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## NHR-49/PAAR $\alpha$ and HLH-30/TFEB cooperate for *C. elegans* host defense via a flavin-containing monooxygenase

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NHR-49/PAAR $\alpha$  and HLH-30/TFEB cooperate for  
*C. elegans* host defense via a flavin-containing  
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UMASS 2020 Retreat

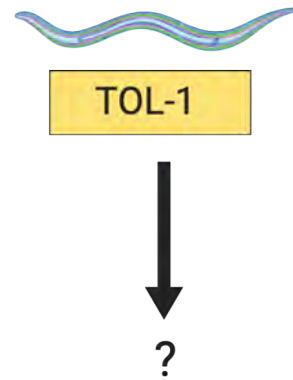
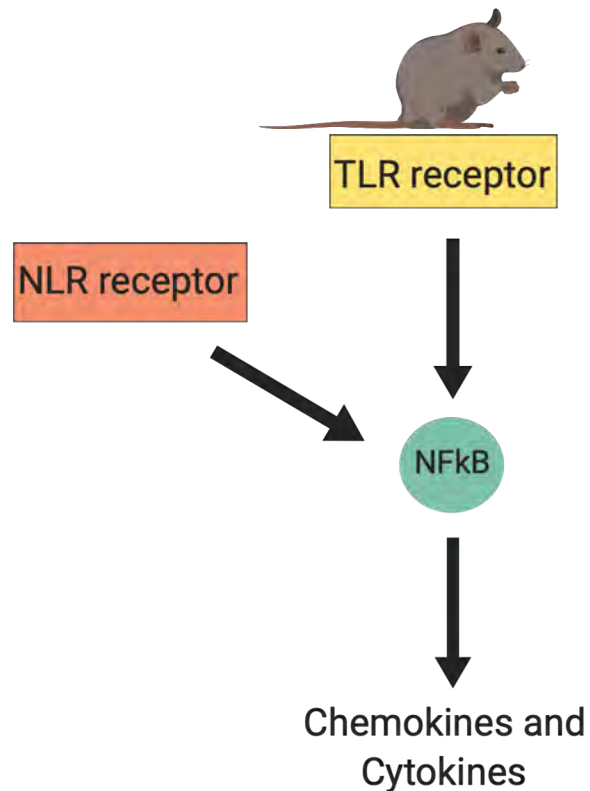
# *C. elegans* natural habitat poses a challenge to survive



Natural habitats and substrates of *C. elegans*

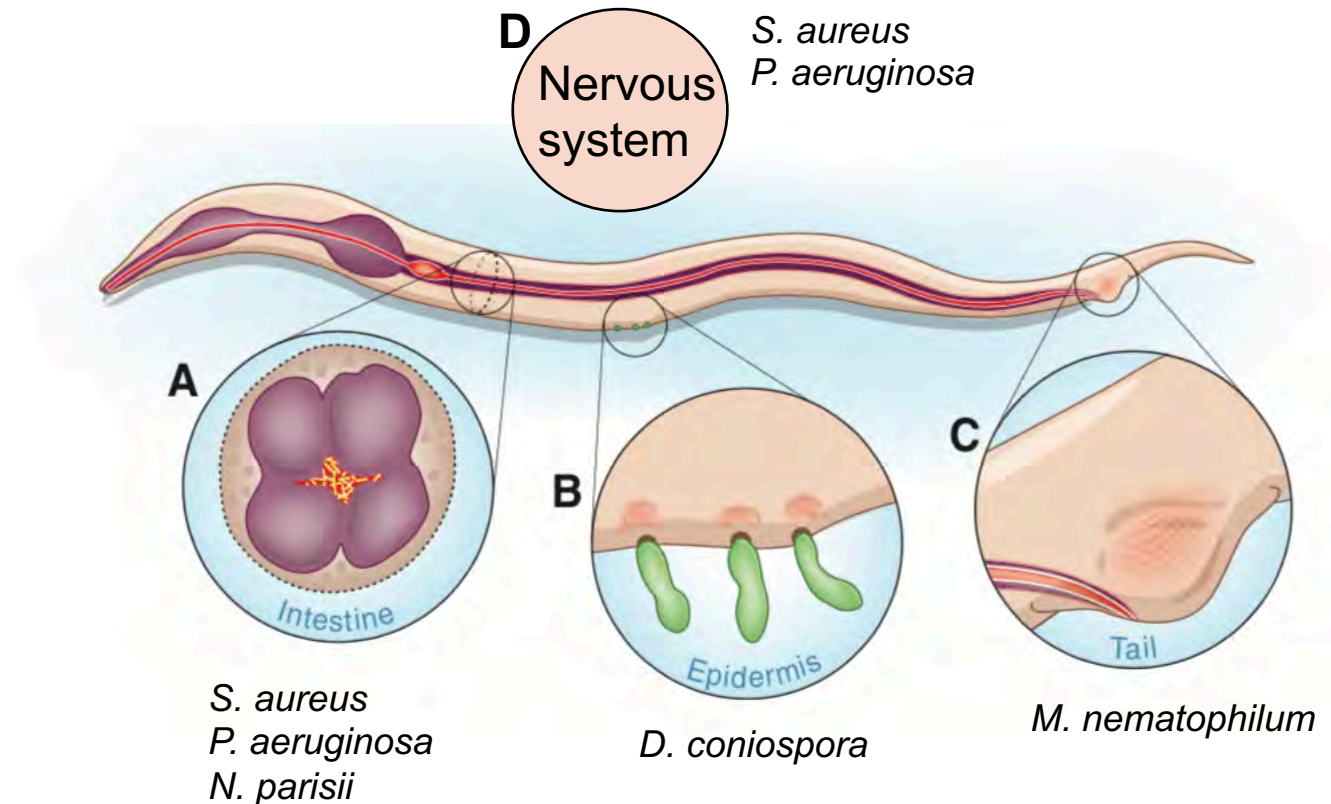
(Hinrich Schulenburg, and Marie-Anne Félix; 2017)

# *C. elegans* lack conventional innate immune response pathways



- It is not clear whether *C. elegans* sole TLR, TOL-1, functions in innate immunity.
- *C. elegans* genome does not encode NFκB.
- Unlike mammals, *C. elegans* lack cell-mediated immunity.

