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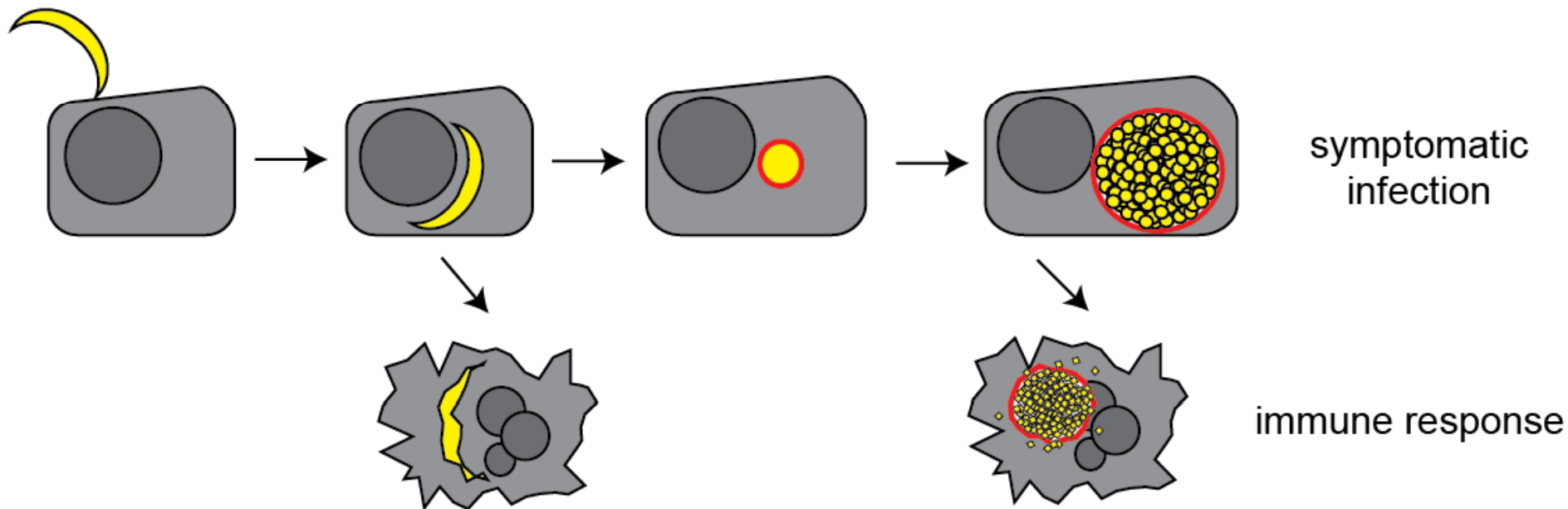
Non-canonical host cell signaling characterizes hepatocyte responses to *Plasmodium* infection

Alexis Kaushansky

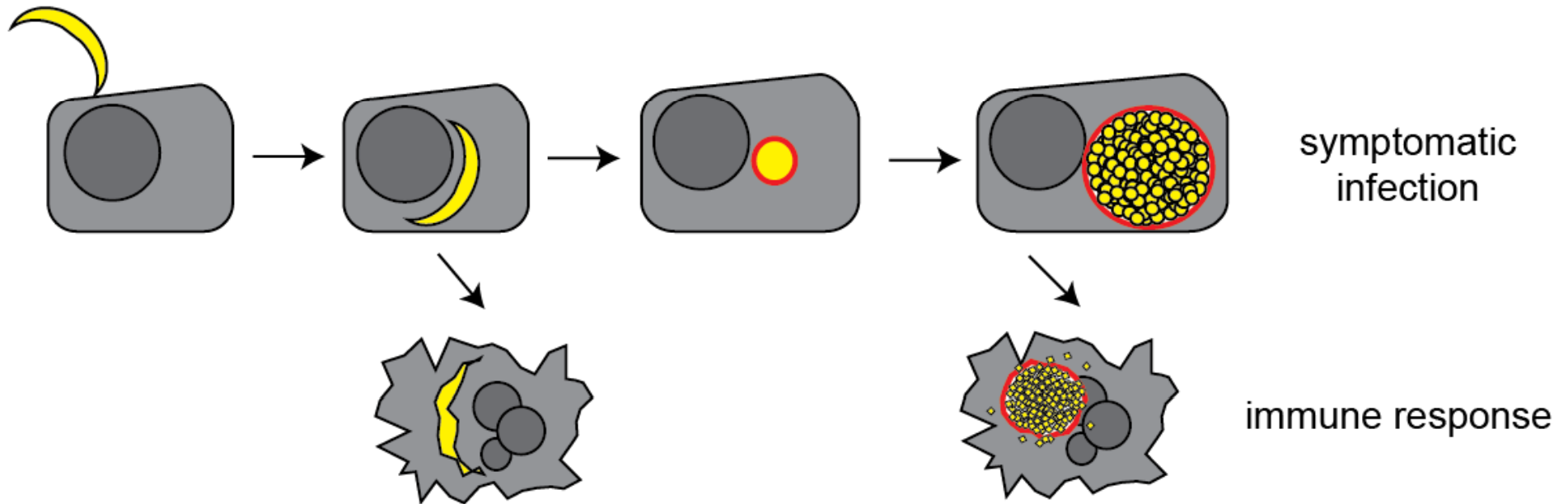
December 2018, JITMM



A substantial fraction of malaria parasites fail to progress through liver stage infection

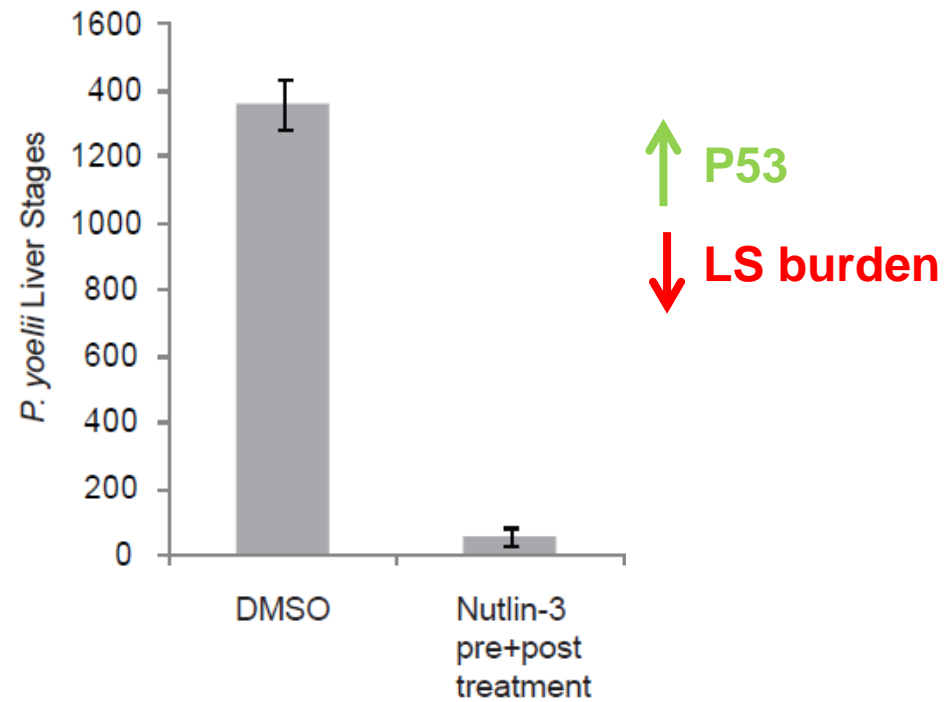
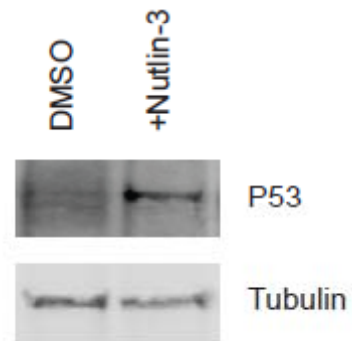


