# Validation of the *Plasmodium falciparum* deoxyhypusine synthase gene as an antimalarial target

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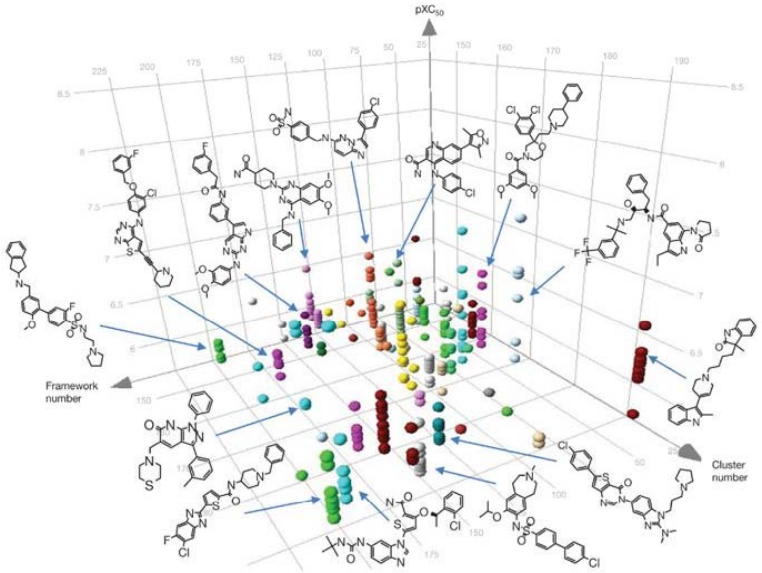
# The scourge of drug-resistant malaria parasites


www.bbc.co.uk

**Alarm as 'super malaria' spreads in South East Asia - BBC News**

# A glut of antimalarial compounds and *Plasmodium falciparum* targets: but how will we find new drugs?

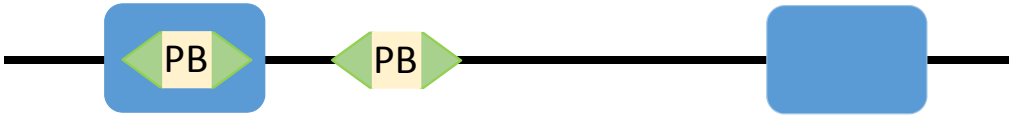
## Compounds




13,533 antimalarial hits from GSK library

(Gamo et al., 2010; *Nature* **465**:305-310)