# *C. elegans* show transcriptional response to pathogens

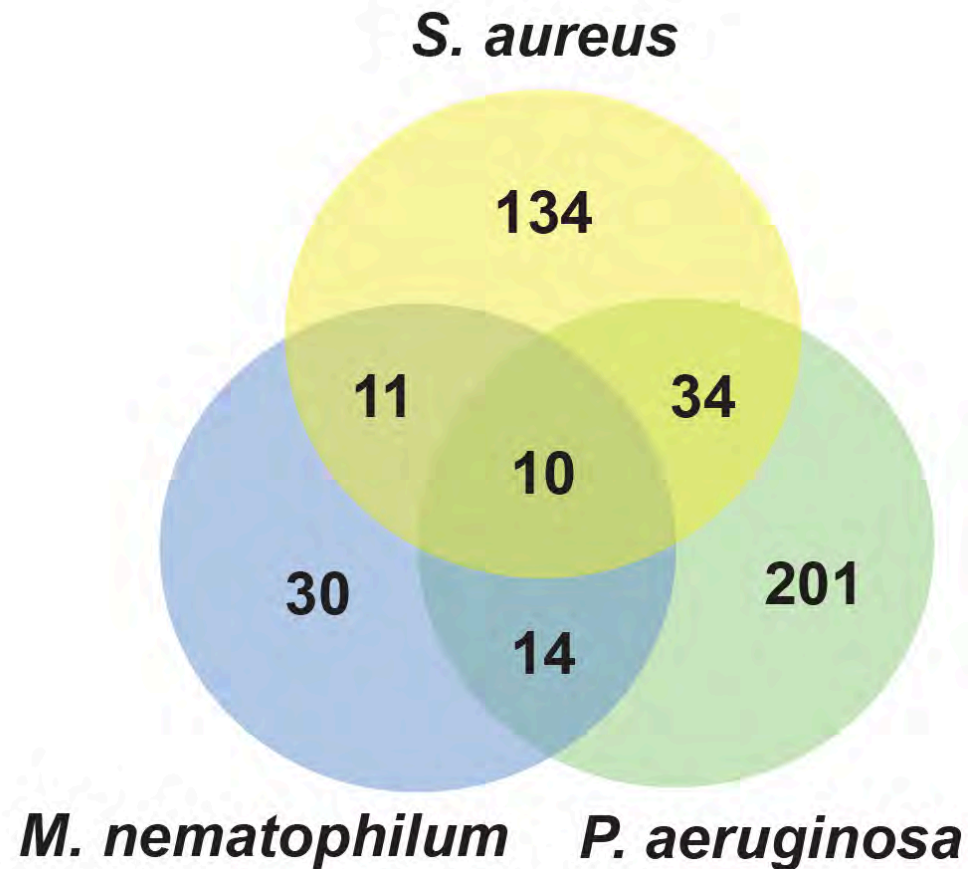


- Host defense genes:
- Anti-microbial peptides
  - Lysozymes
  - Lectins

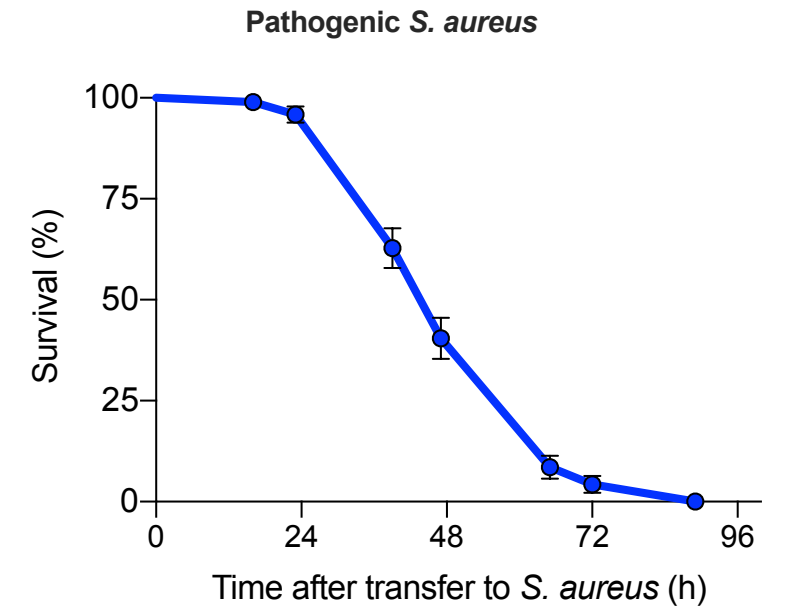
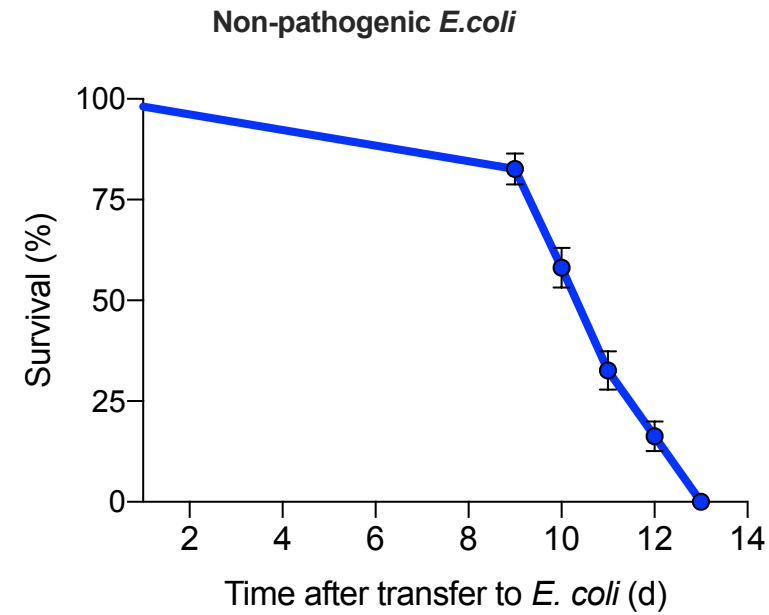
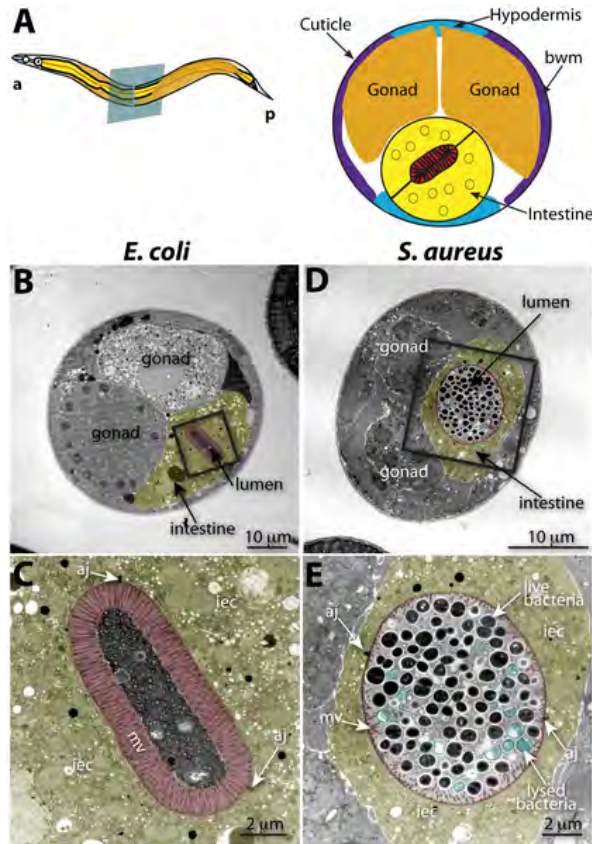
(Picture modified from Kim D, 2008)

(Work carried out in Fred Asubel, Jonathan Hodgkin, Jonathan Ewbank, Dennis Kim, Alejandro Aballay, Emily Troemel, Read Pukkila-Worley, & Javier Irazoqui labs)

# *C. elegans* show a pathogen-specific transcriptional response

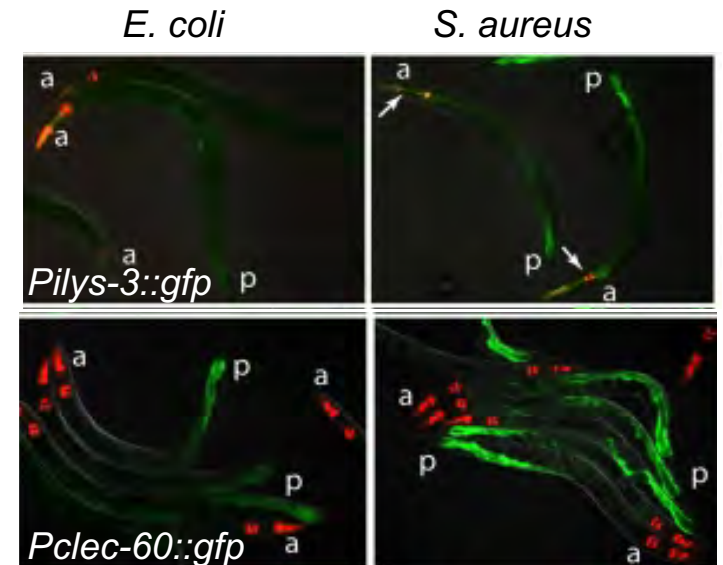
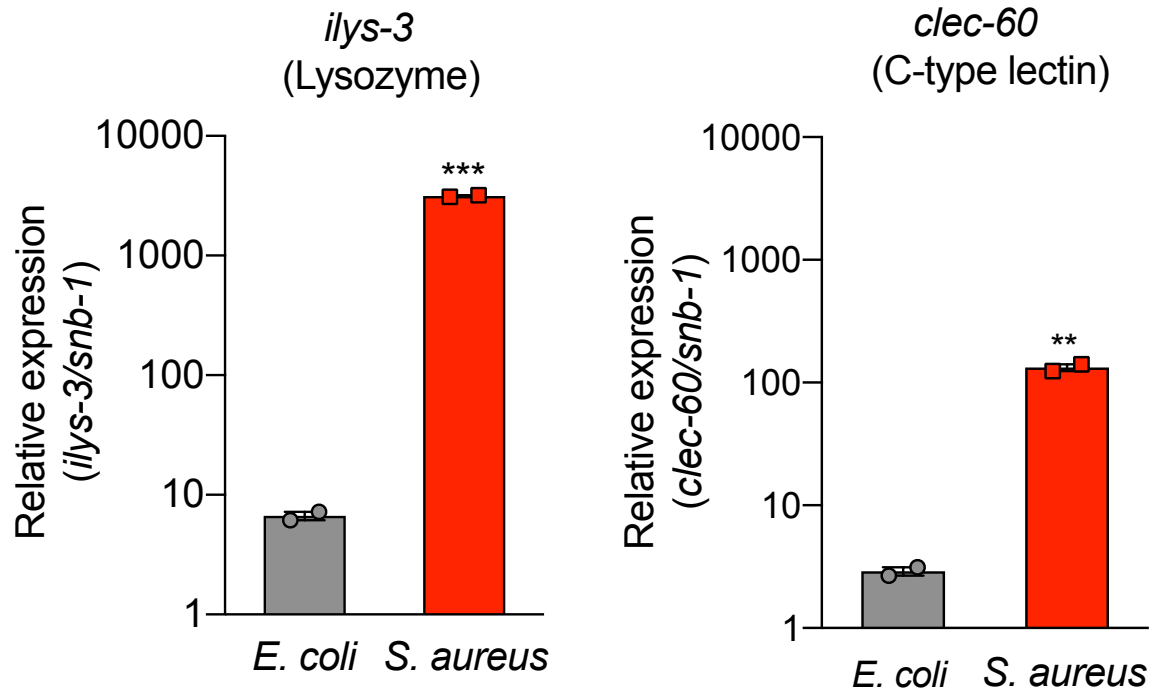


# *S. aureus* destroys *C. elegans* intestinal epithelial cells





# *C. elegans* fight infection by the induction of host defense genes



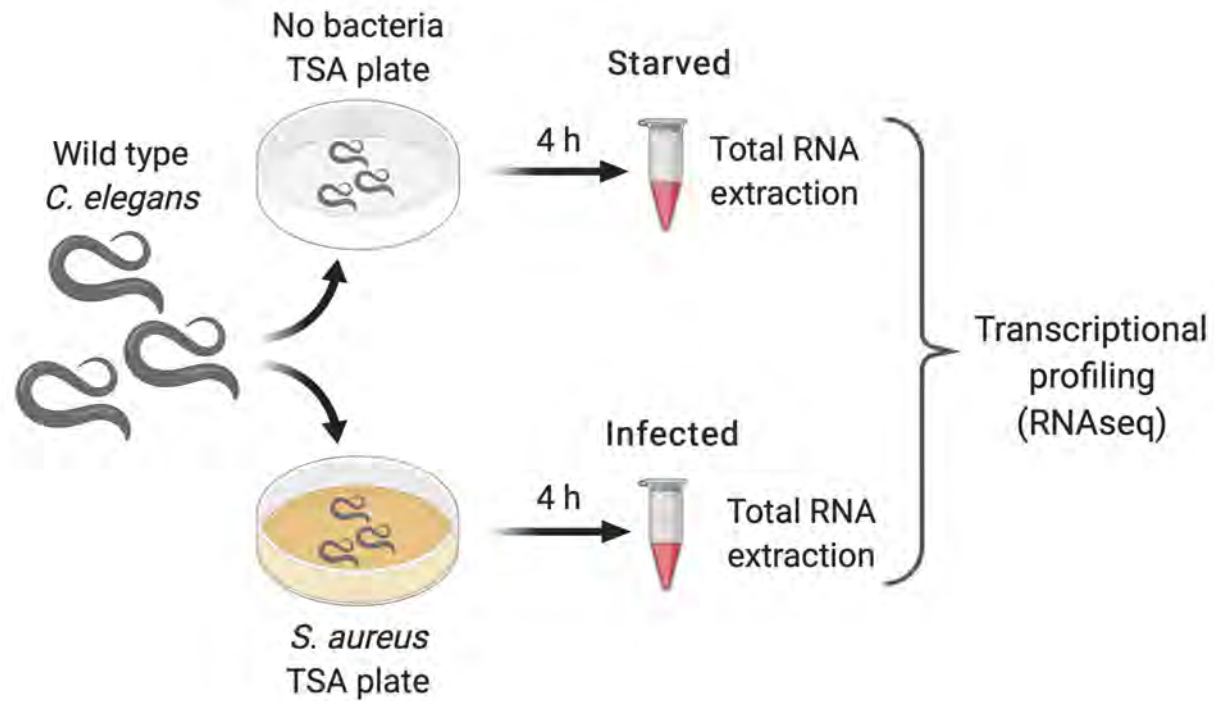
(Irazoqui JE et al; 2010)



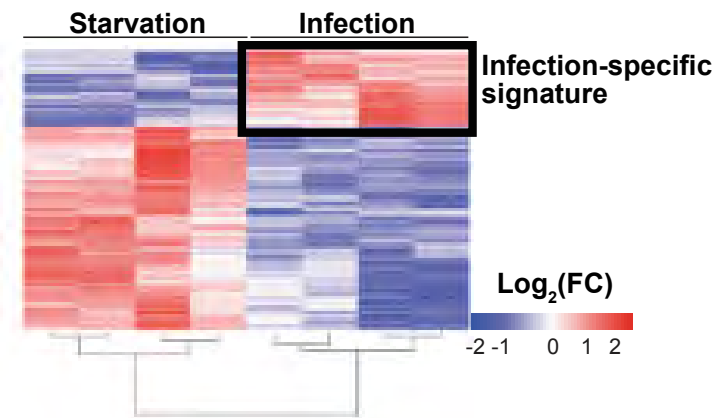
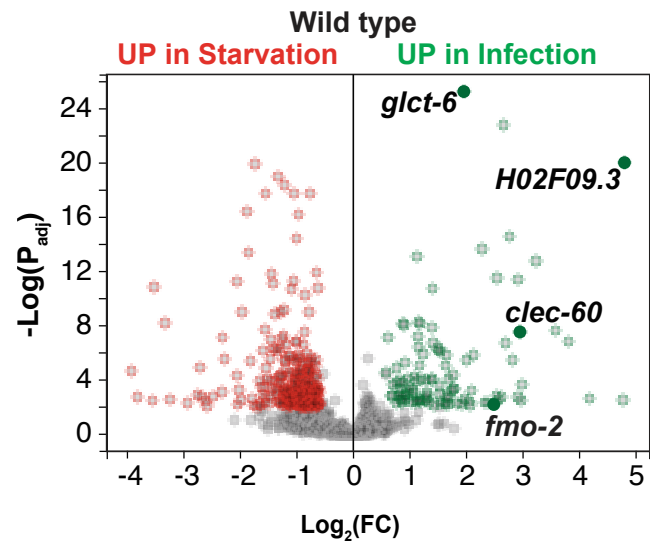
## *S. aureus* infection poses a nutritional challenge

How much of the host response is due to infection as opposed to the nutritional challenge?