A substantial fraction of malaria parasites fail to progress through liver stage infection

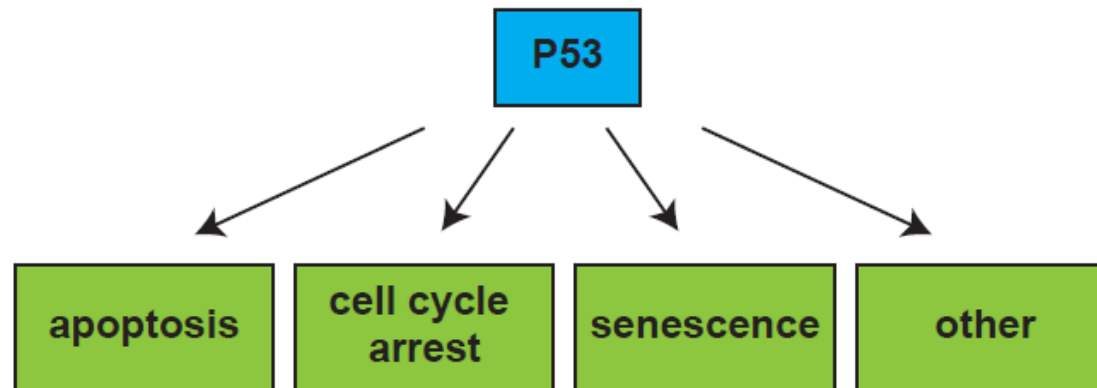


Many classical innate immune and cell death pathways play only a modest role in infection

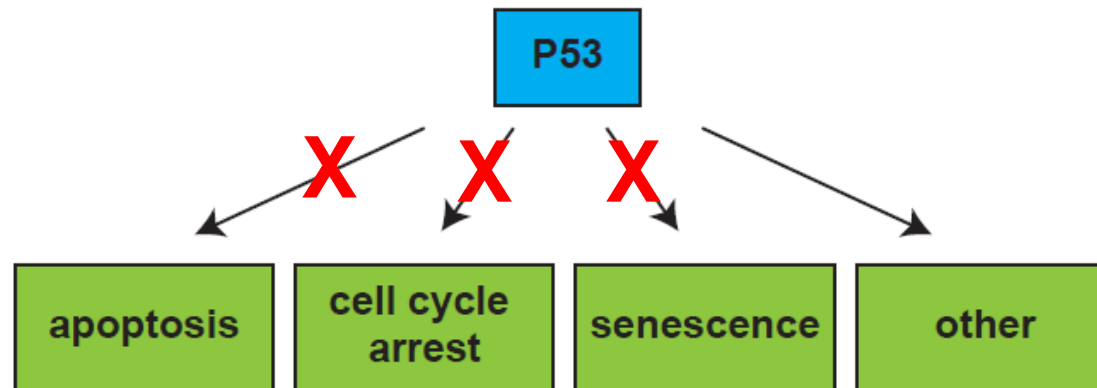
Nutlin-3 boost P53 and eliminates LS infection



P53 has a wide variety of activities within the cell



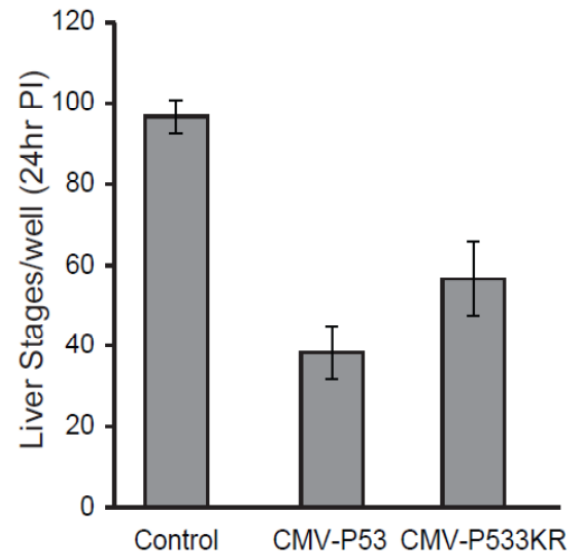
'Non-canonical' P53 biology plays a major role in disease



A Mutant of P53 (P53^{3KR}) that is deficient in apoptosis, cell cycle arrest and senescence retains potent tumor suppressor activity

This mutant is still capable of inducing 'ferroptosis'

Overexpression of P53 3KR variant reduces liver stage infection



Heather Kain

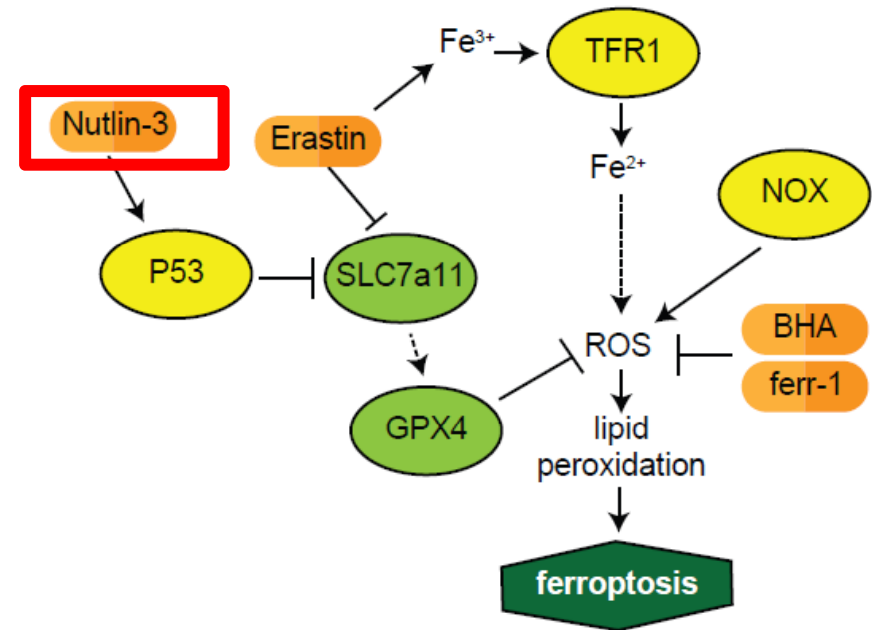
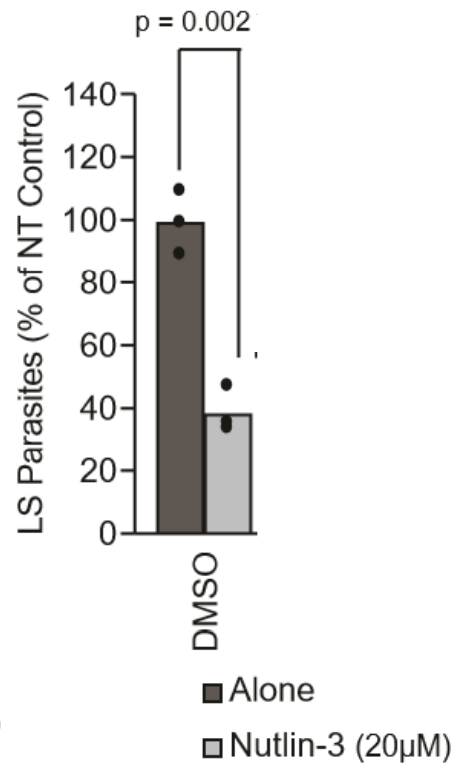
A Mutant of P53 (P53^{3KR}) that is deficient in apoptosis, cell cycle arrest and senescence retains potent tumor suppressor activity