## Targets



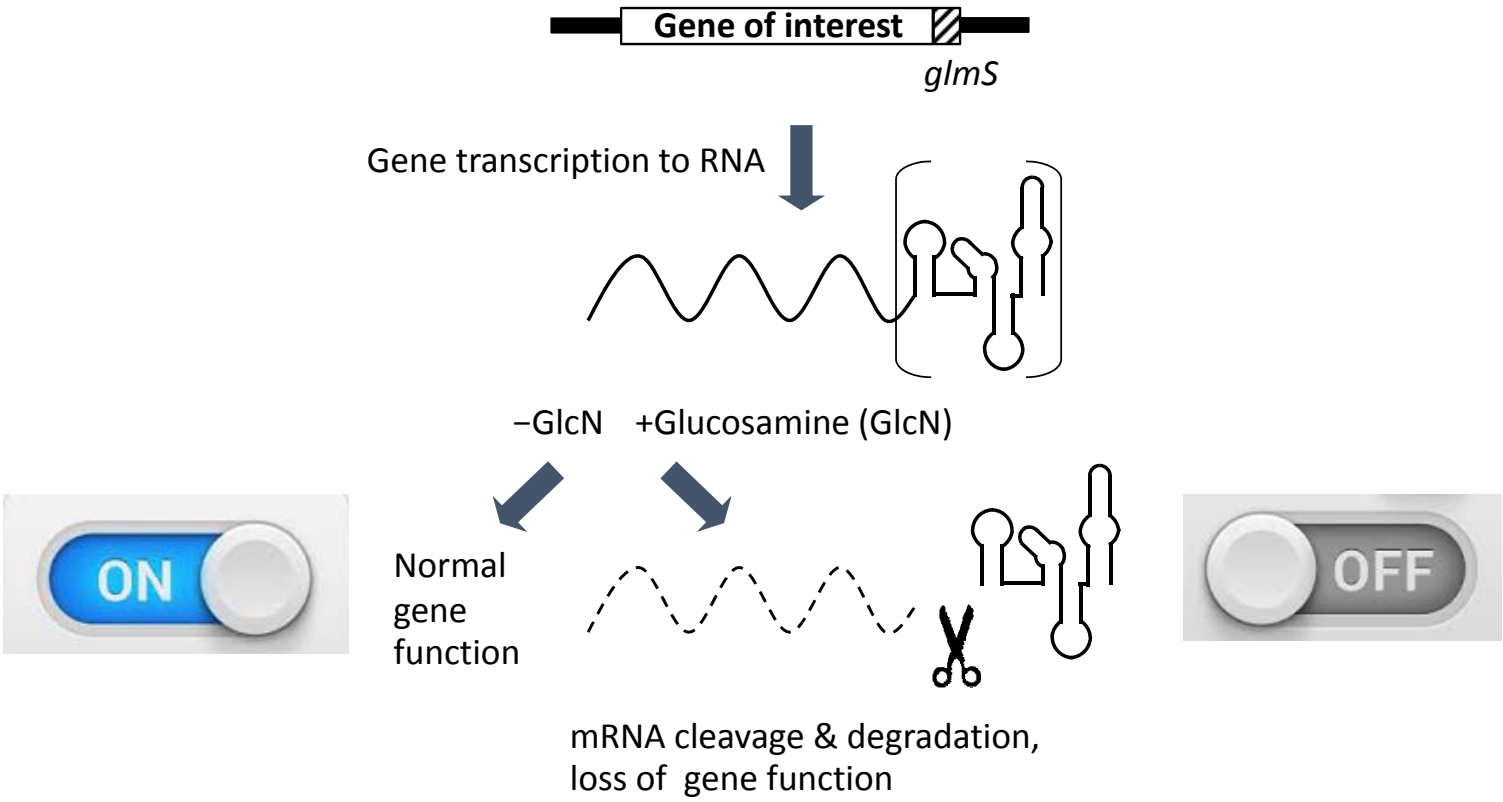

2042
mutable genes;
dispensable in asexual stages

3357
non-mutable genes;
likely essential

*piggyBac* (PB) saturation mutagenesis

(Zhang et al., 2018; *Science* **360**: 3688)

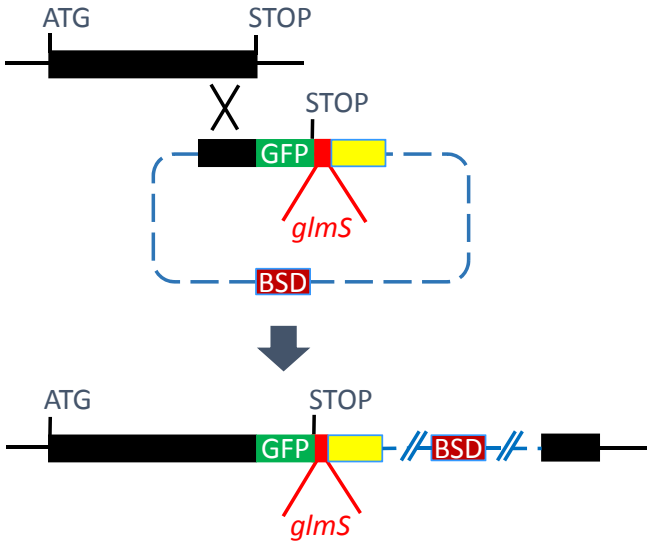
# The *glmS* riboswitch reverse genetic tool for knockdown of *Plasmodium* gene expression