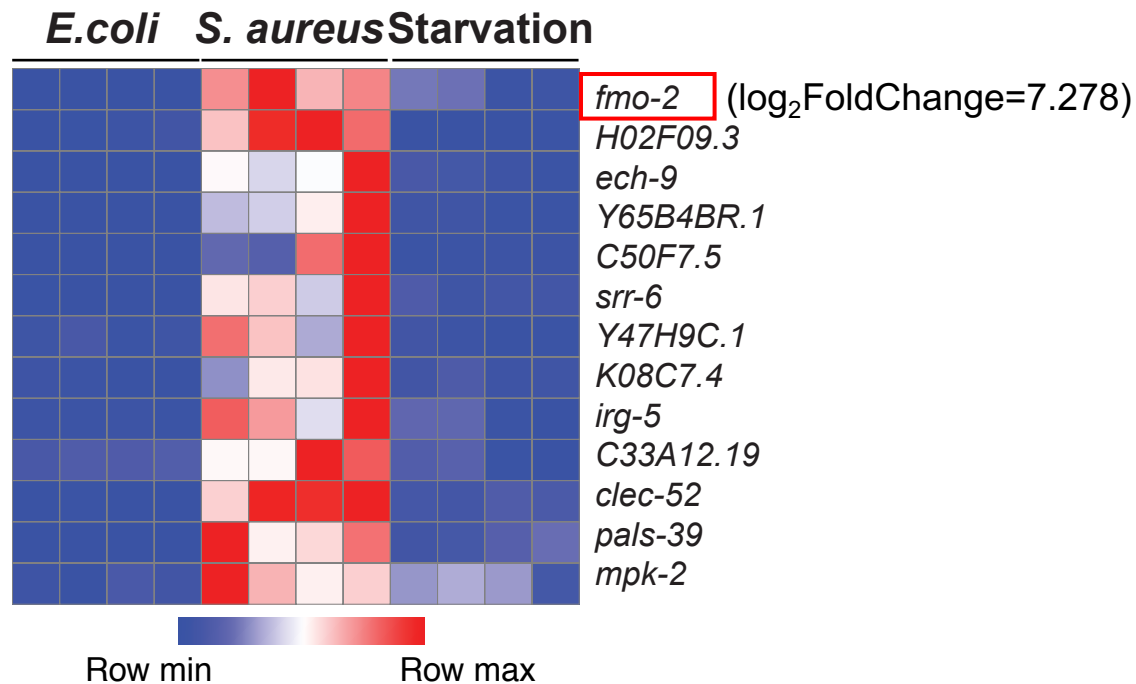
# Can we separate metabolic stress from infection?



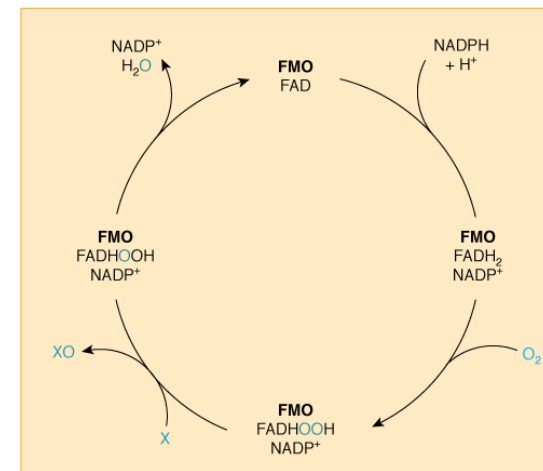
# Identification of infection-specific gene signature



# FMO-2 is a highly-induced infection-specific gene

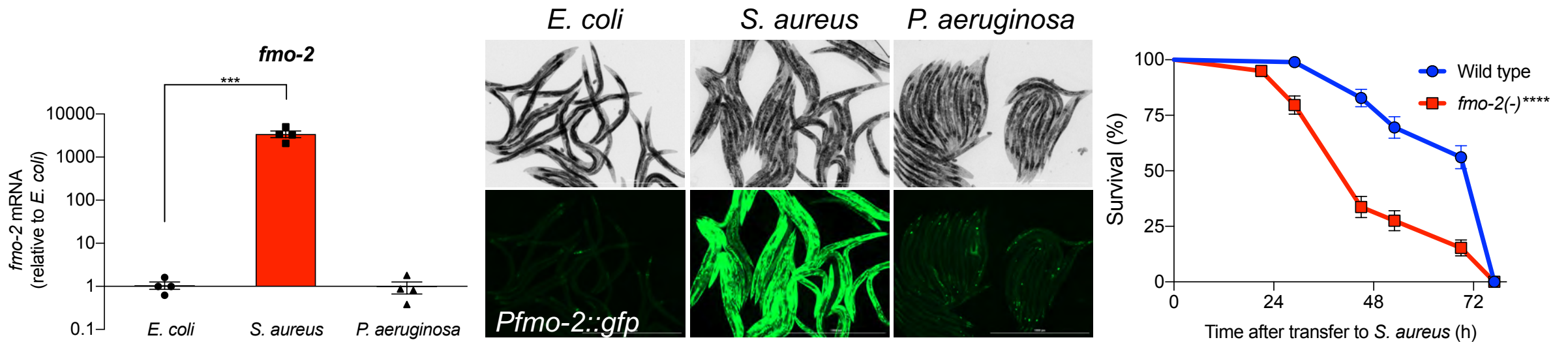


- *fmo-2* encodes flavin-containing monooxygenase
- Detoxification of xenobiotic substances
- In Arabidopsis, FMO1 functions in host defense



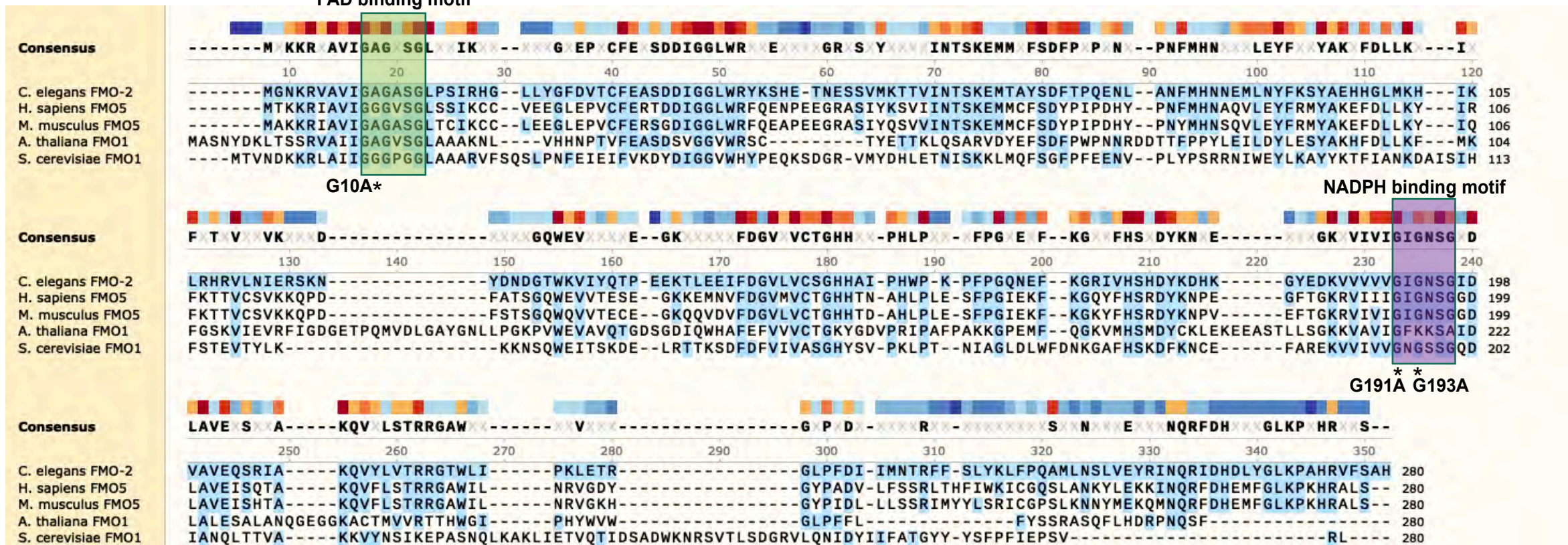
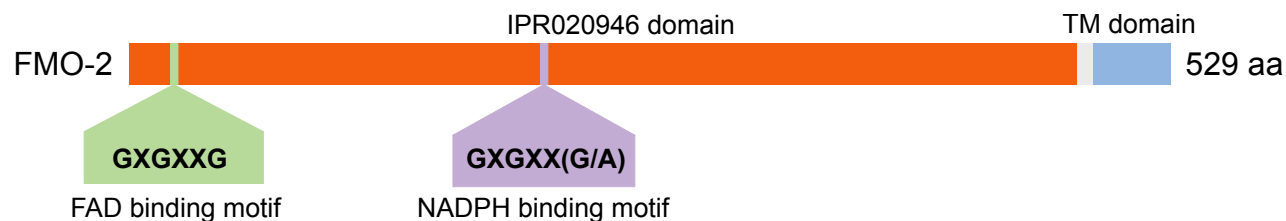
Source: Klaassen CD, Watkins JB: Casarett & Doull's Essentials of Toxicology, 2nd Edition: <http://www.accesspharmacy.com>  
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# FMO-2 is a pathogen-specific host defense gene