This mutant promotes tumor suppression via 'ferroptosis'

Ferroptosis is an iron-dependent, caspase-independent form of cell death

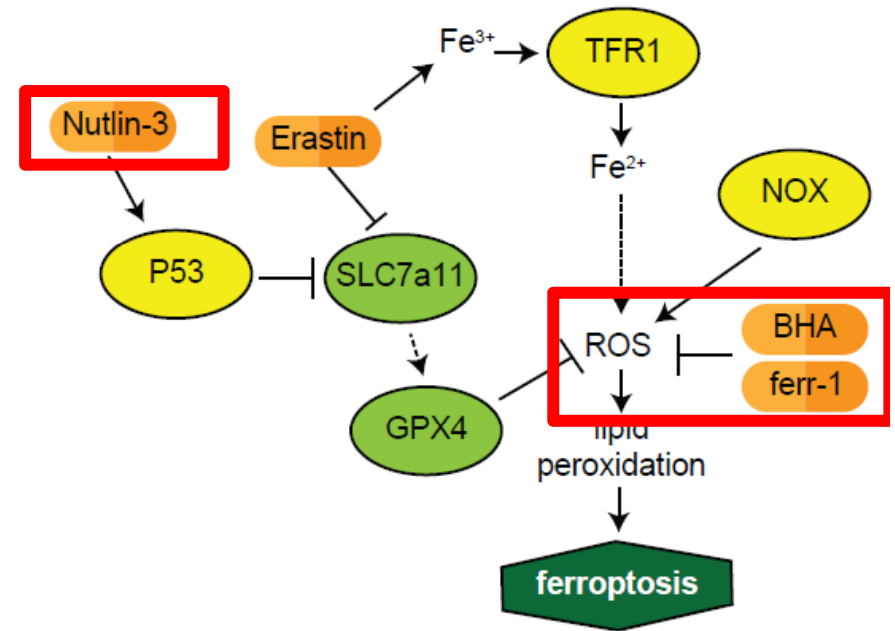
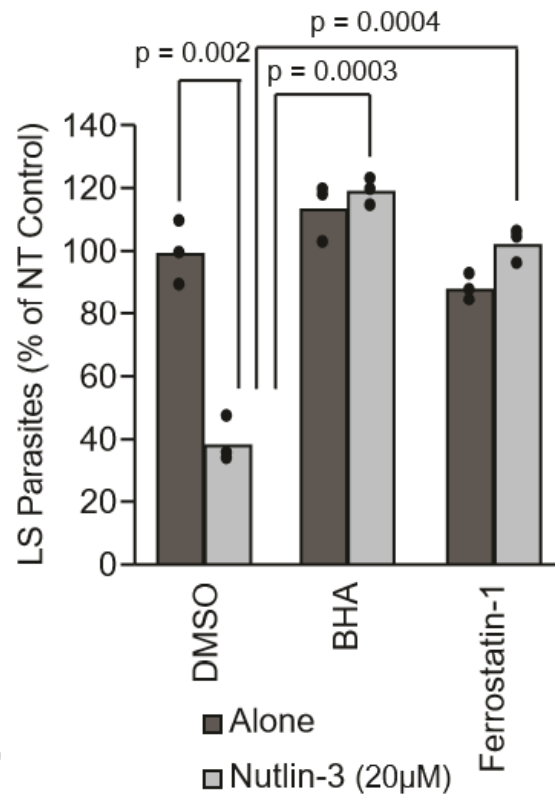
- Susceptibilities vary dramatically across cell types, many “normal/healthy” cell types are not susceptible
- Many contributions: fatty acid composition, amino acid availability, glutathione biosynthesis, etc.

Scavenging ROS or blocking ferroptosis reverses the effect of Nutlin-3 on liver stage parasite infection

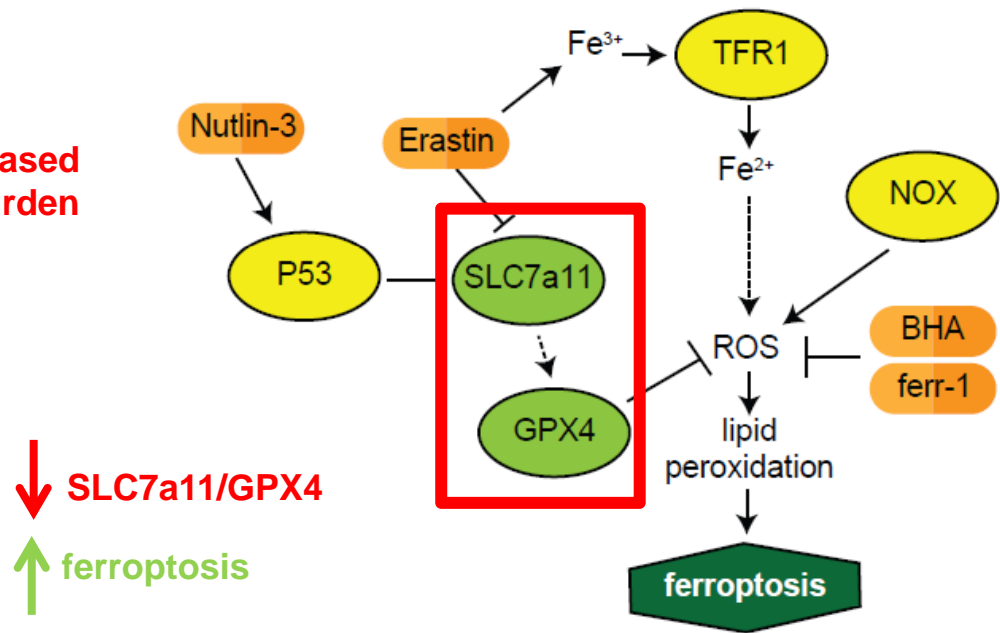
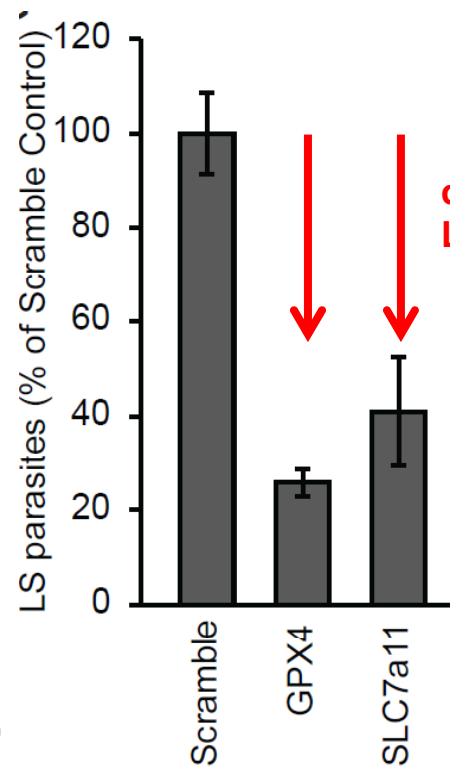