Shaw & Aroonsri (2017) *Int J Parasitol* **47**:385-398

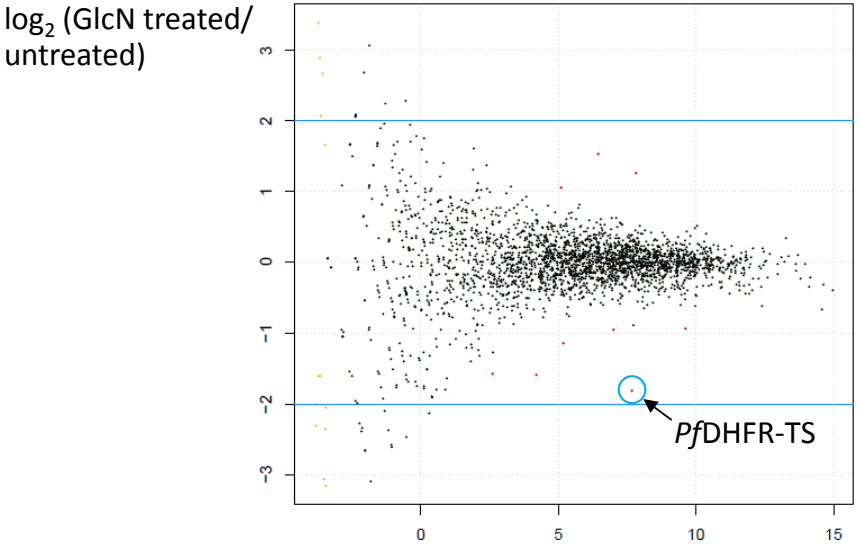
# *glmS* riboswitch-mediated knockdown of *Pf*DHFR-TS gene expression