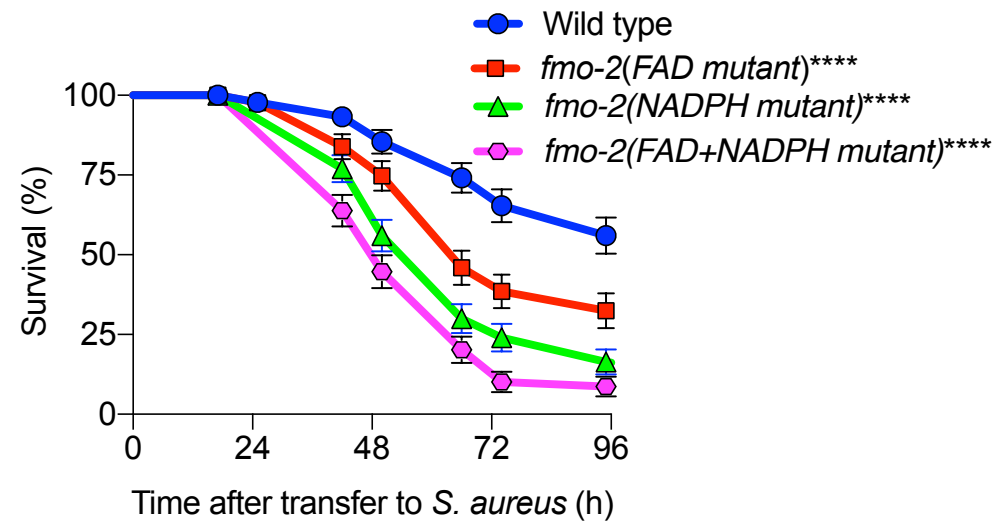




# FAD and NADPH motifs are evolutionarily conserved

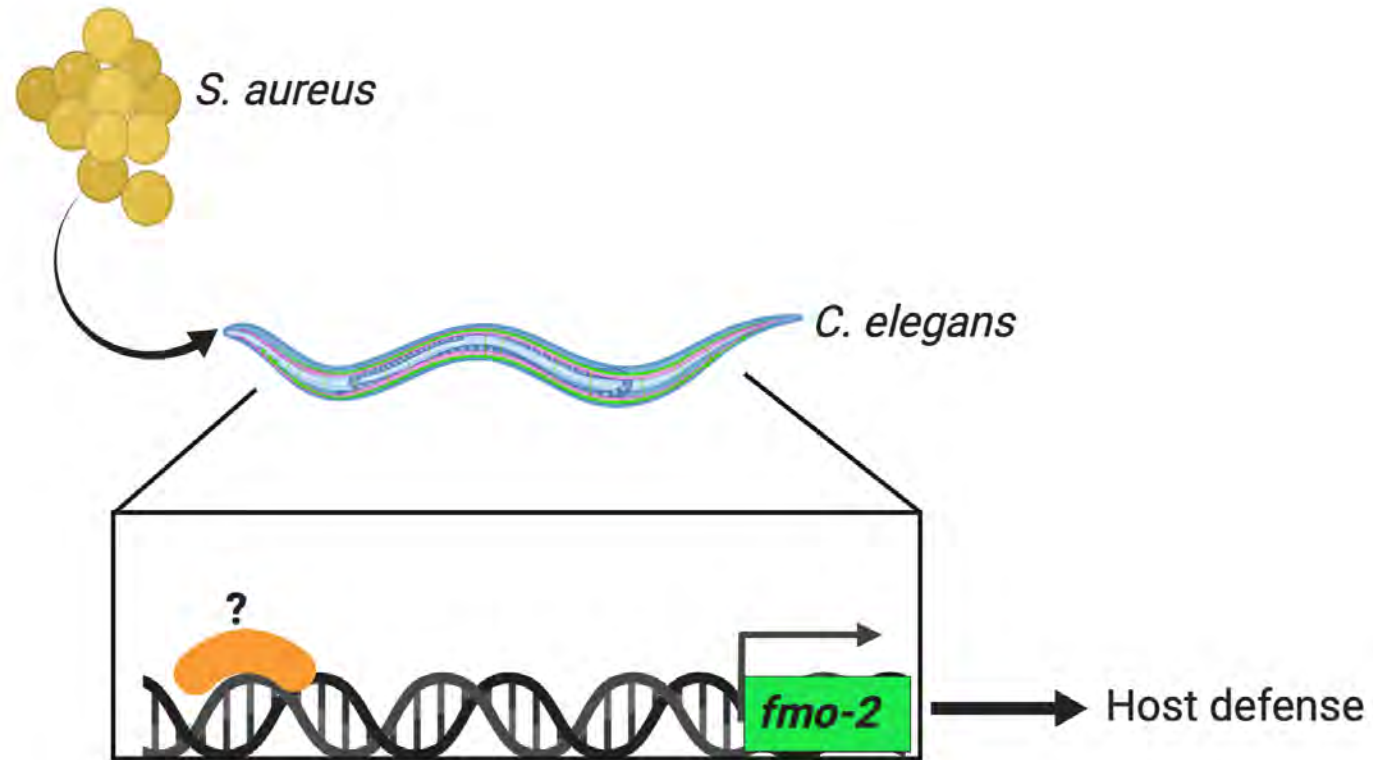


# FMO-2 catalytic activity is required for host defense

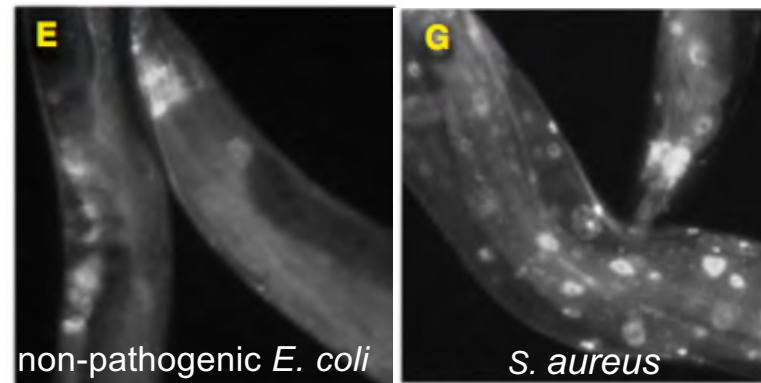
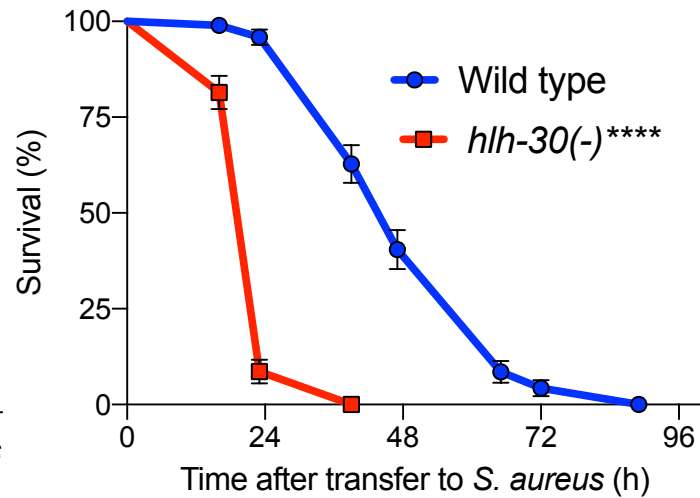
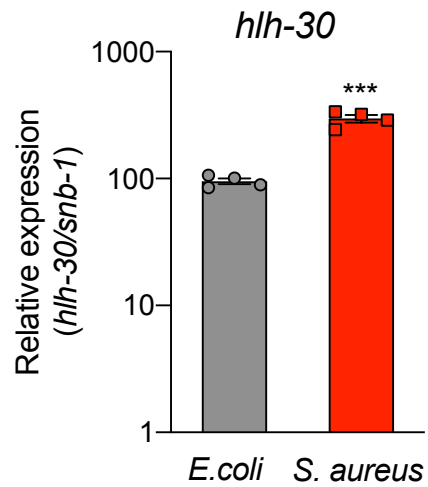




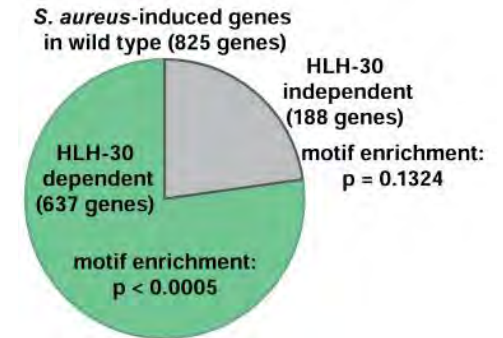
# *fmo-2* induction is required for host defense



# HLH-30/TFEB is important for host response to infection

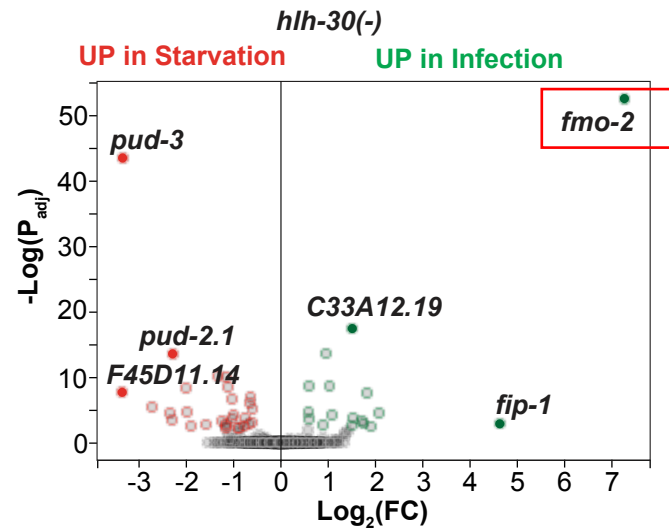
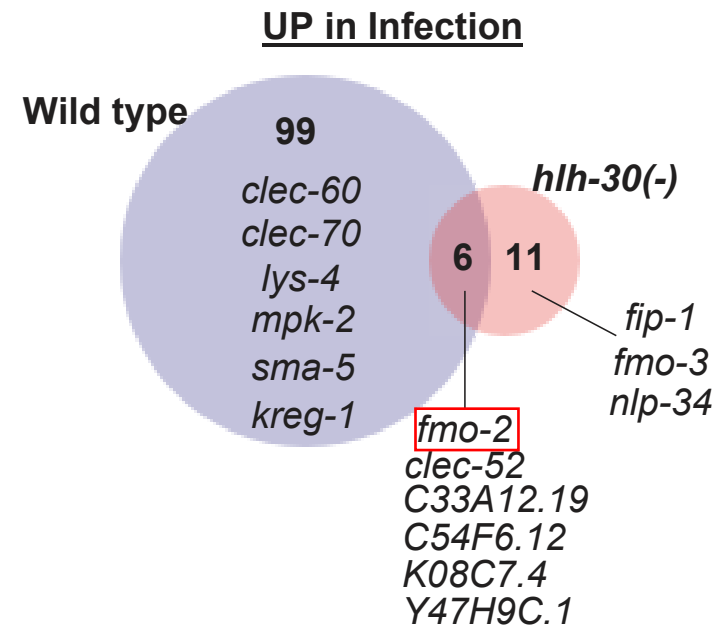
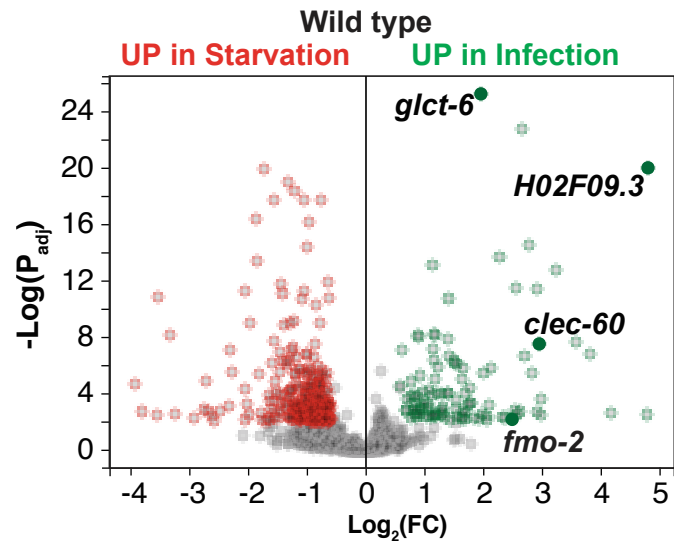