Kain et al, BioRxiv

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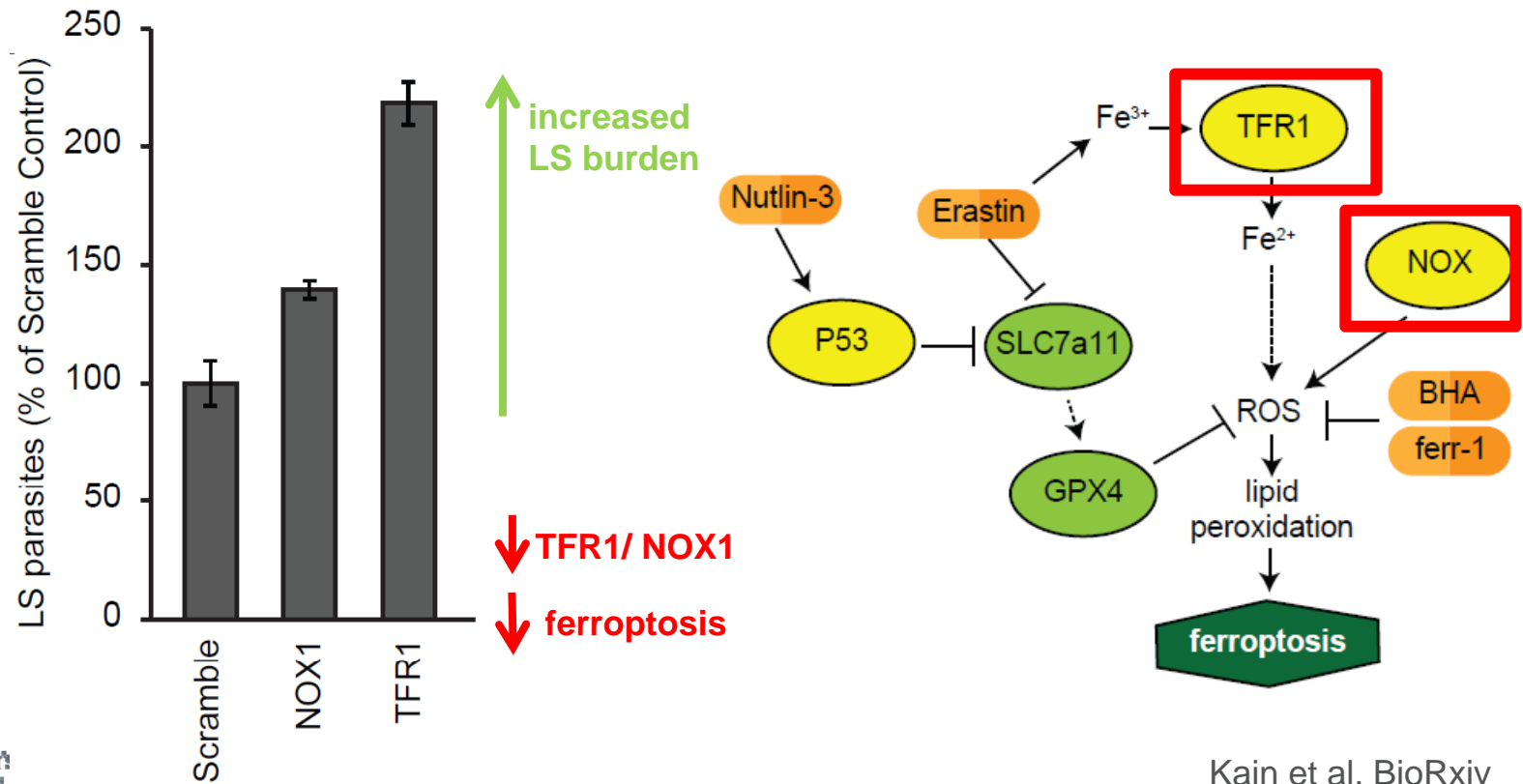


Knockdown of SLC7a11 and GPX4, negative regulators of ferroptosis, decrease infection

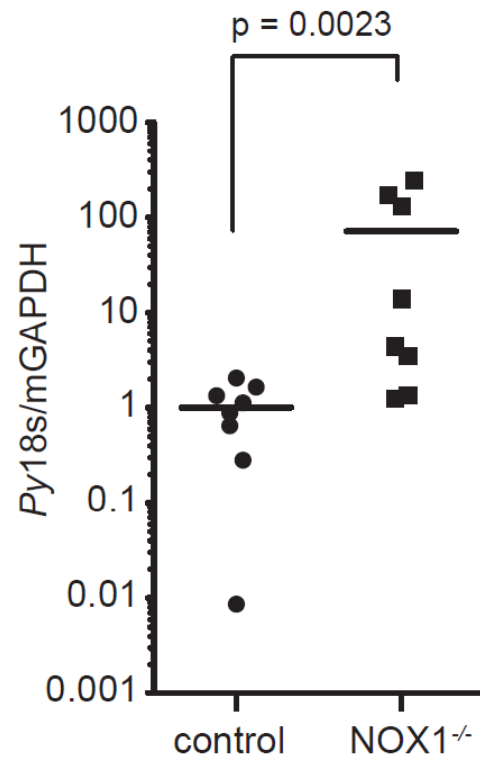


↓ SLC7a11/GPX4
↑ ferroptosis

Knockdown of NOX1 and TFR1, positive regulators of ferroptosis, decrease infection

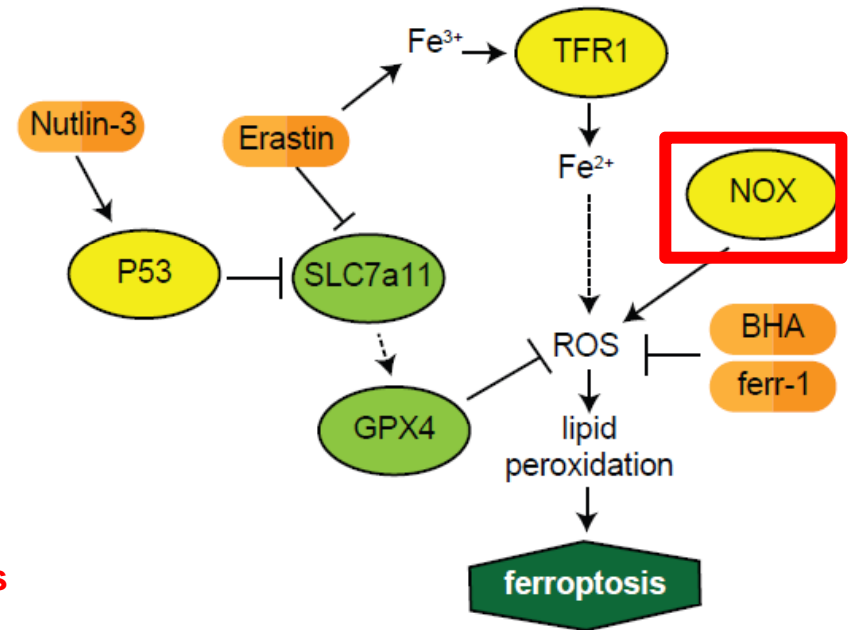


Knockout of NOX1, a potent regulator of ferroptosis, alters *Plasmodium* infection *in vivo*

