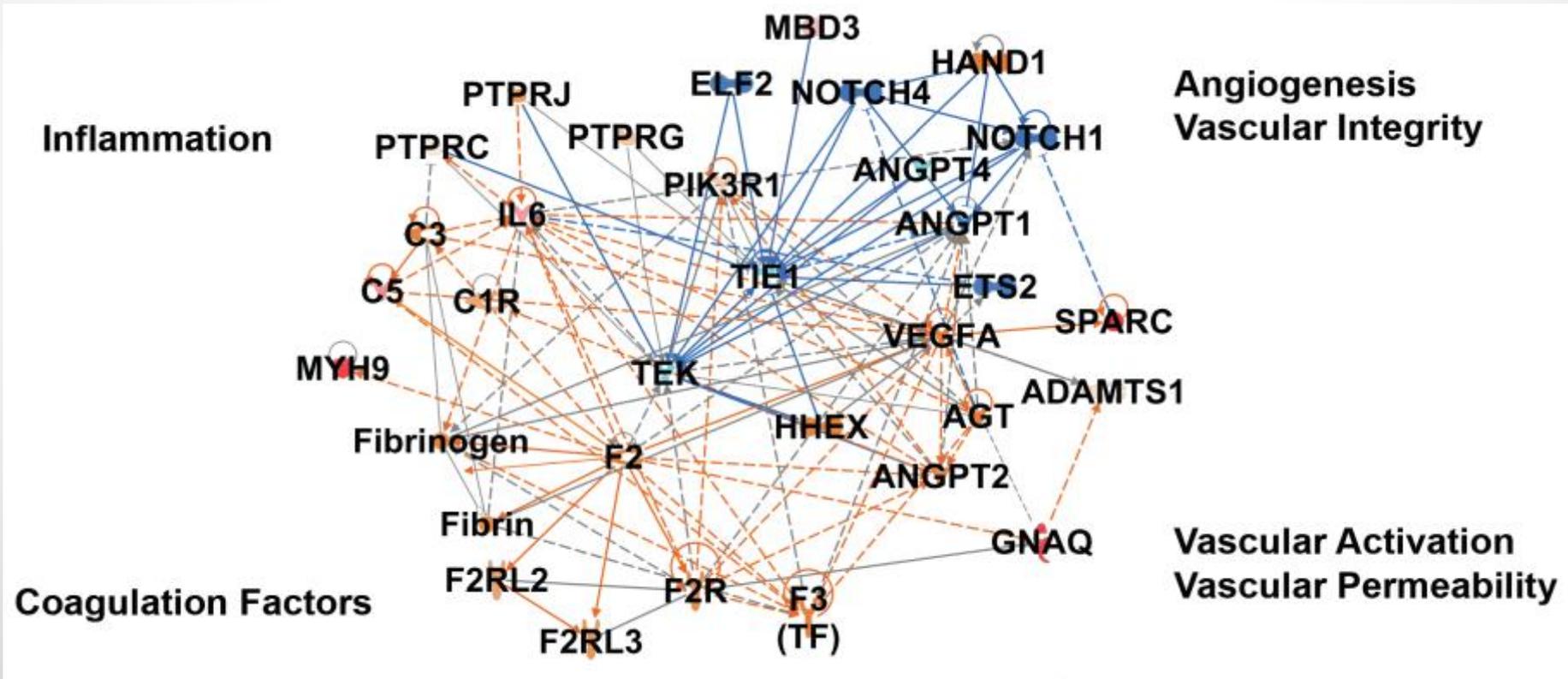
c



d



Central disregulated network in hemorrhagic line



Tie1 and Tek central to disregulated network in hemorrhagic line

Tie1 and Tek ~20MBp distant on Chr4

For both our hemorrhagic (13140x3015) and survival (15156x1566) RIXes
The maternal RI contribute an NZO haplotype. Paternal haplotypes differ.