*Phlh-30::hlh-30::gfp*

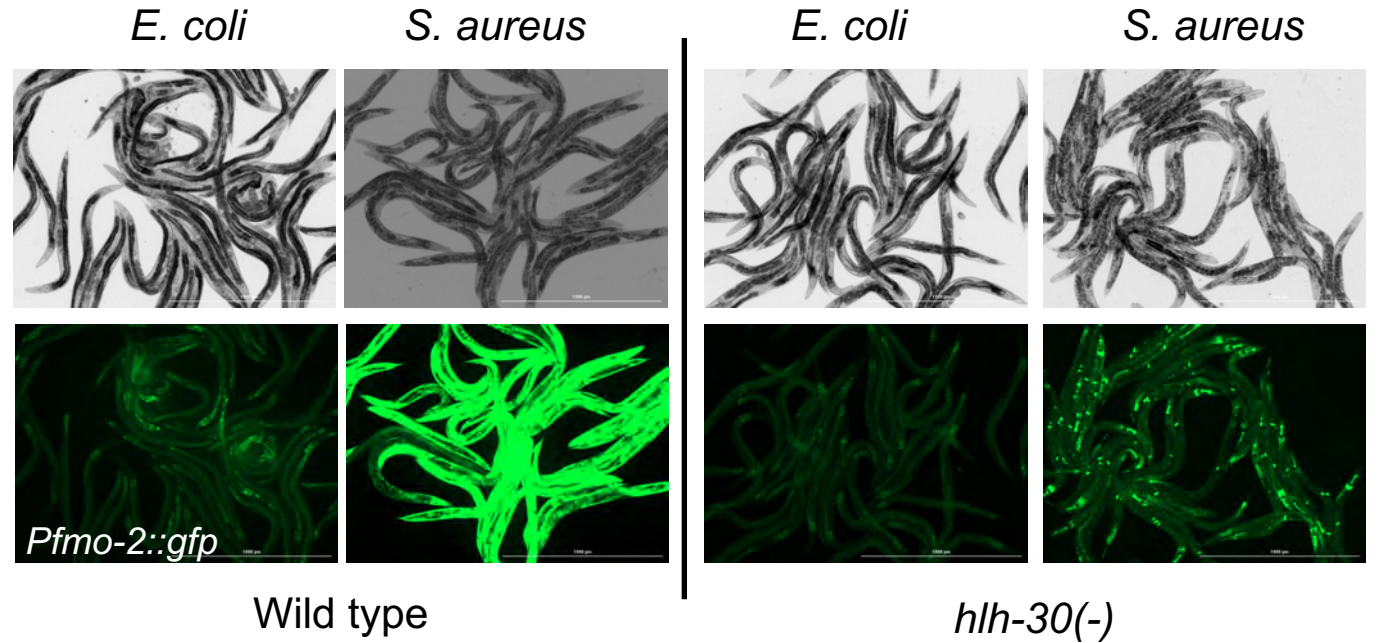
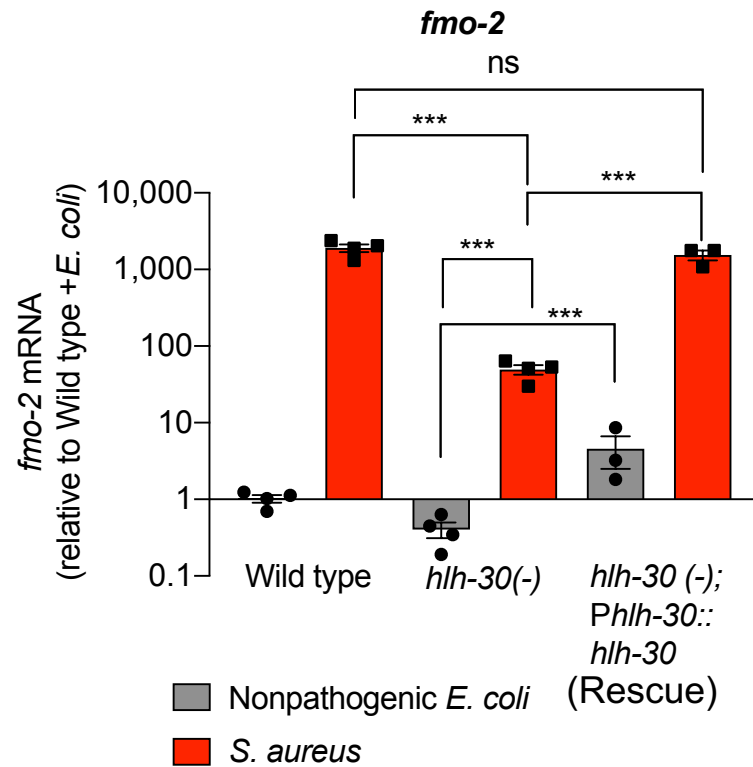


~80% HLH-30-dependent genes

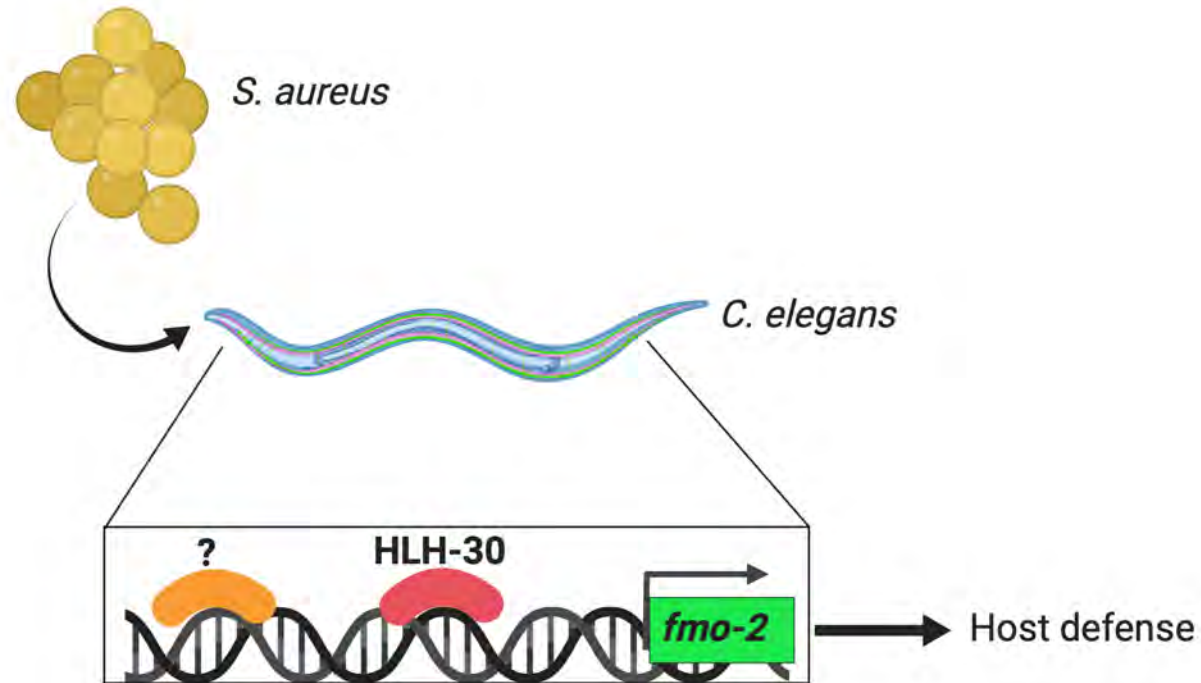
# *fmo-2* induction is independent of HLH-30/TFEB



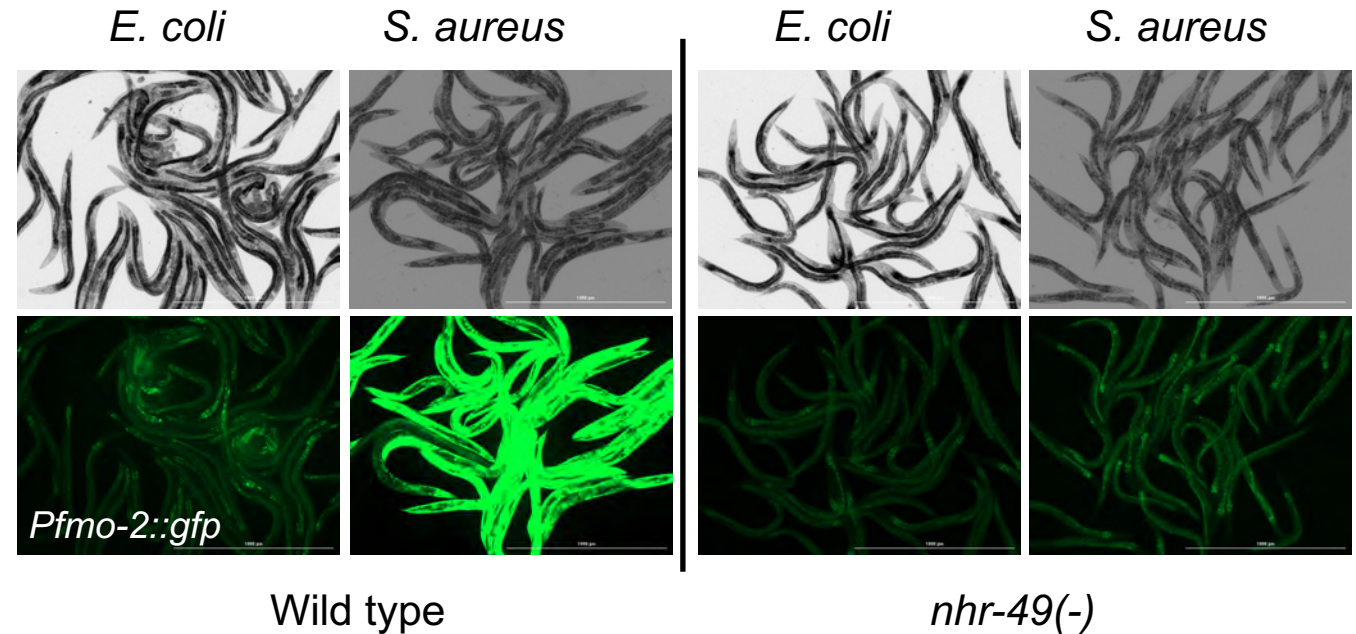
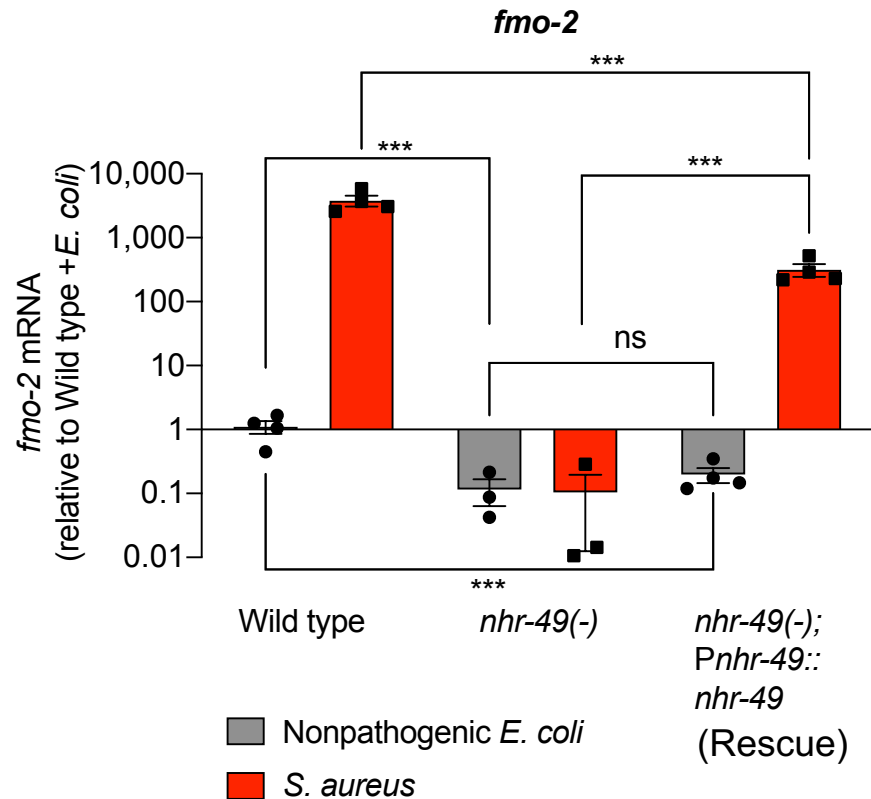
# HLH-30/TFEB is partially required for *fmo-2* induction during infection