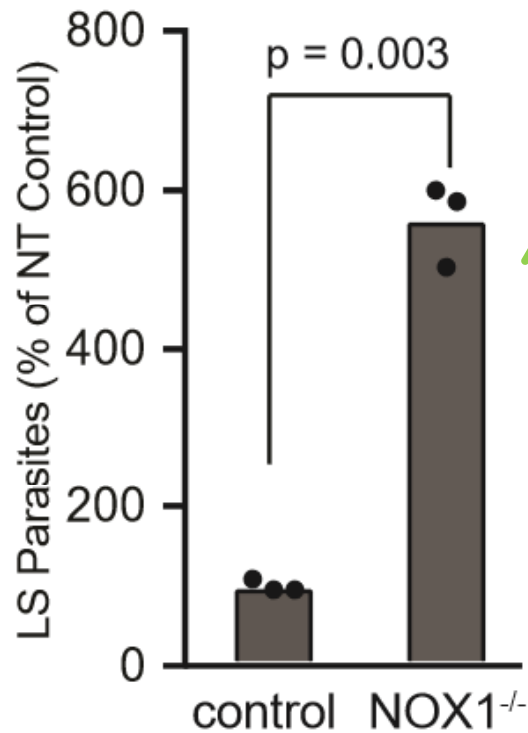


↑ increased LS burden *in vitro*

↓ NOX1
↓ ferroptosis



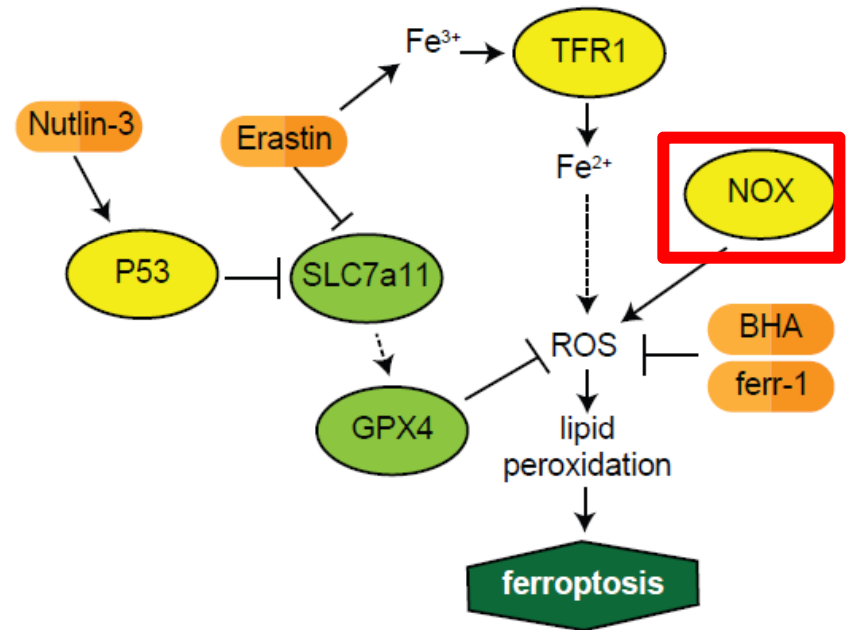
NOX1 impact on *Plasmodium* infection is hepatocyte-specific



