

# Experimental reverse zoonosis of Plasmodium falciparum in mouse erythrocytes reveals key cellular pathways for anti-malarial drug discovery



LB-RES-020

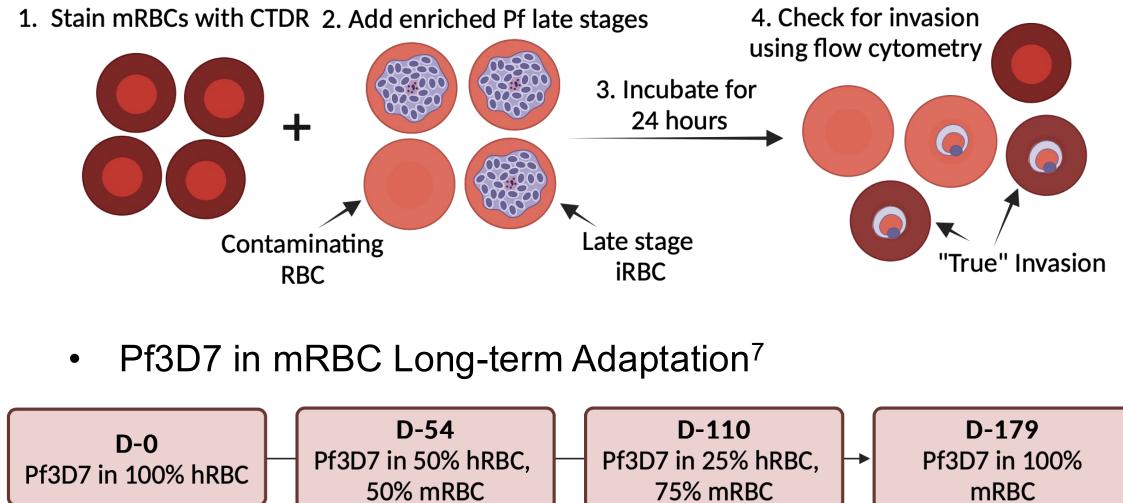
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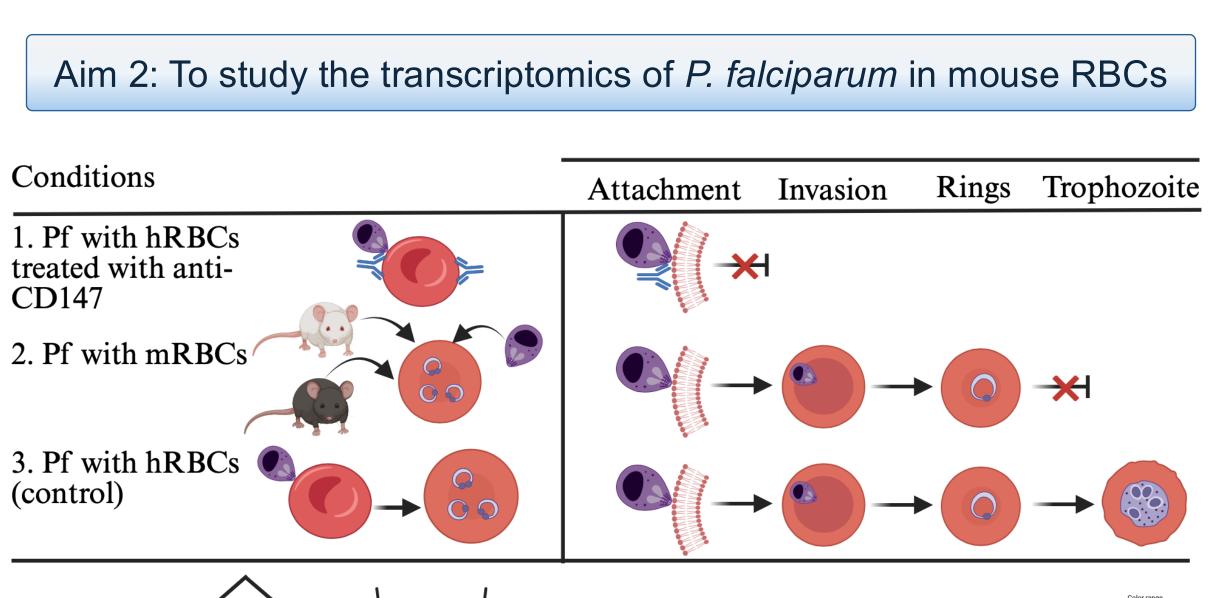
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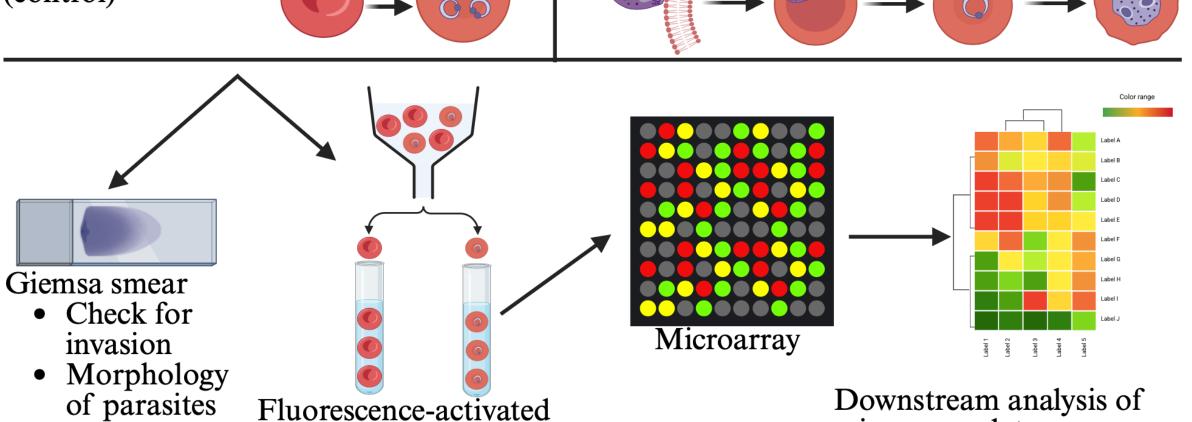
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# INTRODUCTION P. falciparum blood cycle Malaria In 2022, 249 million cases<sup>1</sup> Trophozoite 608,000 deaths<sup>1</sup> 8 Dormancy Merozoites Temporary growth arrest Presence of pyknotic rings Hypothermic and hyperthermic conditions can result in dormancy<sup>2</sup> P. falciparum erythrocyte invasion Host receptor-parasite ligand interactions PfRH5 binds to erythrocyte receptor CD147<sup>3</sup> P. falciparum animal models Non-human primates Ethical and cost issues<sup>4</sup> Humanized mice Hostile mouse environment (Liver-humanized/hRBC and need for immunocompromised mice<sup>5</sup> engraftment) Research gap Essential parasite pathways to circumvent drug resistance PROJECT AIMS & METHODS