**Modification of the PF3D7_0417200 gene (dihydrofolate reductase-thymidylate synthase, *Pf*DHFR-TS)**



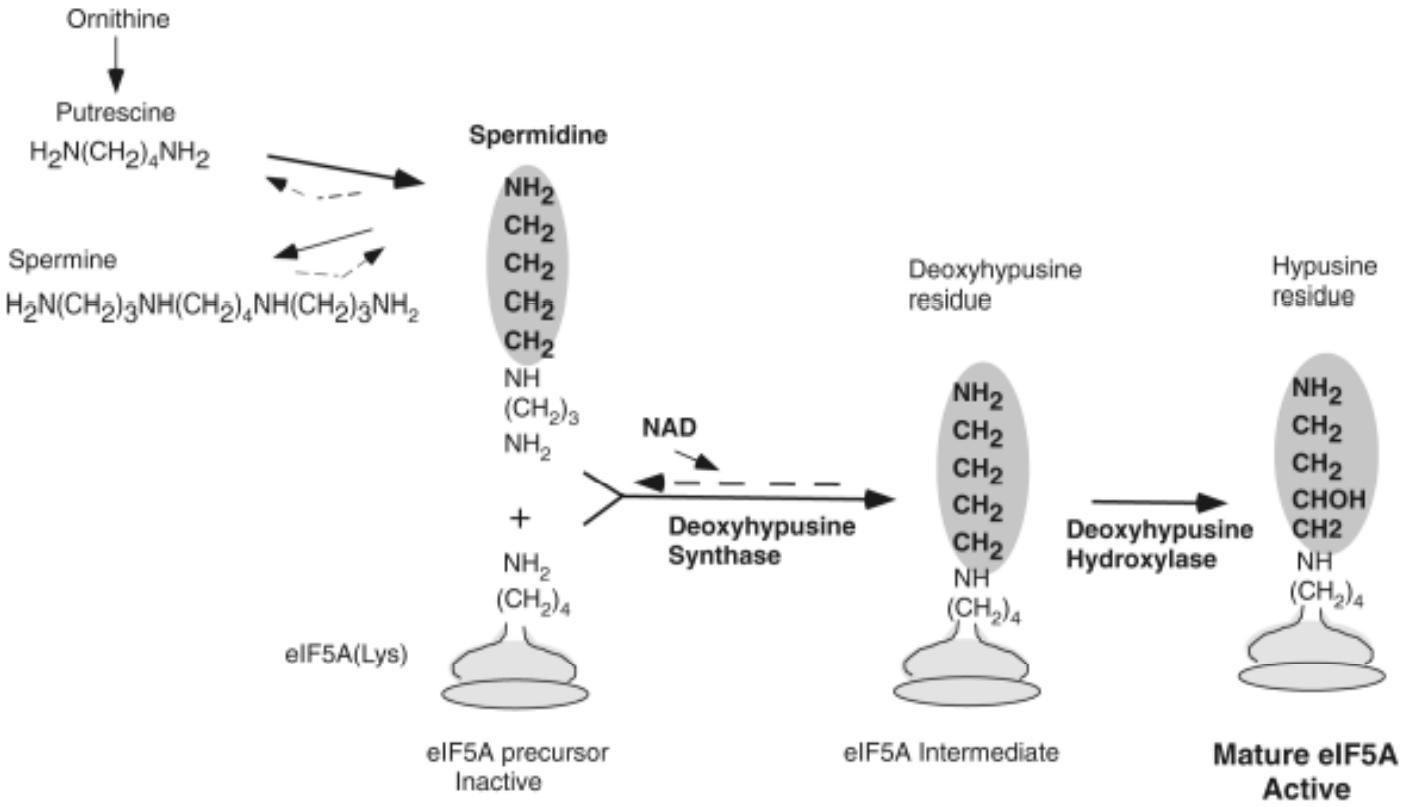

*Pf*DHFR-TS_*glmS* transgenic parasite

***Pf*DHFR-TS_*glmS* parasite RNA-seq (2648 genes)**



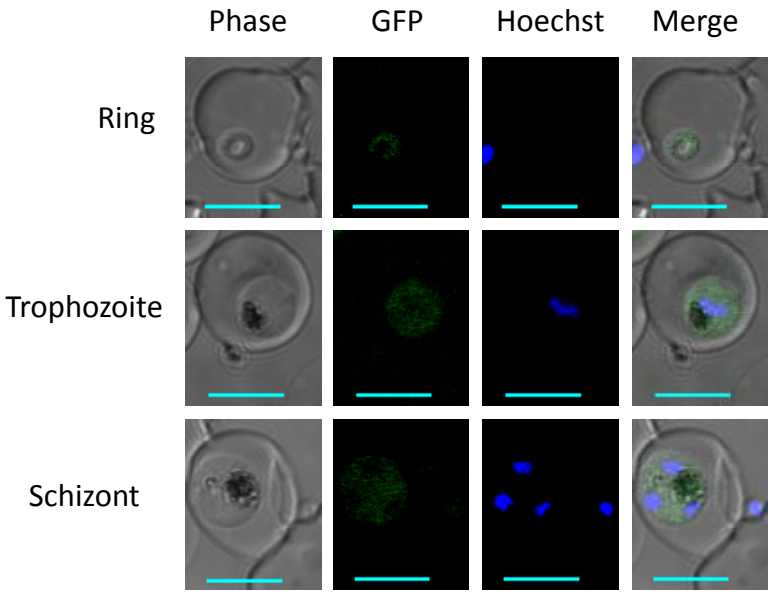

Prommana et al. (2013) *PLoS ONE* **8**(8):e73783

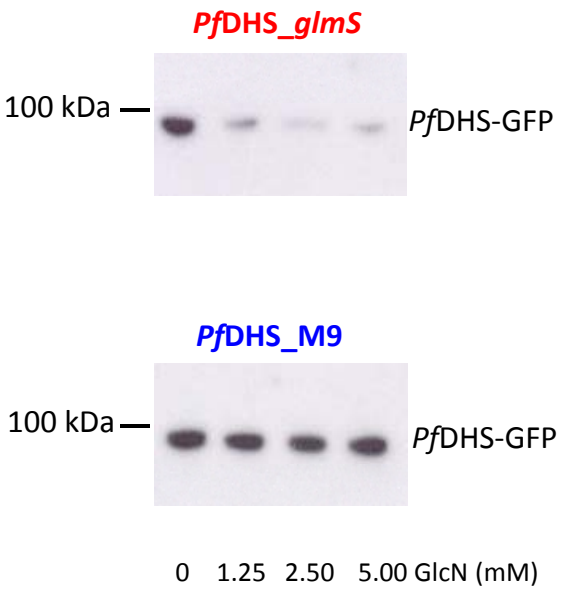
# Hypusination as a putative antimalarial target