increased LS burden *in vitro*

↓ NOX1

↓ ferroptosis



Kain et al, BioRxiv

Hepatocytes isolated from C57Bl/6 mice

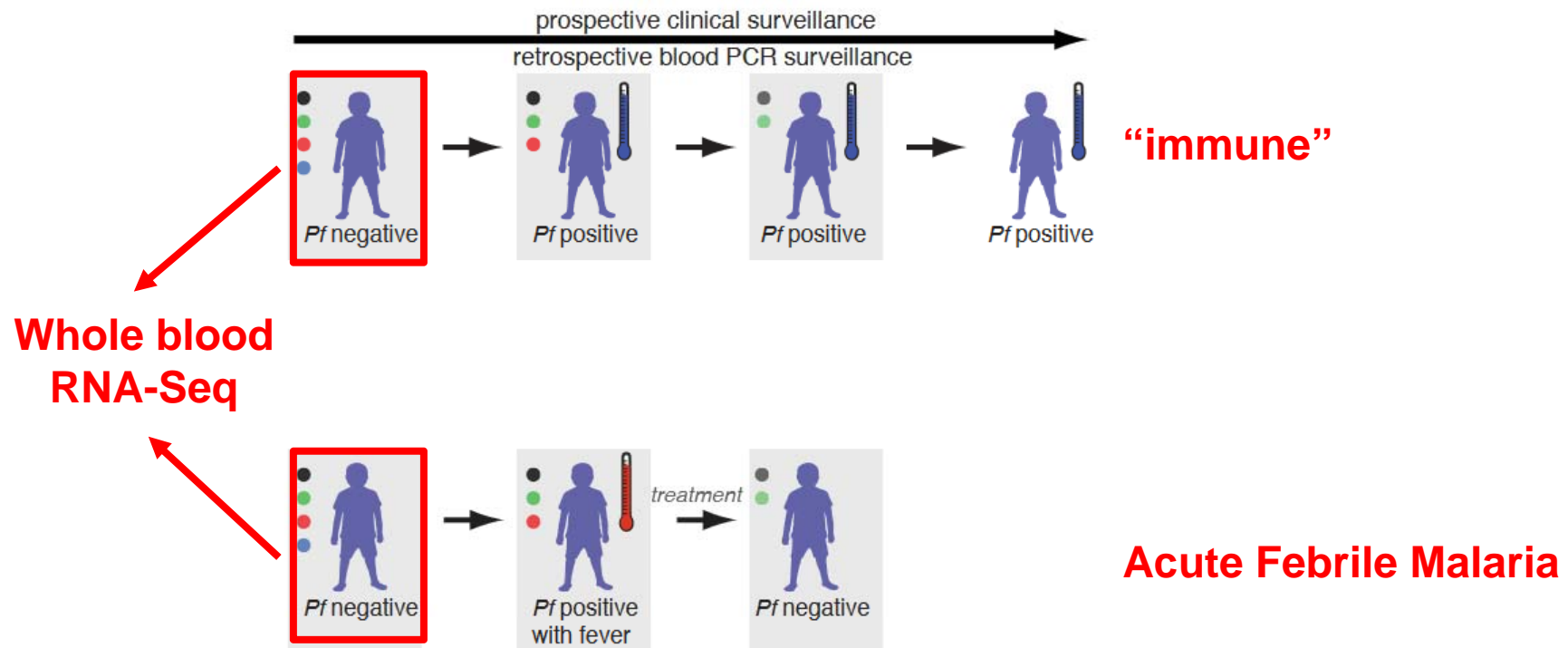


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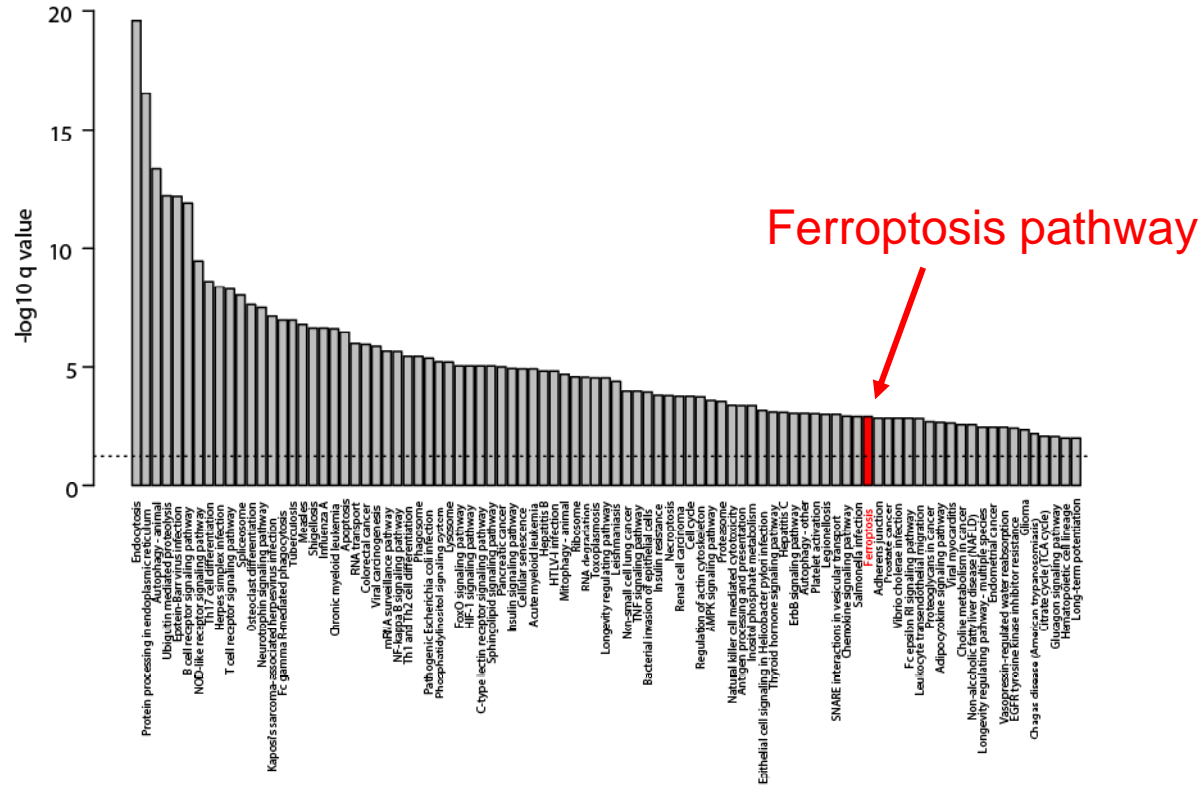
Does ferroptosis-associated signaling alter susceptibility to malaria in the field?



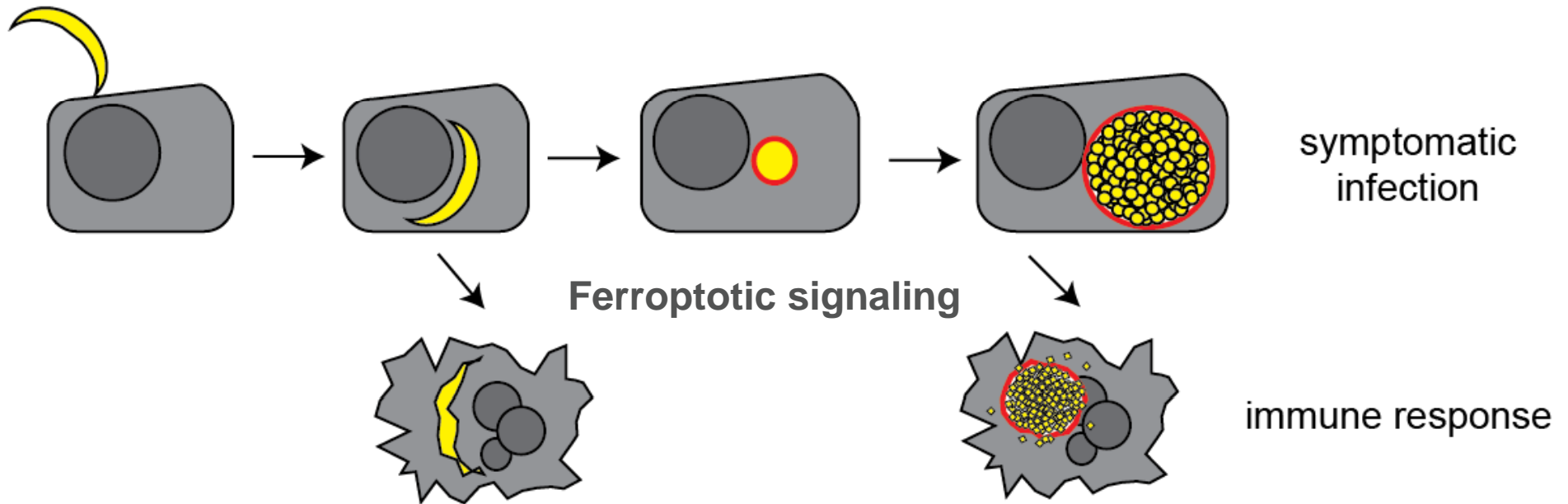
Prospective study of individuals with differential susceptibility to malaria disease in Mali



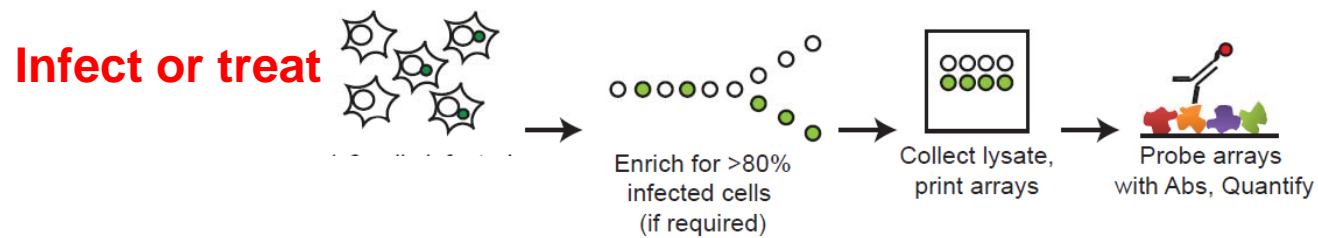
KEGG ferroptosis pathway enrichment: ferroptosis is a differentially regulated in immune individuals



A substantial fraction of malaria parasites fail to progress through liver stage infection