# Aim 1: To culture and adapt *P. falciparum* in mouse RBCs in vitro Pf3D7 in mRBC Invasion Assay<sup>6</sup> 1. Stain mRBCs with CTDR 2. Add enriched Pf late stages 4. Check for invasion using flow cytometry 3. Incubate for 24 hours Contaminating Late stage







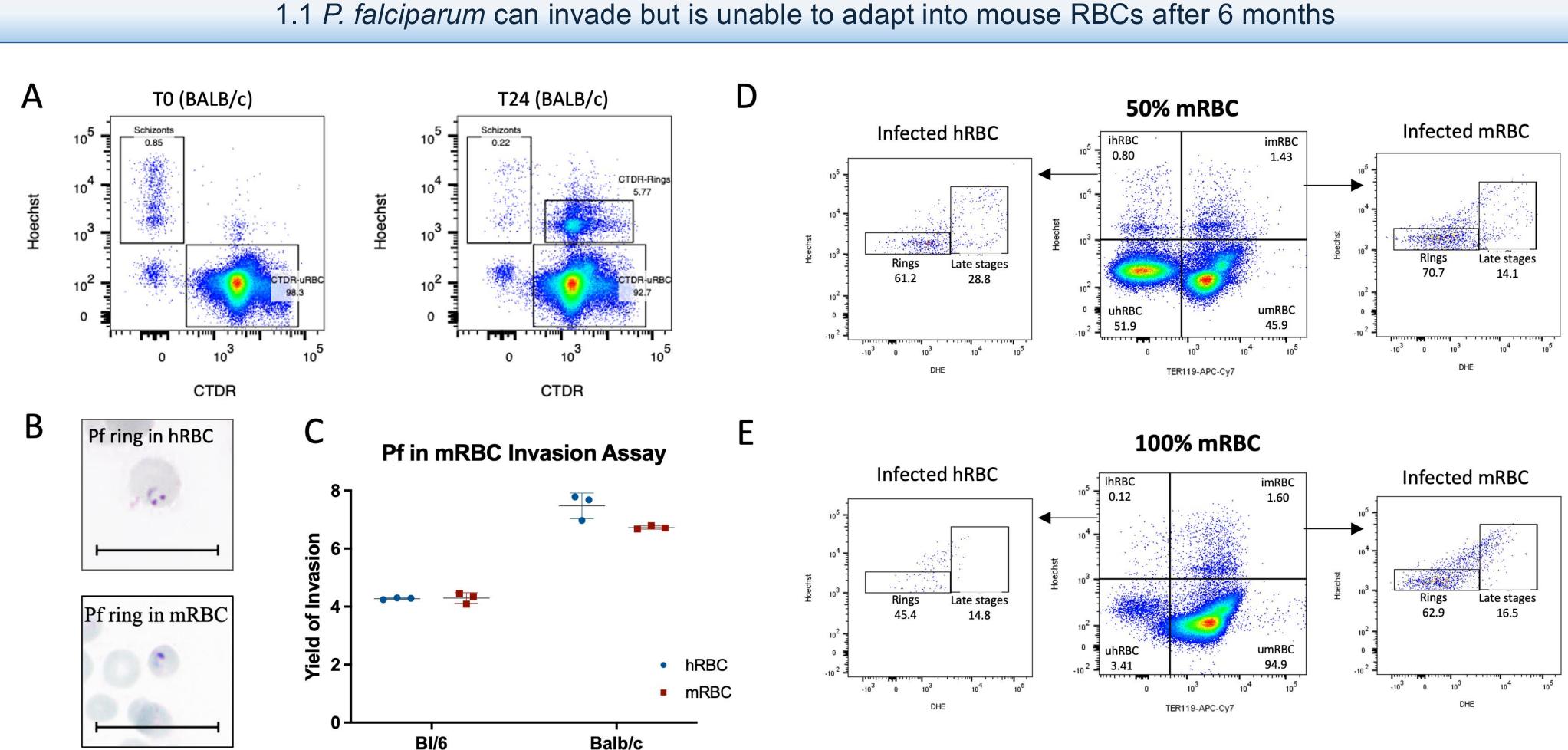
• Parasitemia cell sorting Staging Stain samples with Hoechst and DHE