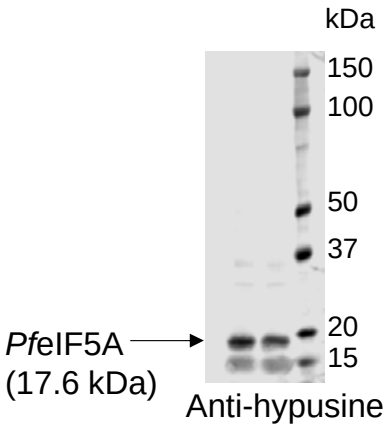

Park et al. (2010) *Amino acids* **38**:491-500

# *glmS* riboswitch-mediated knockdown of *P. falciparum* deoxyhypusine synthase (*Pf*DHS) expression

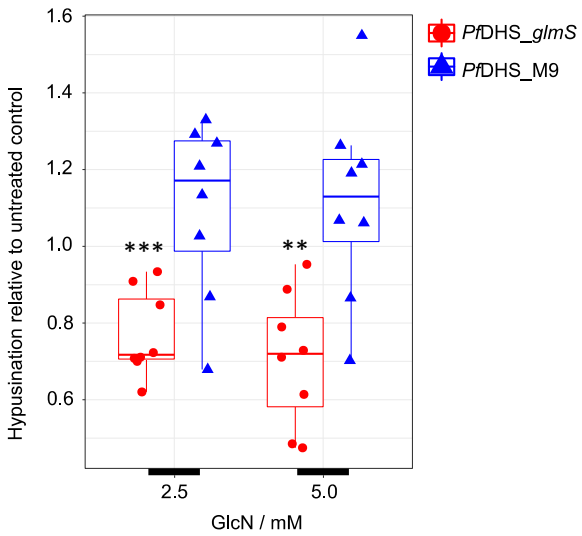


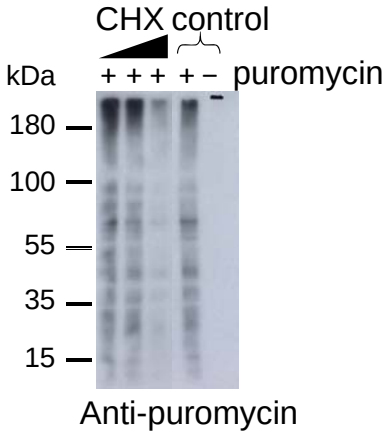



# Short-term *Pf*DHS knockdown affects hypusination, but not global protein synthesis

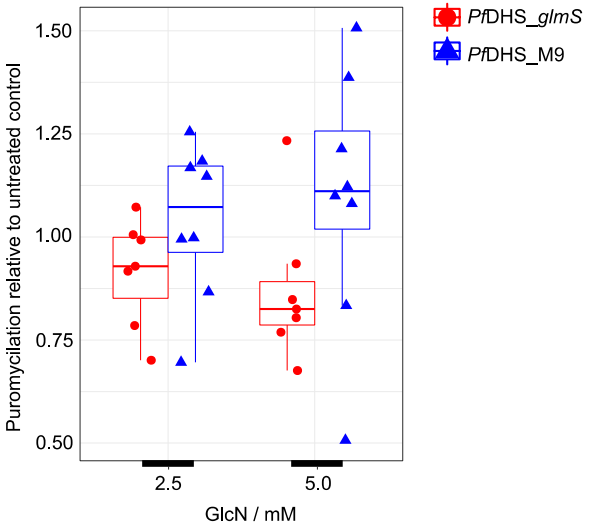