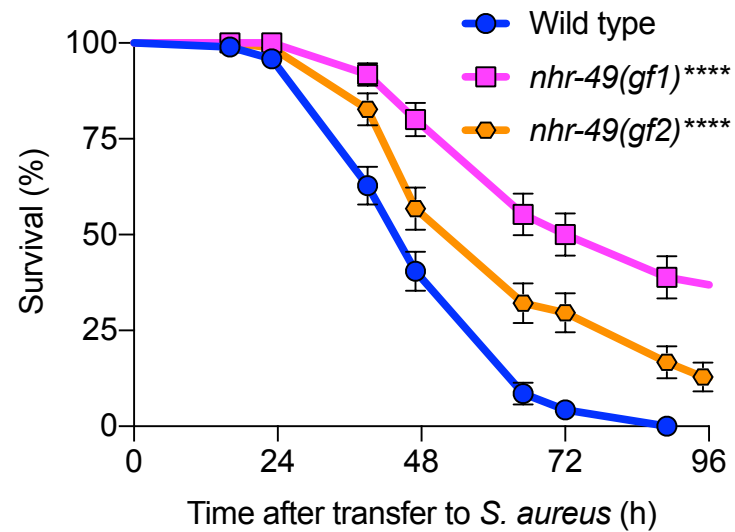
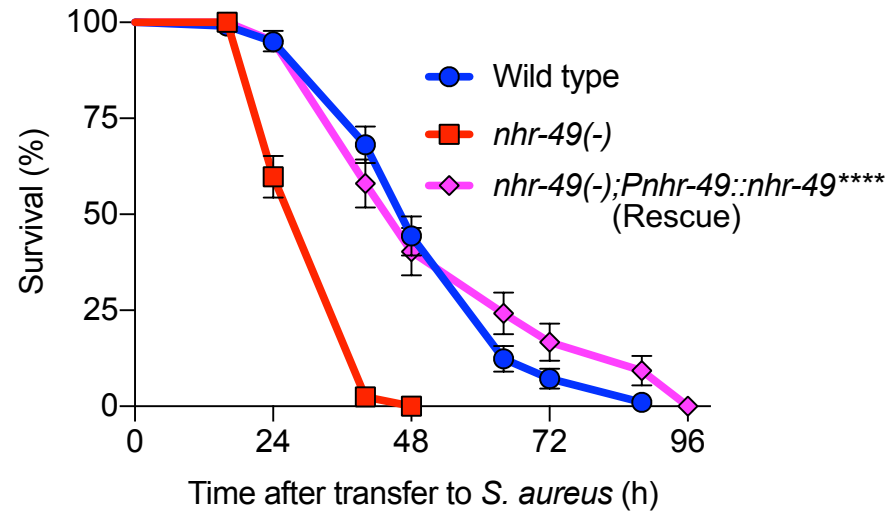
# What else does regulate *fmo-2* induction during infection?



# NHR-49/PPAR $\alpha$ is essential for *fmo-2* induction during infection



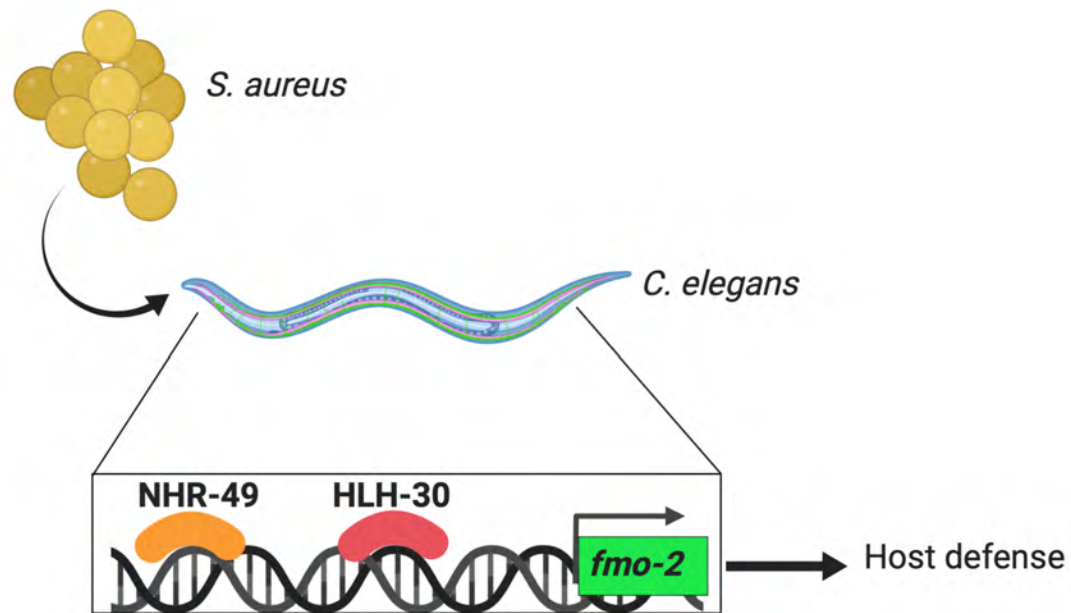
# NHR-49/ PPAR $\alpha$ is necessary and sufficient for host survival



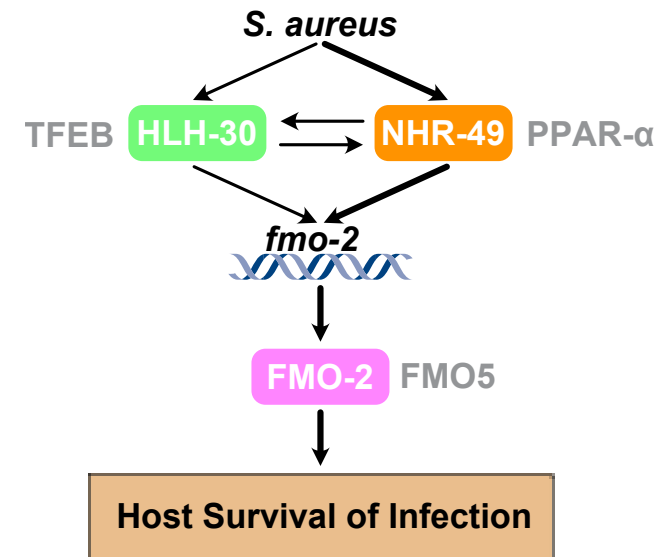
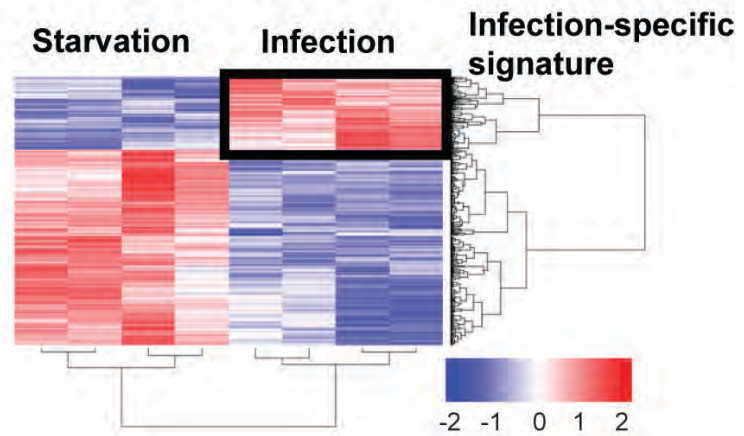
*gf*= gain of function