Fluorescence-activated

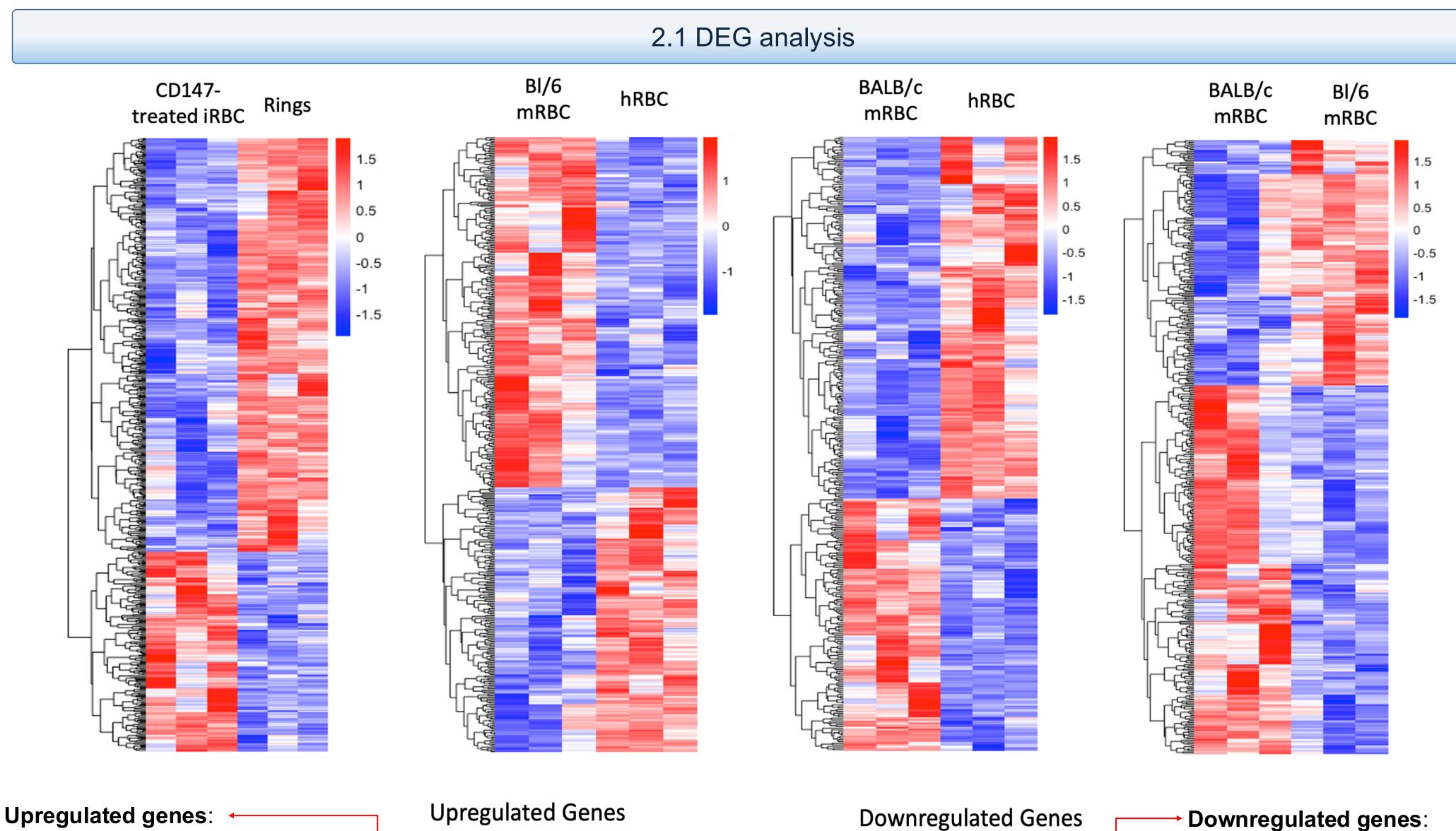
- Sort Hoechst<sup>pos</sup> and DHE<sup>low</sup> population for "Rings"
- Downstream analysis of microarray data Find genes and
- pathways exclusive to Pf in mRBC condition by excluding similar genes in CD147-treated condition