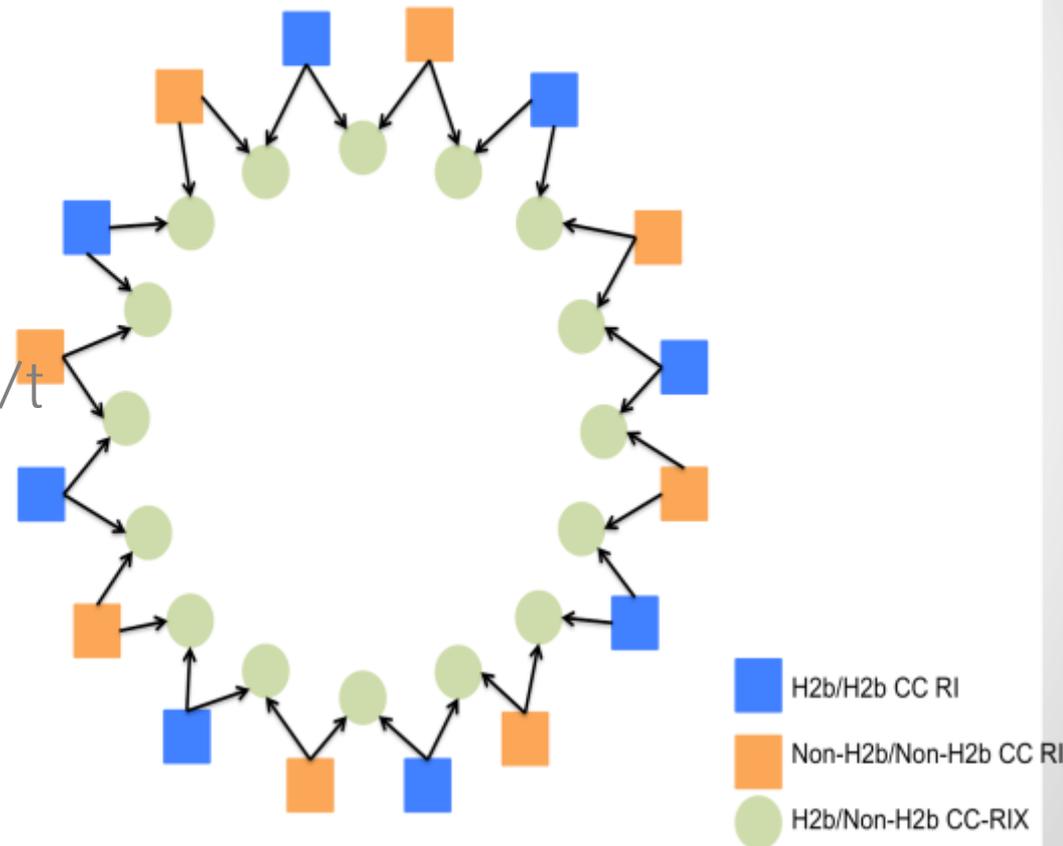


Emergent Disease Models

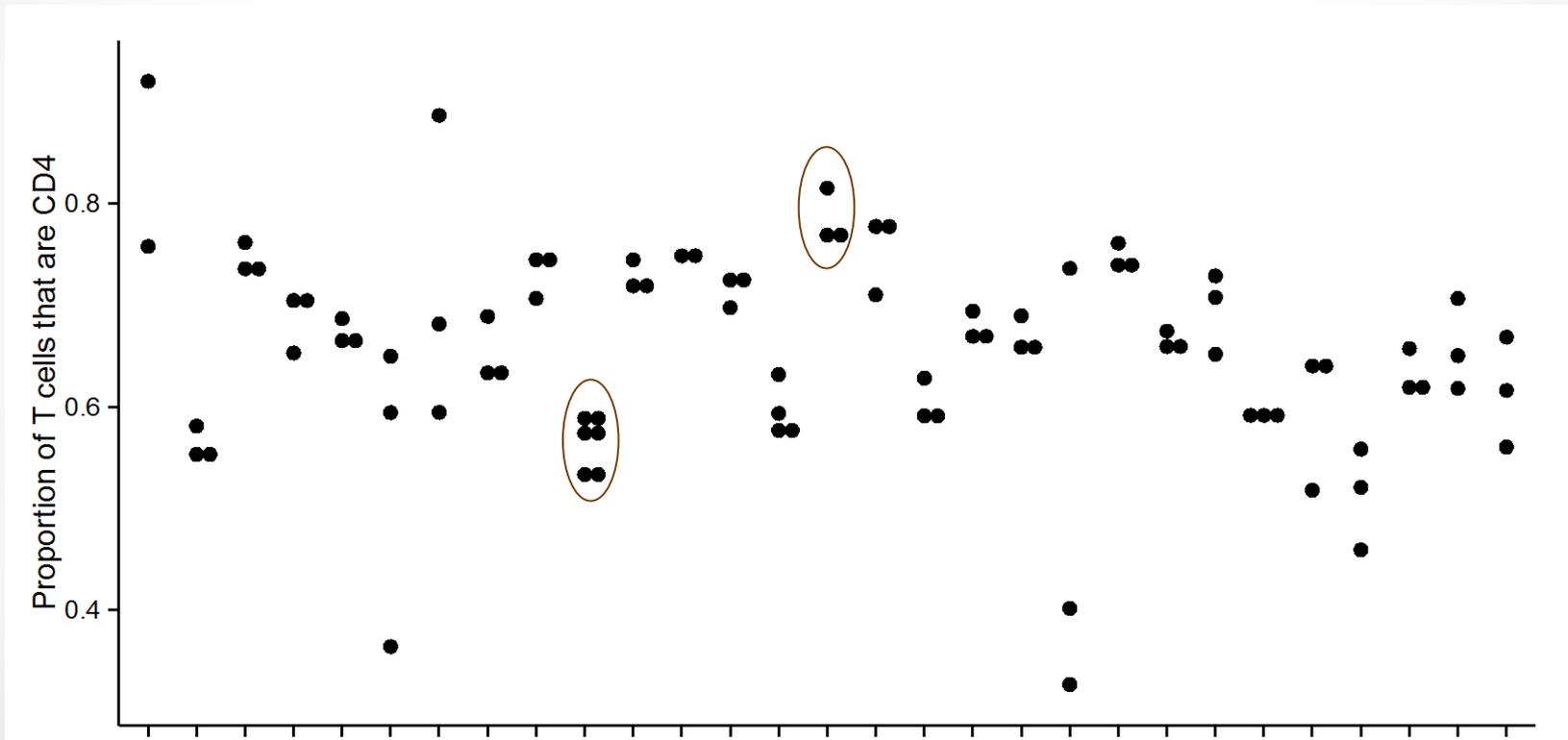
- Host genetic variation directly impacts disease phenotypes
- Can provide information on the breadth of potential responses
 - Can provide new actionable models of disease
 - Can disassociate disease responses
- Identification of potential contributing genetic variants underlying disease responses

CC-RIX (F1s between CC lines)