# HLH-30 and NHR-49 regulate host defense via *fmo-2* induction



# Summary



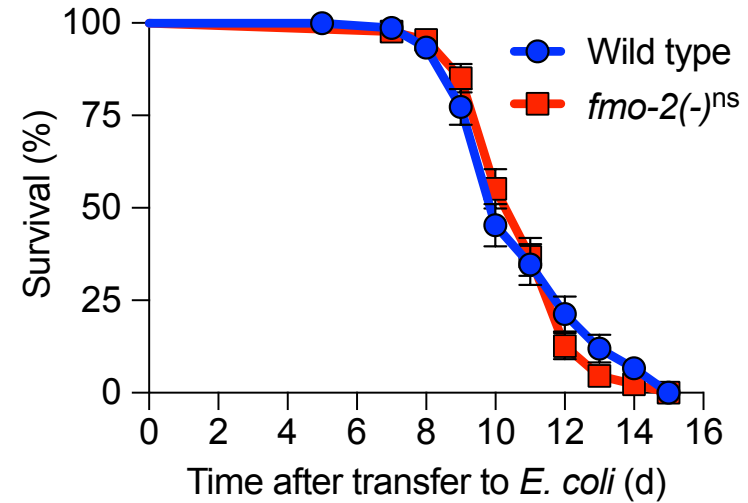
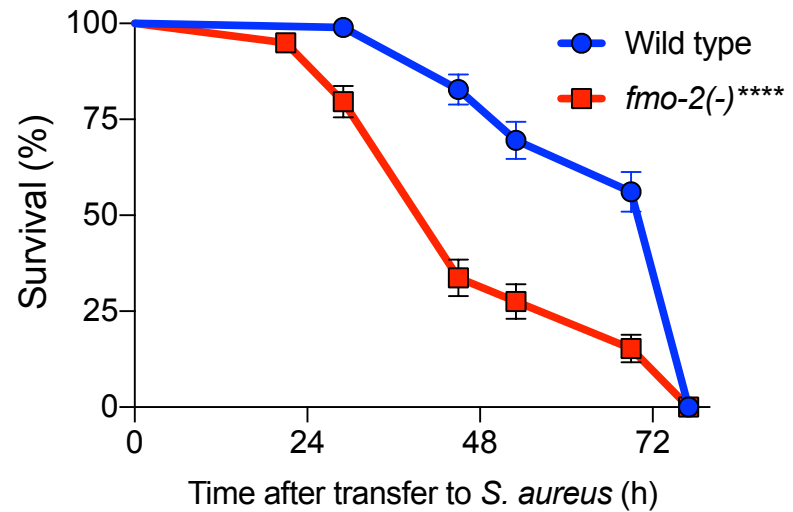
# Acknowledgements

- Javier Irazoqui
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- Joseph Moreau
- Xavier Gonzales
- Havisha Honwad

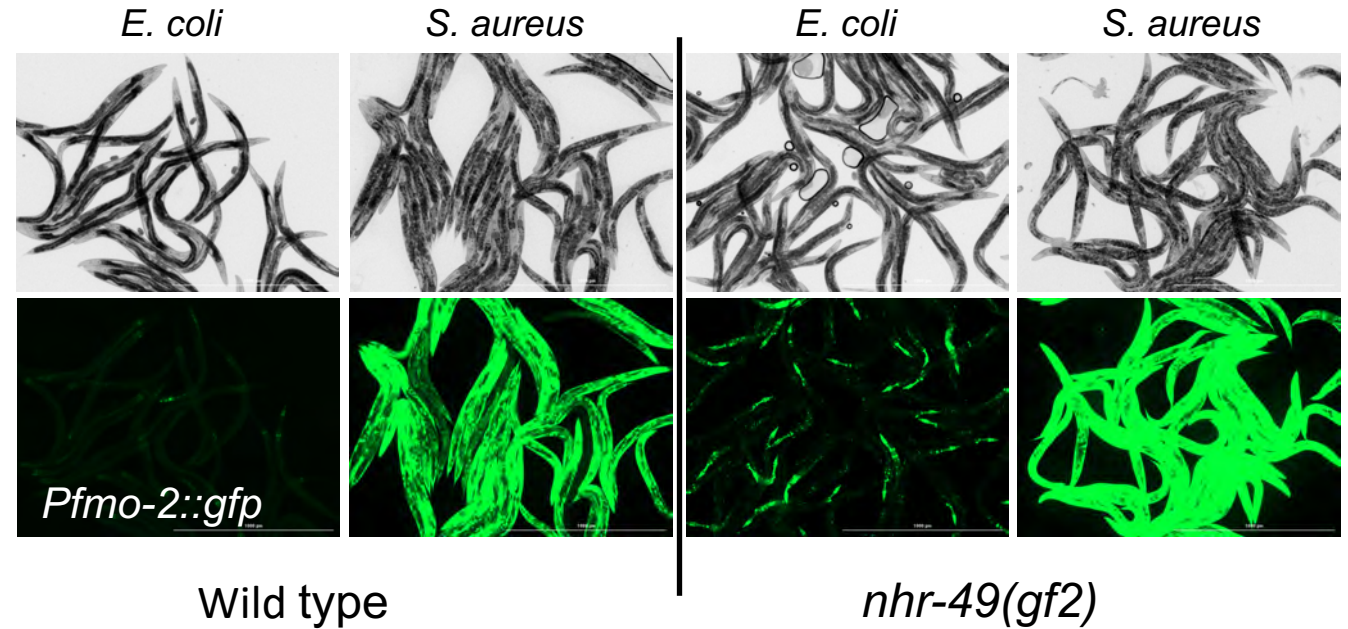
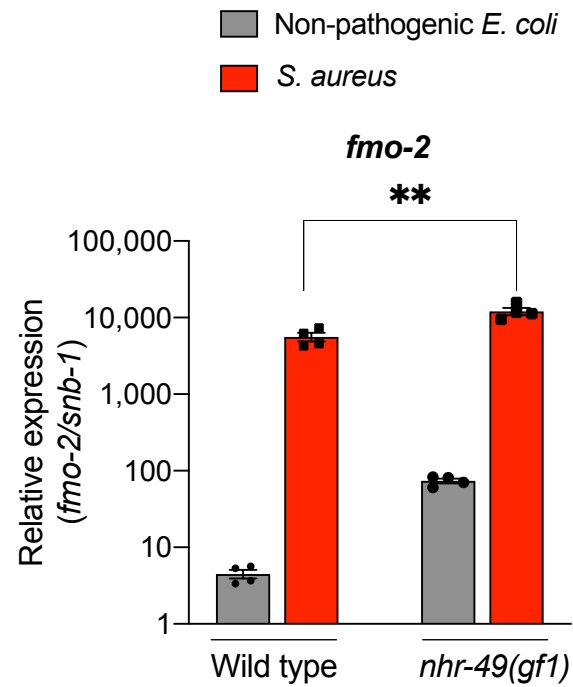
## Collaborators:

- Stefan Taubert (Univ. of British Columbia)
- Arjumand Ghazi (Univ. of Pittsburgh)
- Ramesh Ratnappan (Ghazi lab)