**Hypusination**

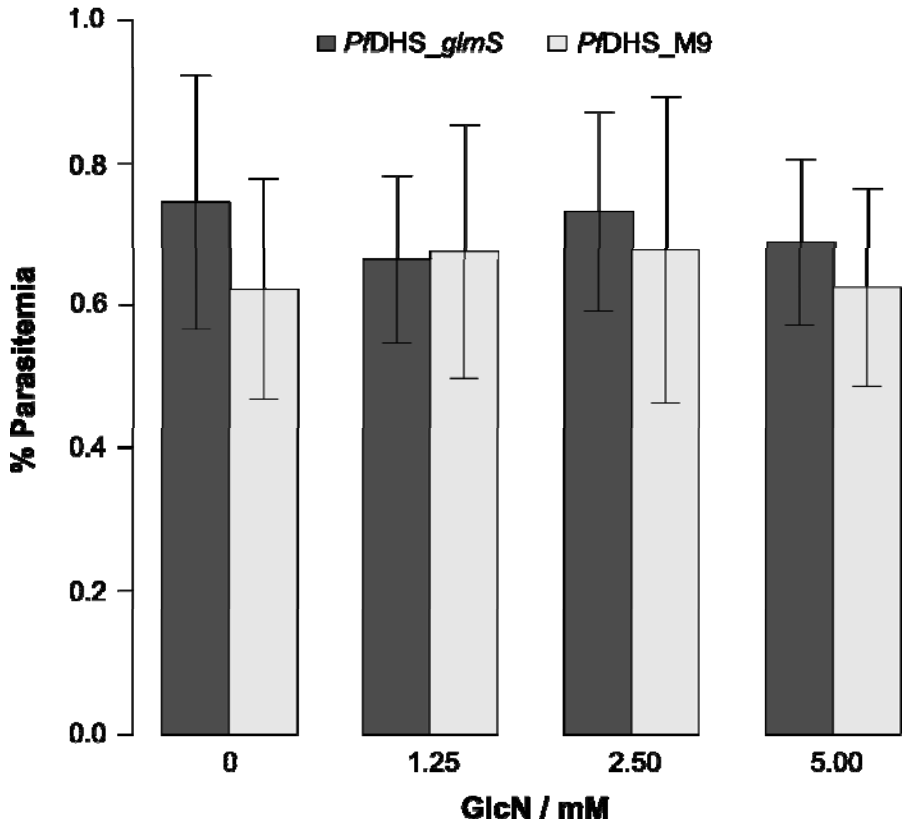



**Protein synthesis**

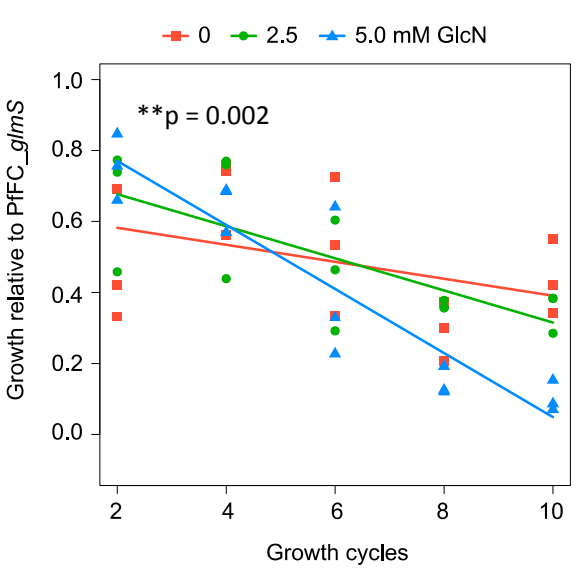


# Short-term *Pf*DHS knockdown does not affect growth

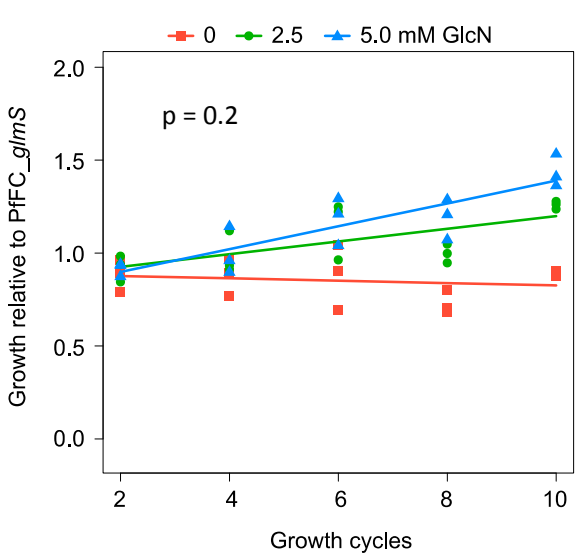


# Knockdown of *Pf*DHS leads to a latent growth defect

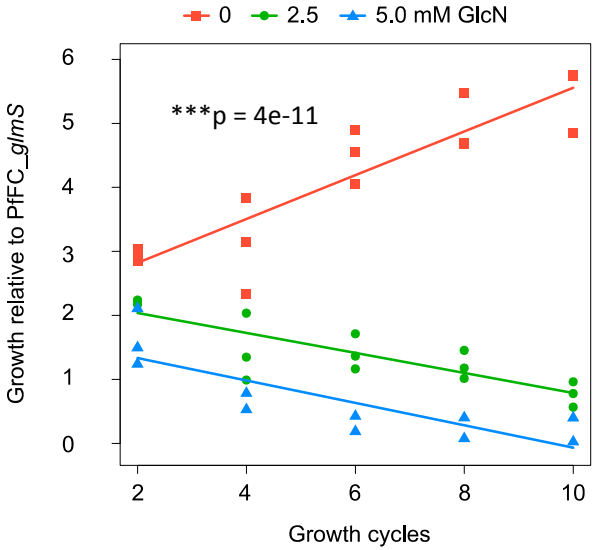
***Pf*DHS_*glmS***



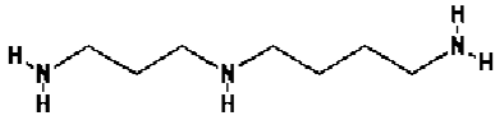

***Pf*DHS_M9**



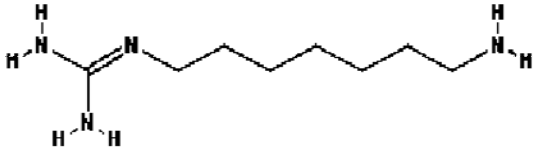