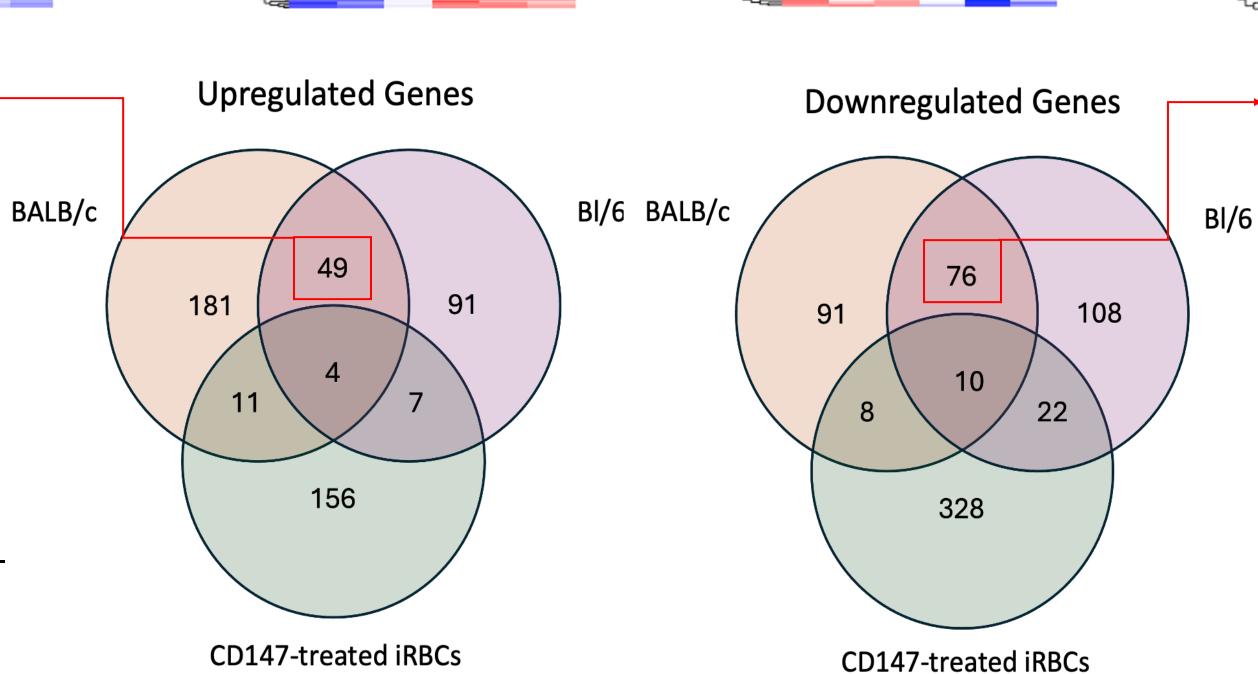
# RESULTS AND DISCUSSION

#### AIM 1: TO CULTURE AND ADAPT P. FALCIPARUM IN MOUSE RBCS IN VITRO



AIM 2: TO STUDY THE TRANSCRIPTOMICS OF *P. FALCIPARUM* IN MOUSE RBCS





- Genes involved in energy metabolic pathways
  - PfPPCS (in CoA biosynthesis pathway)
- PfFbpA (in glycolysis
- pathway) PflspE (in MEP pathway
- in apicoplast) Genes involved in protein
- trafficking
- PfDHHC4, PfDHHC5 (palmitoylation for protein trafficking)
- PfPTEX88 (protein trafficking into host cell)

# CONCLUSIONS

Genes involved in stress

PfGILP (glyoxalase I)

protein quality control

PF3D7\_0312100,

protein ligases)

PfHRD1 (E3 ubiquitin-

and detoxification

• PfFeSOD (Fe

superoxide

dismutase)

Genes involved in

and **degradation** 

responses

# **AIM** 1:

- Pf3D7 can invade mRBCs and develop into rings
- Pf3D7 is unable to adapt into mouse RBCs after 6 months

# **AIM 2:**

- Upregulated genes suggest elevated oxidative or metabolic stress and proteostasis -> parasite adaption to a different intracellular environment
- Downregulated genes suggest reduced or altered energy metabolism and protein trafficking -> transcriptionally inactive state

# REFERENCES

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