Reverse Phase Protein Arrays can be used to evaluate cell signaling

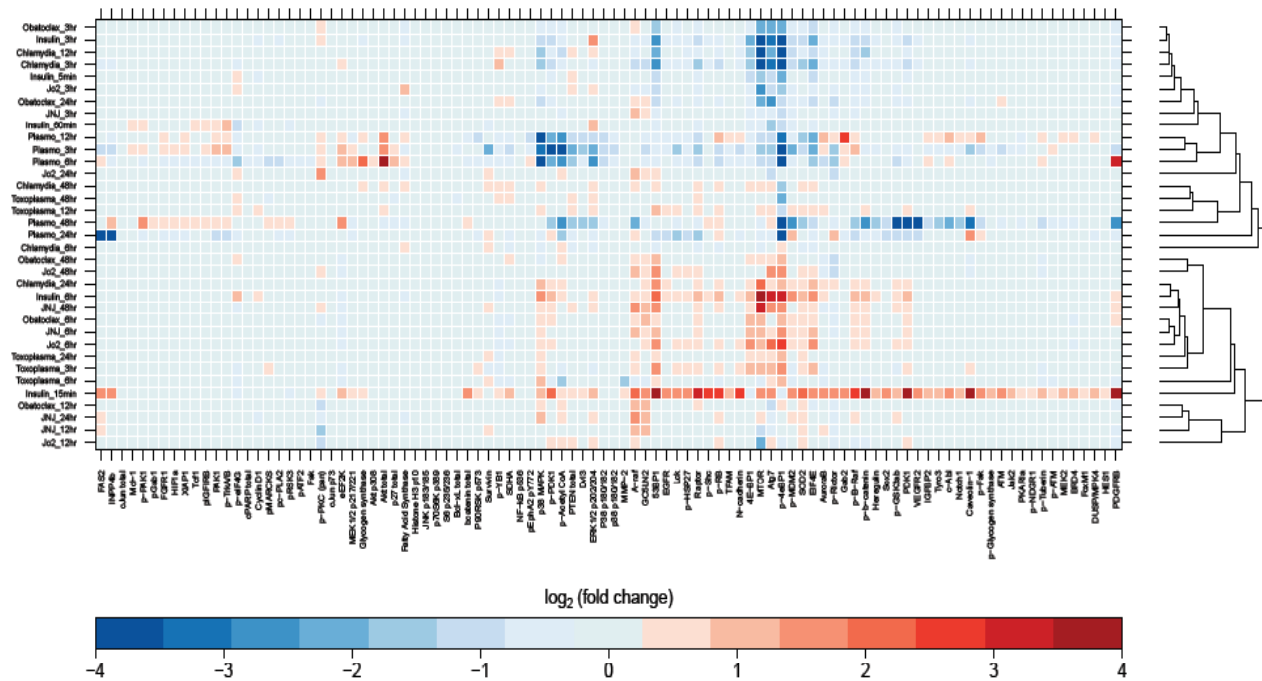


Evaluate host cells signaling proteins involved in cell survival, death, growth, autophagy, nutrient update, etc.

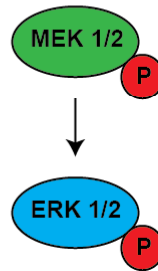
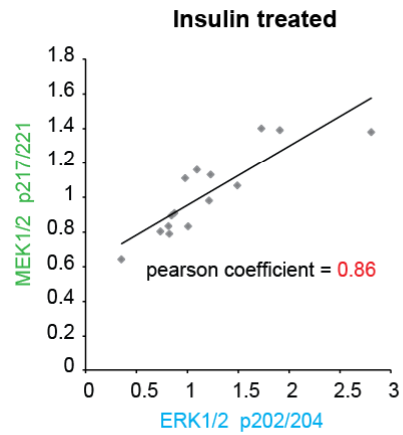


Lizzy Glennon

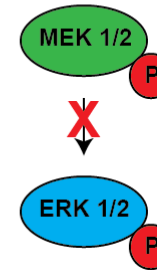
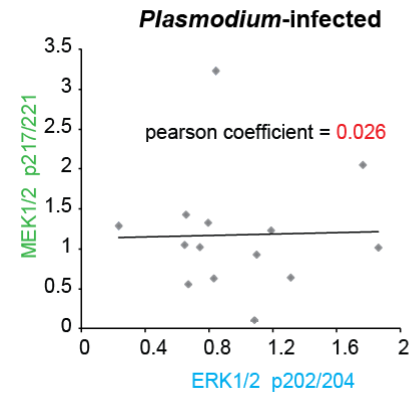
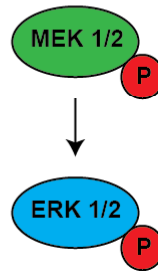
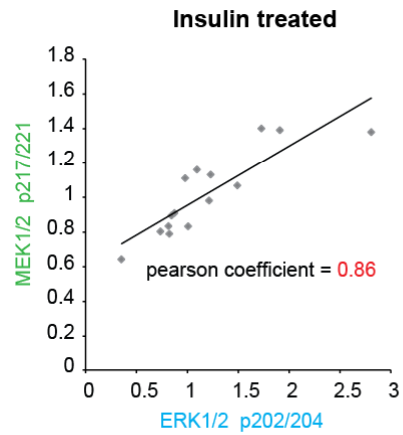
A diverse range of signaling pathways are altered during infection



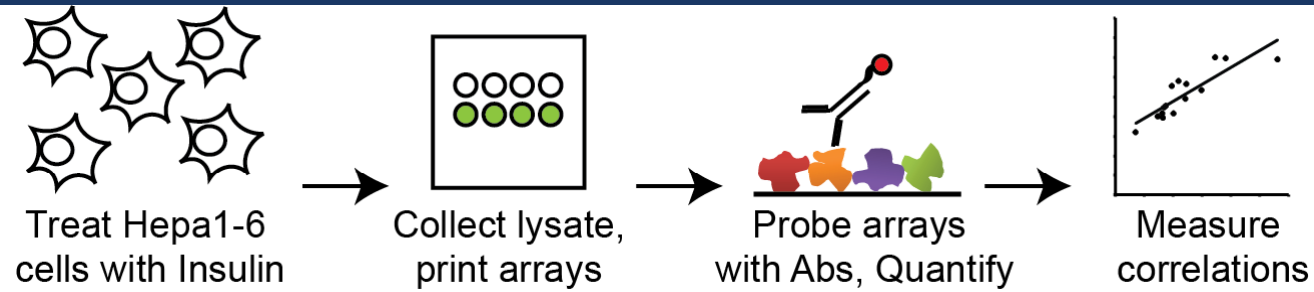
RPPA data can give insights into associations between proteins