***Pf*DHFR-TS_*glmS***



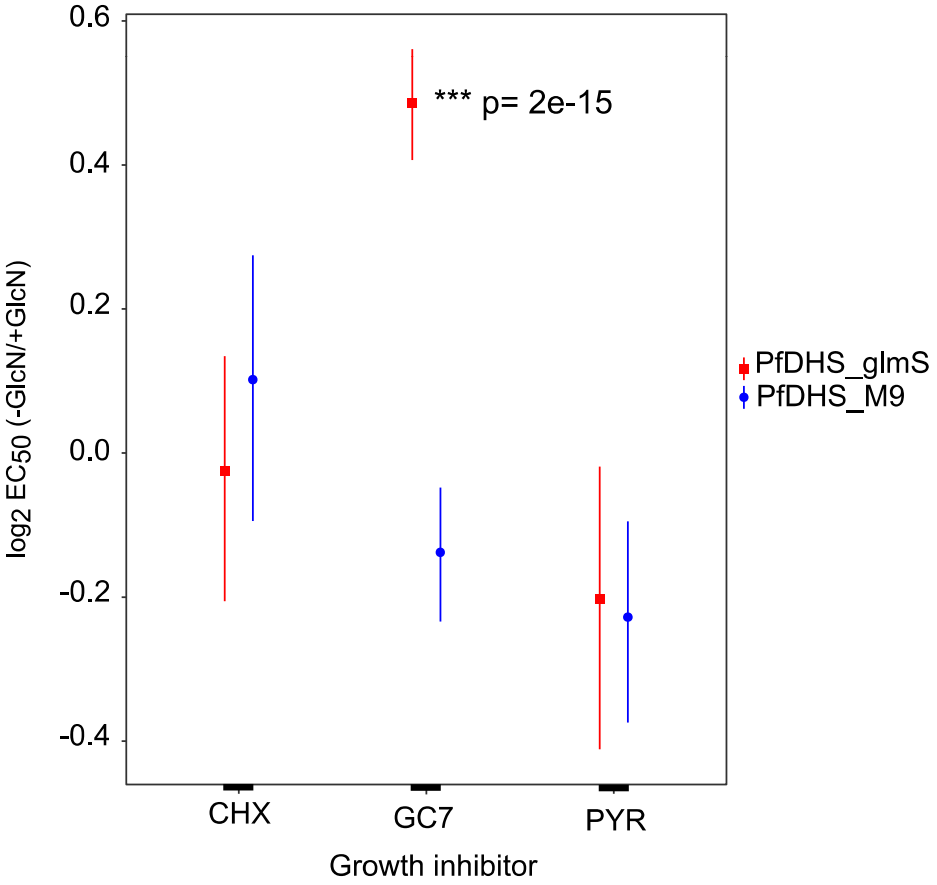
# Chemogenomic profiling of *Pf*DHS transgenic parasites



Spermidine (*Pf*DHS substrate)



N1-Guanyl-1,7-diaminoheptane (GC7)



## Summary

- Knockdown of *Pf*DHS function causes reduction of hypusination
- Growth defect (latent) in *Pf*DHS mutant
- *Pf*DHS mutant sensitized to GC7

# Acknowledgements

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