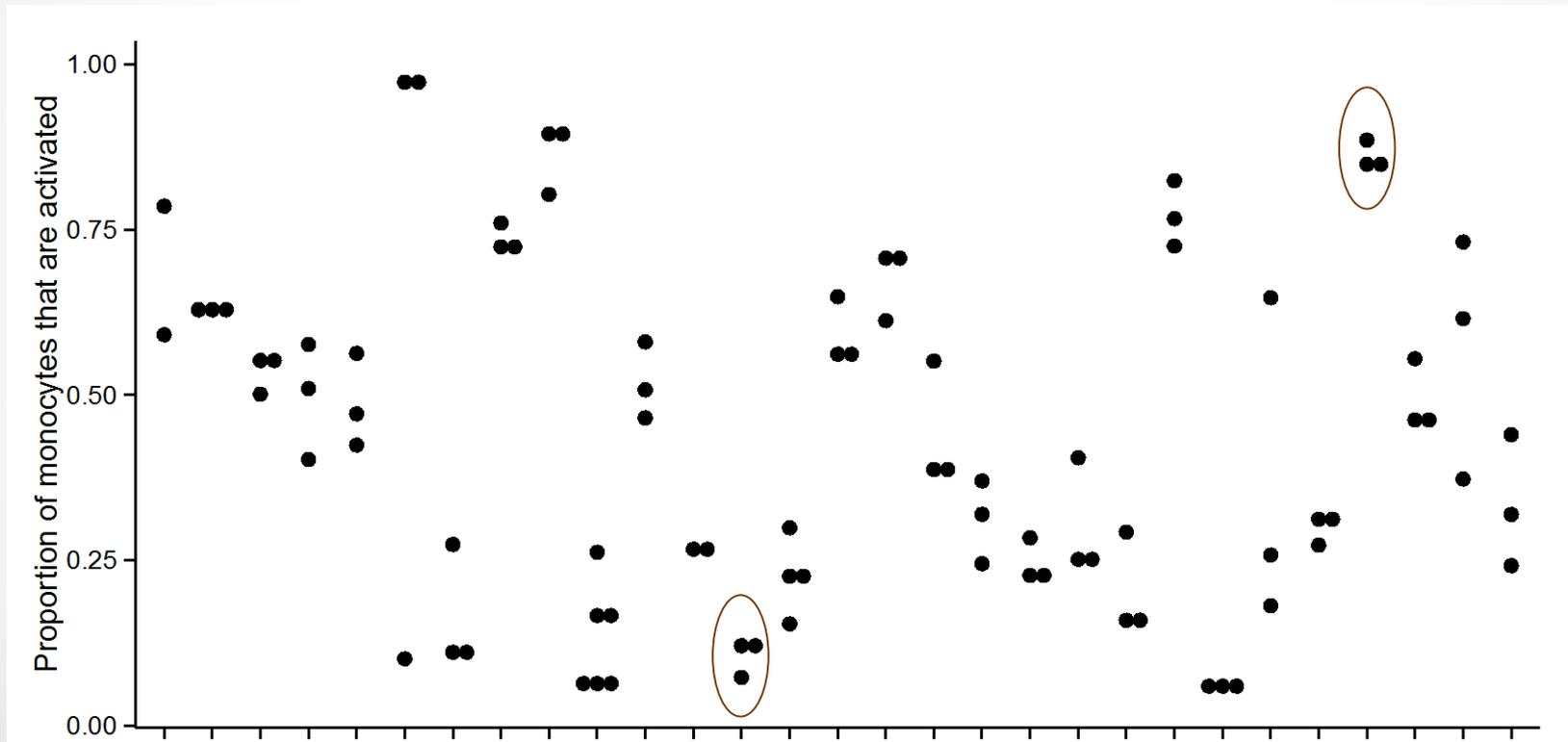
- Integration of this RIX population across pathogens/timepoints/t issues



Variation in basal inflammatory profiles



Variation in basal inflammatory profiles



Variation in basal inflammatory profiles

- As usage of these populations increase, there is an increasing pool of data to draw from improving experimental design and/or line selection
- Complex interplay in roles of basal levels/populations/activation states can lead to variation in downstream response profiles

Acknowledgements

Heinz Feldman

Frederike Feldman

Rachel LaCasse

Michael Katze

Angie Rasmussen

Atsu Okamura

Richard Green

Fernando Pardo-Manuel de Villena

Darla Miller

Ginger Shaw

Ralph Baric

Mark Heise

Alan Whitmore



SystemsImmunoGenetics