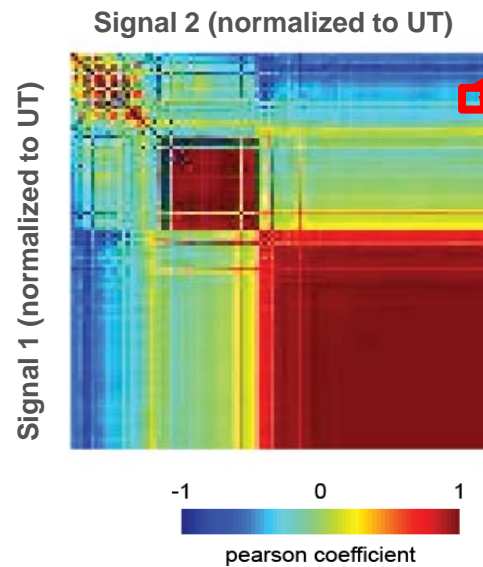
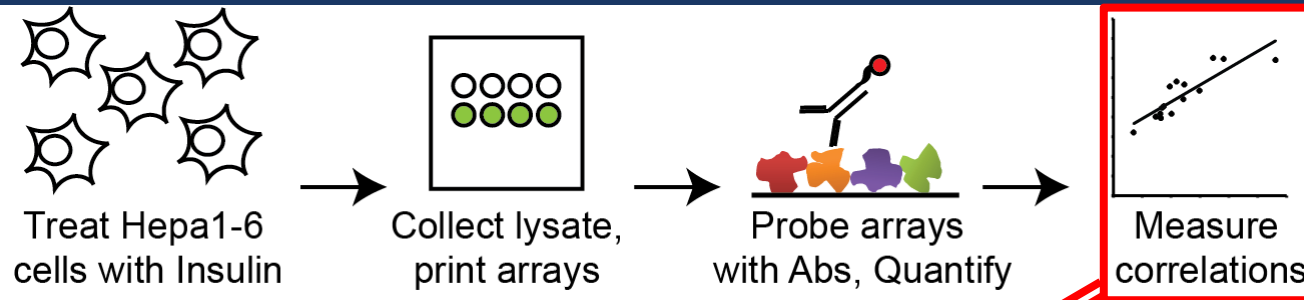
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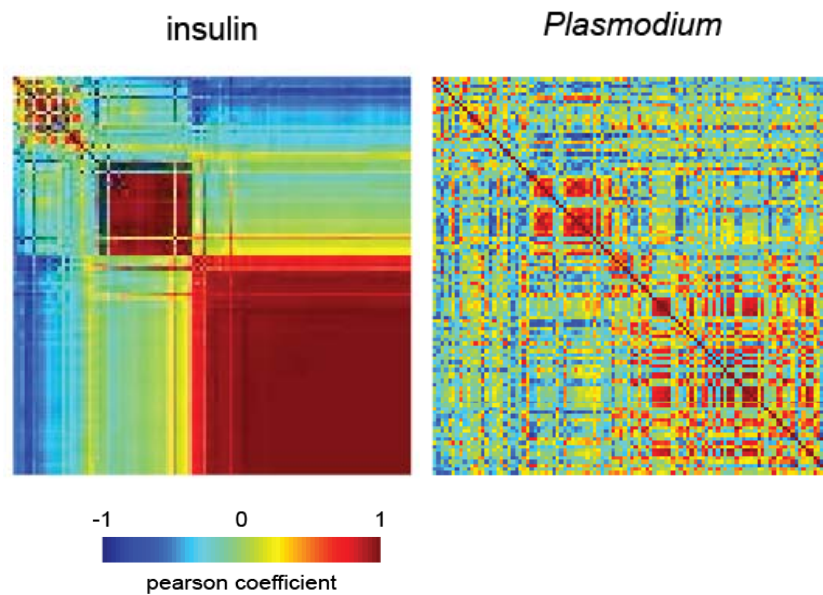
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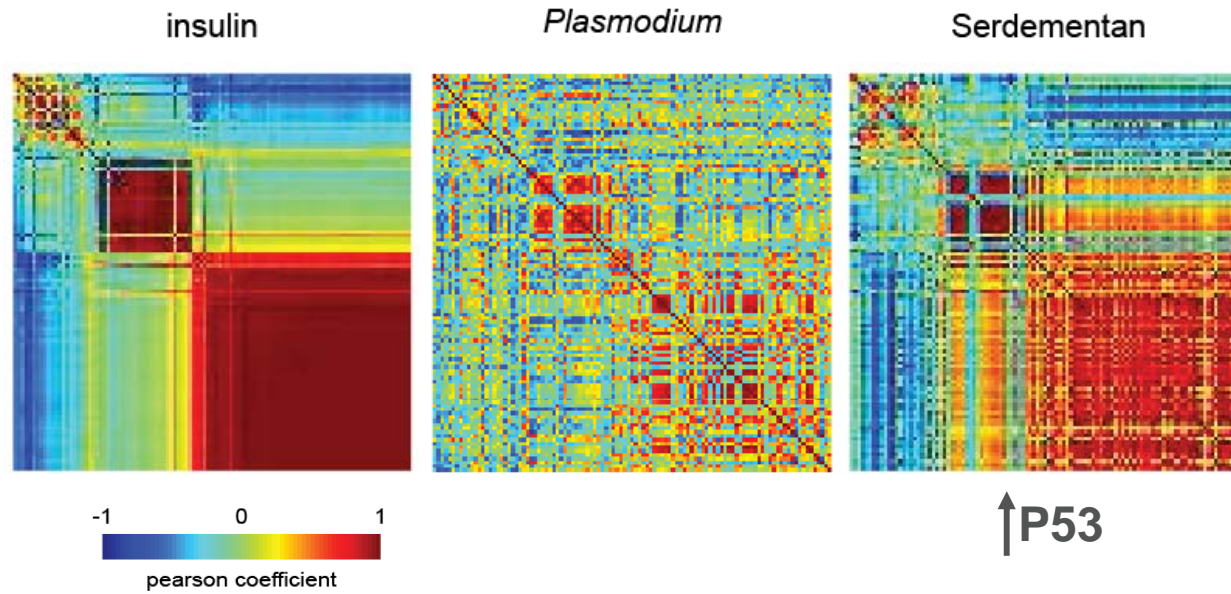
A number of hepatocyte signals are tightly correlated



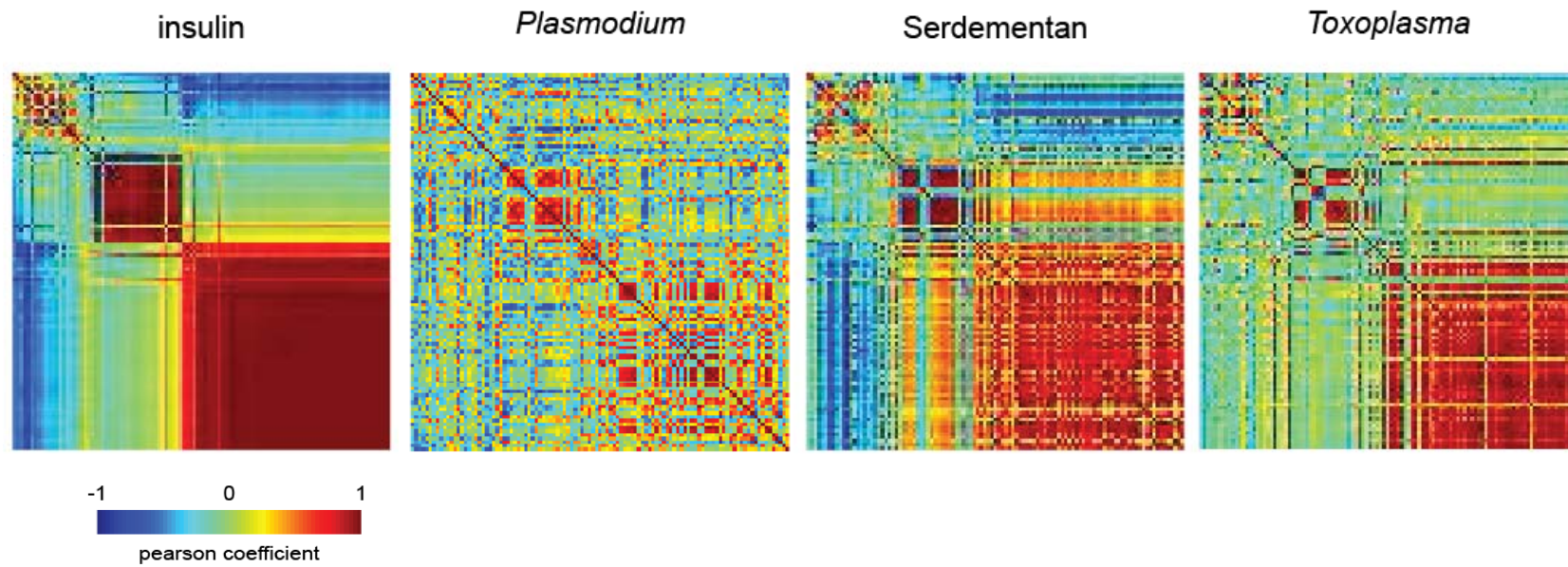
Disruption of signaling correlations appears to be *Plasmodium*-infection specific



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Disruption of signaling correlations appears to be *Plasmodium*-infection specific



Conclusions

- Non-canonical P53-driven signaling is a strong cell-intrinsic innate control mechanism against *Plasmodium* LS infection
- Many of the factors that are responsible for LS clearance are shared with a form of cell death called ferroptosis
- Transcripts of non-canonical P53 signaling are enriched in “immune” individuals in the field
- Many signaling pathways in *Plasmodium*-infected hepatocytes are extensively rewired

Non-canonical signaling that is absent in most ‘normal’ cell types may provide an opportunity to target infection

Acknowledgements



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