# *fmo-2* mutants are hypersensitive to infection

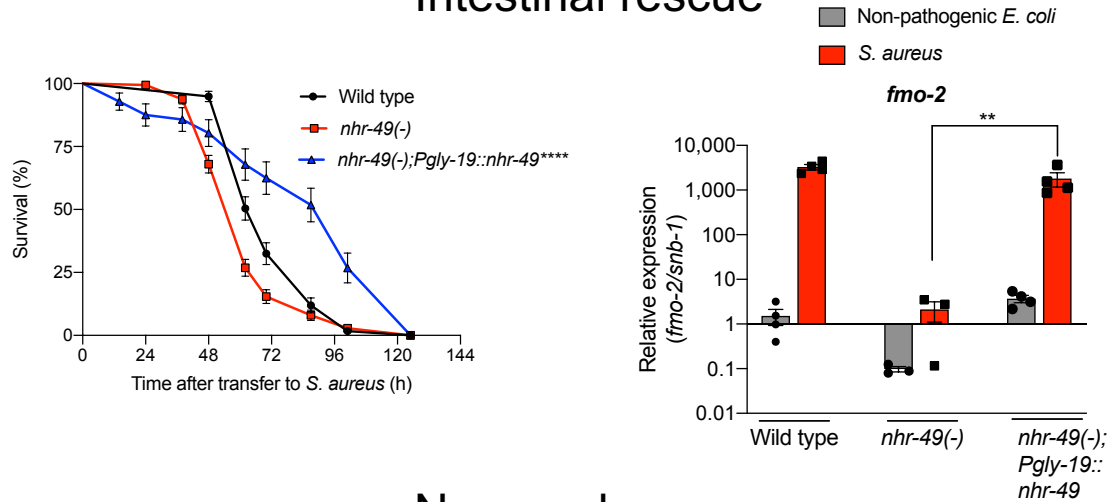


# NHR-49 gain-of-function causes *fmo-2* overexpression

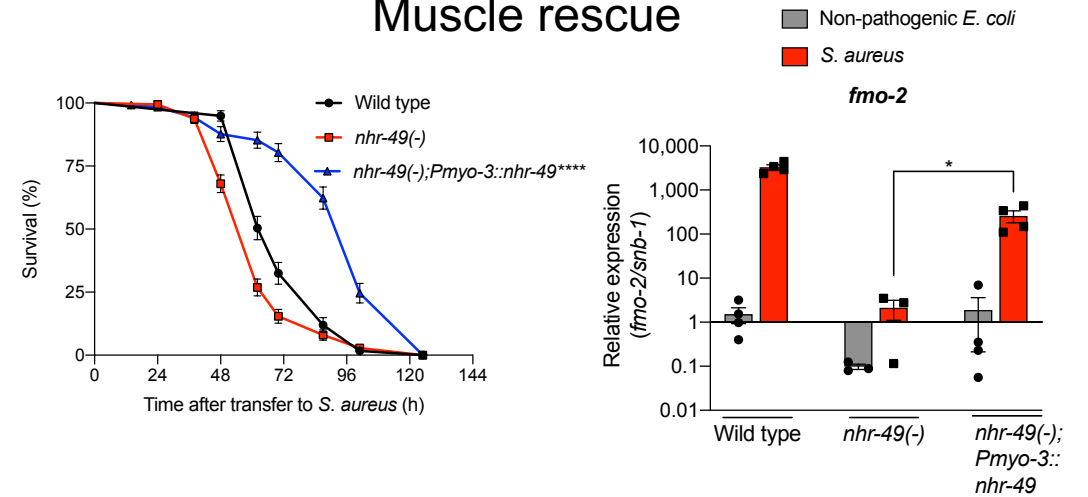


# NHR-49 functions cell non-autonomously for host defense and *fmo-2* induction

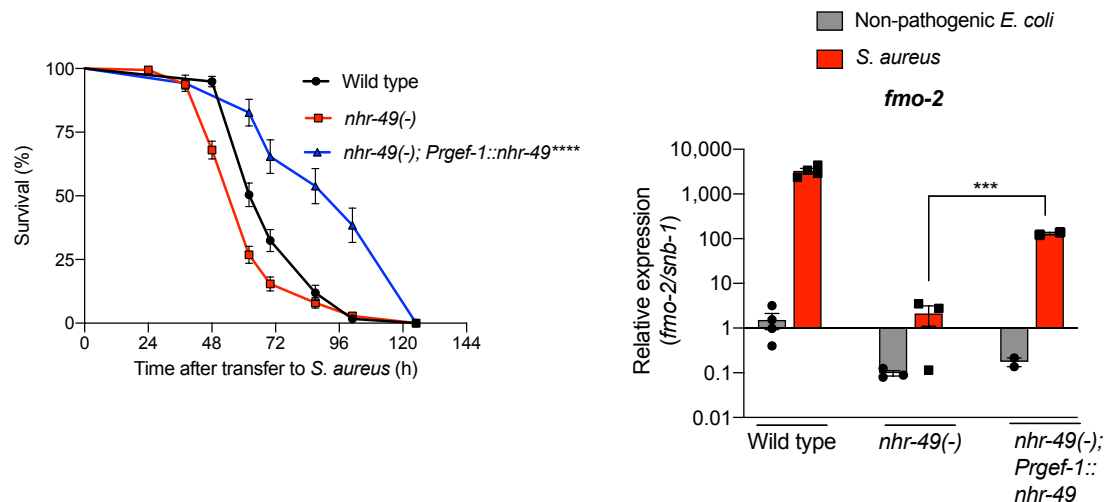
## Intestinal rescue



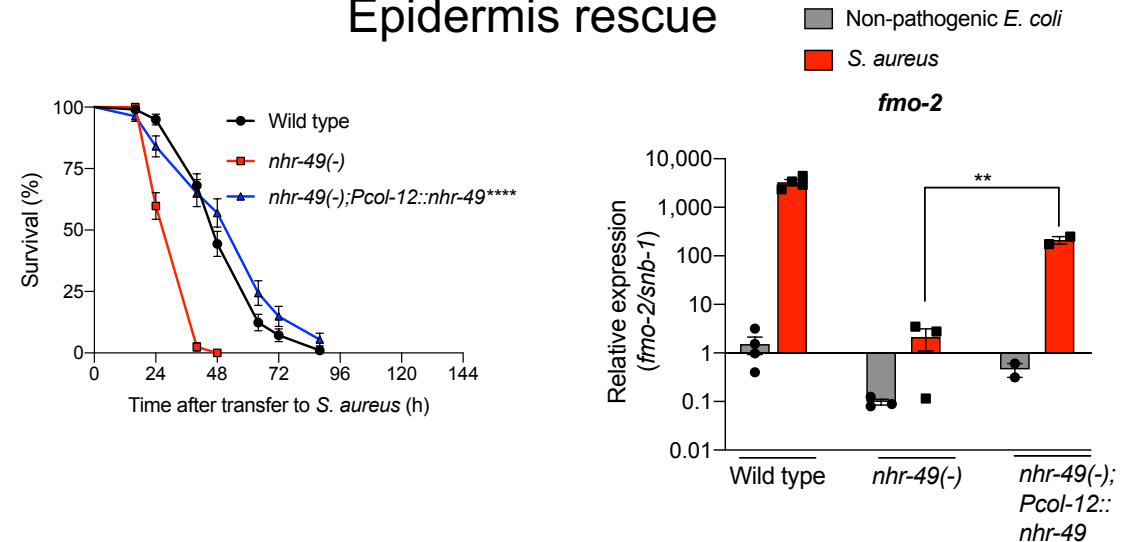
## Muscle rescue



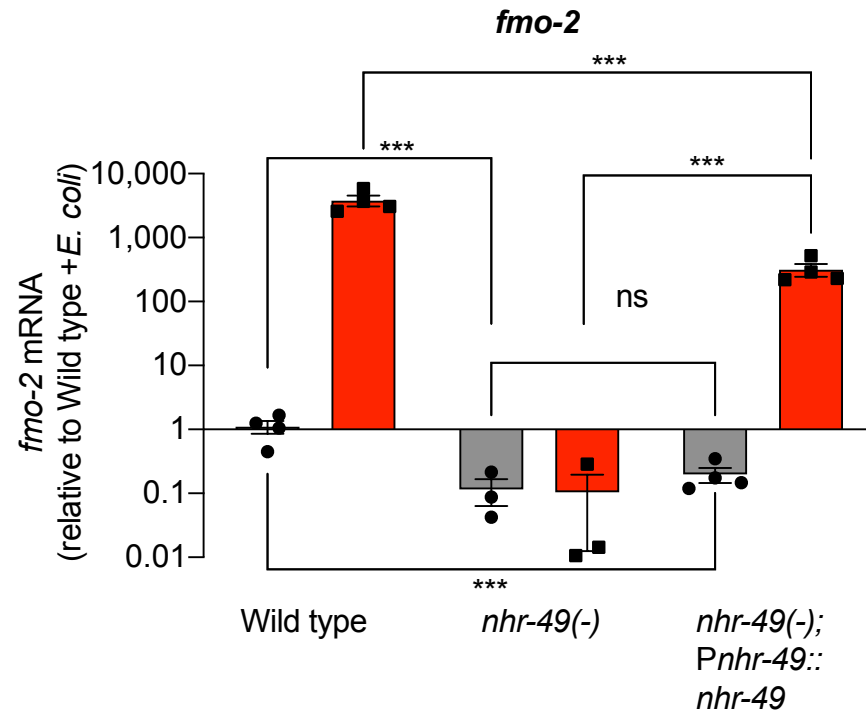
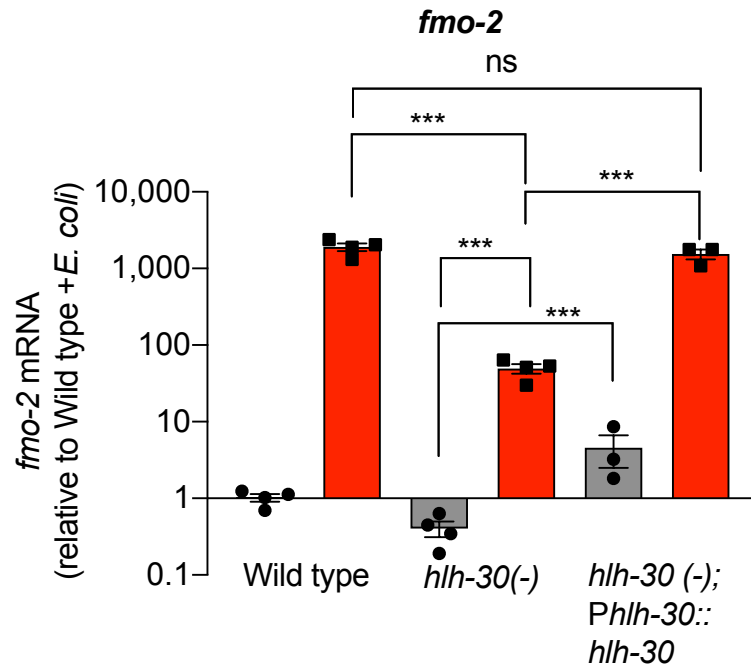
## Neuronal rescue



## Epidermis rescue

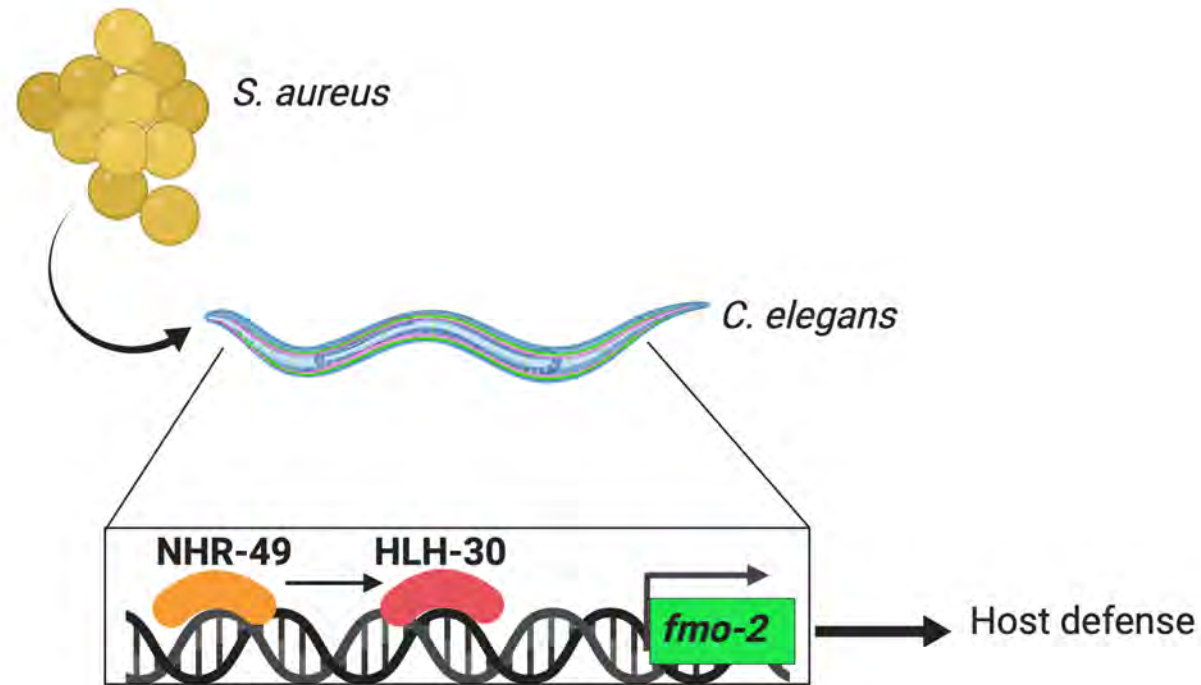


# Loss of NHR-49 is stronger than loss of HLH-30

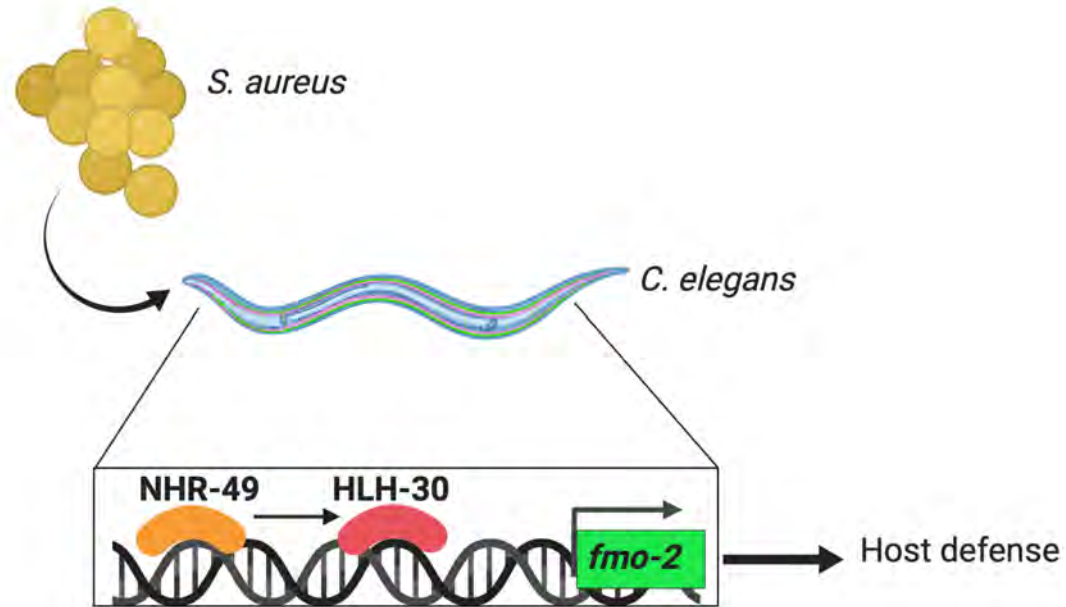




# HLH-30 functions downstream/parallel to NHR-49 for host defense and *fmo-2* induction



# Does HLH-30 function downstream/parallel to NHR-49?



# HLH-30 functions downstream/parallel to NHR-49 for host defense and *fmo-2* induction

