



**HAL**  
open science

## **EVOLUTION OF THE NUCLEAR RECEPTOR DAF-12 IN PARASITIC NEMATODES**

Rémy Bétous, Anthony Emile, Hua Che, Eva Guhen, Didier Concordet,  
Thavy Long, Sandra Noack, Paul M Selzer, Roger K. Prichard, Anne Lespine

► **To cite this version:**

Rémy Bétous, Anthony Emile, Hua Che, Eva Guhen, Didier Concordet, et al.. EVOLUTION OF THE NUCLEAR RECEPTOR DAF-12 IN PARASITIC NEMATODES. Nuclear Receptors and Metabolism. The MetNet-NuRCaMeIn-French Liaison, Oct 2023, Barcelona, Spain. hal-04700573

**HAL Id: hal-04700573**

**<https://hal.science/hal-04700573v1>**

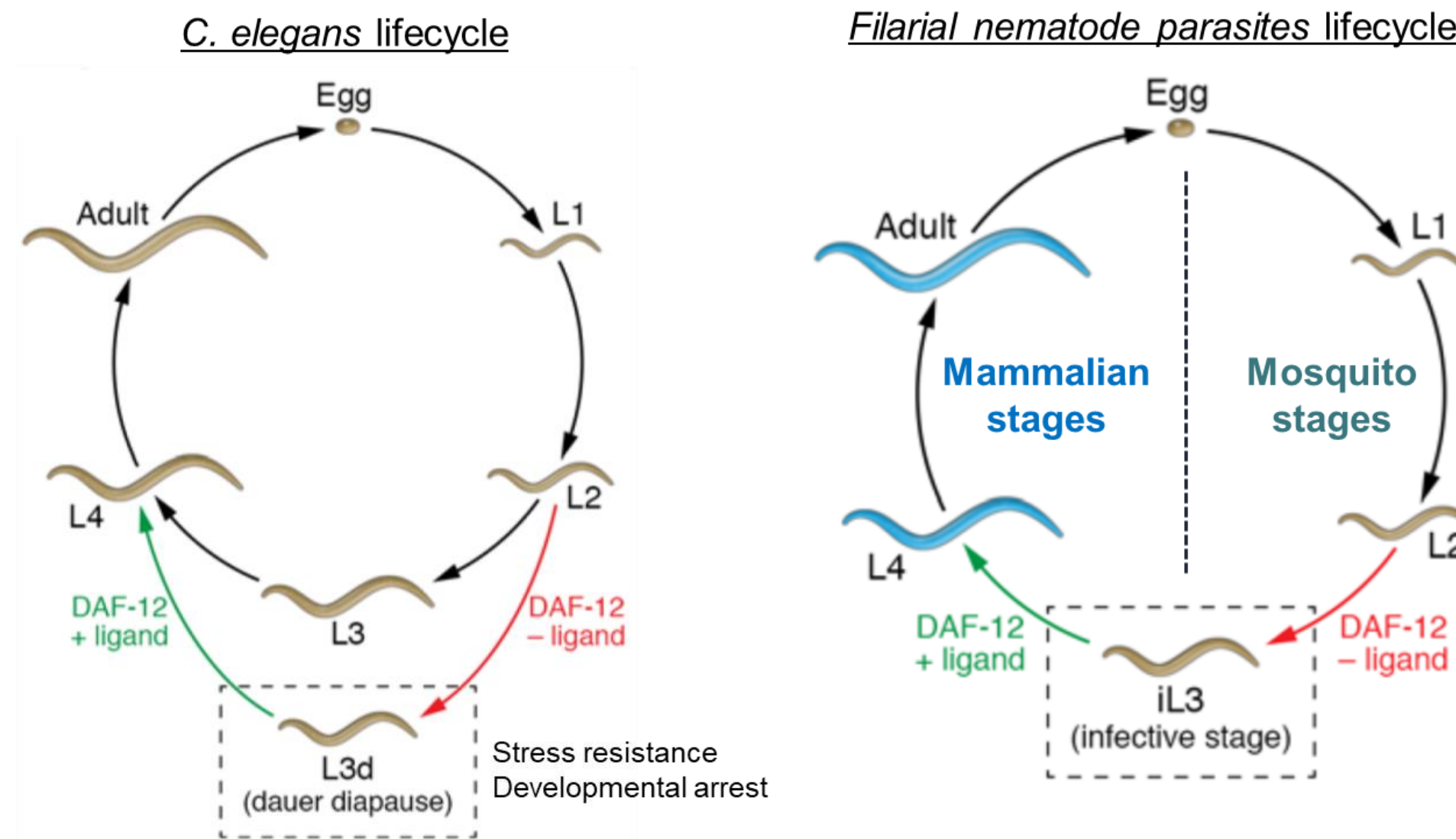
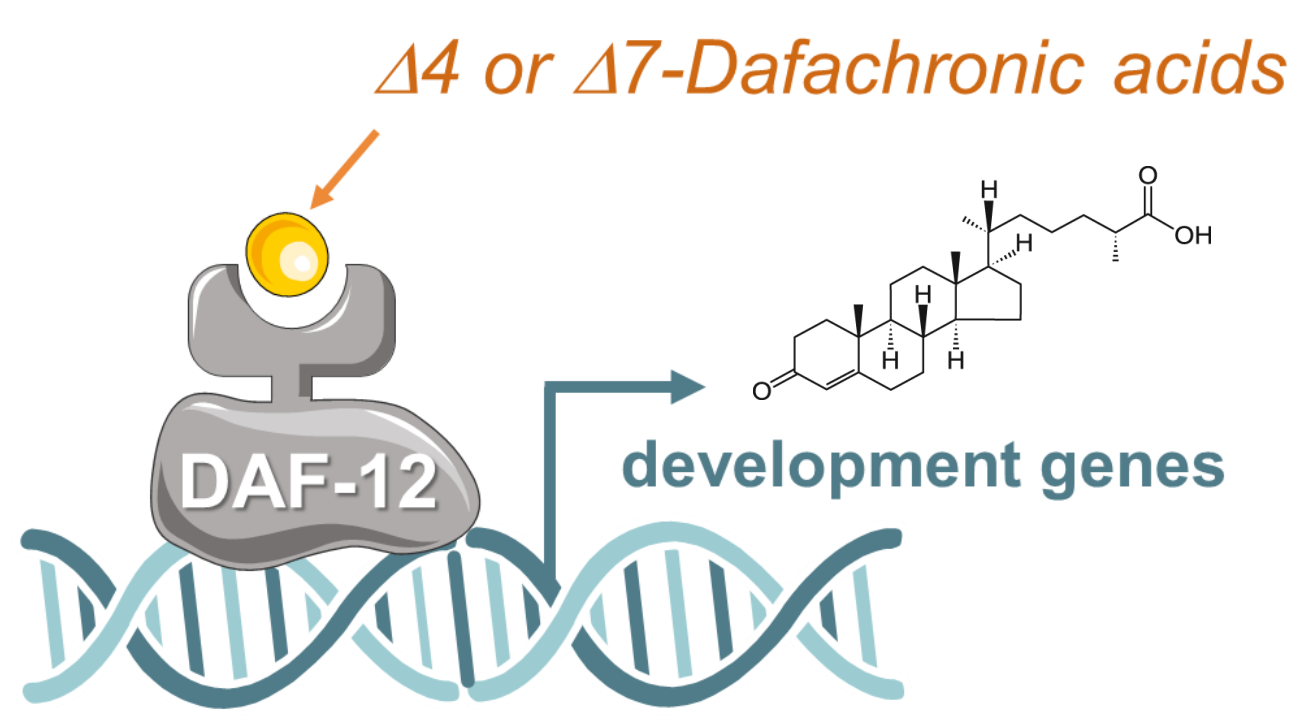
Submitted on 19 Sep 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

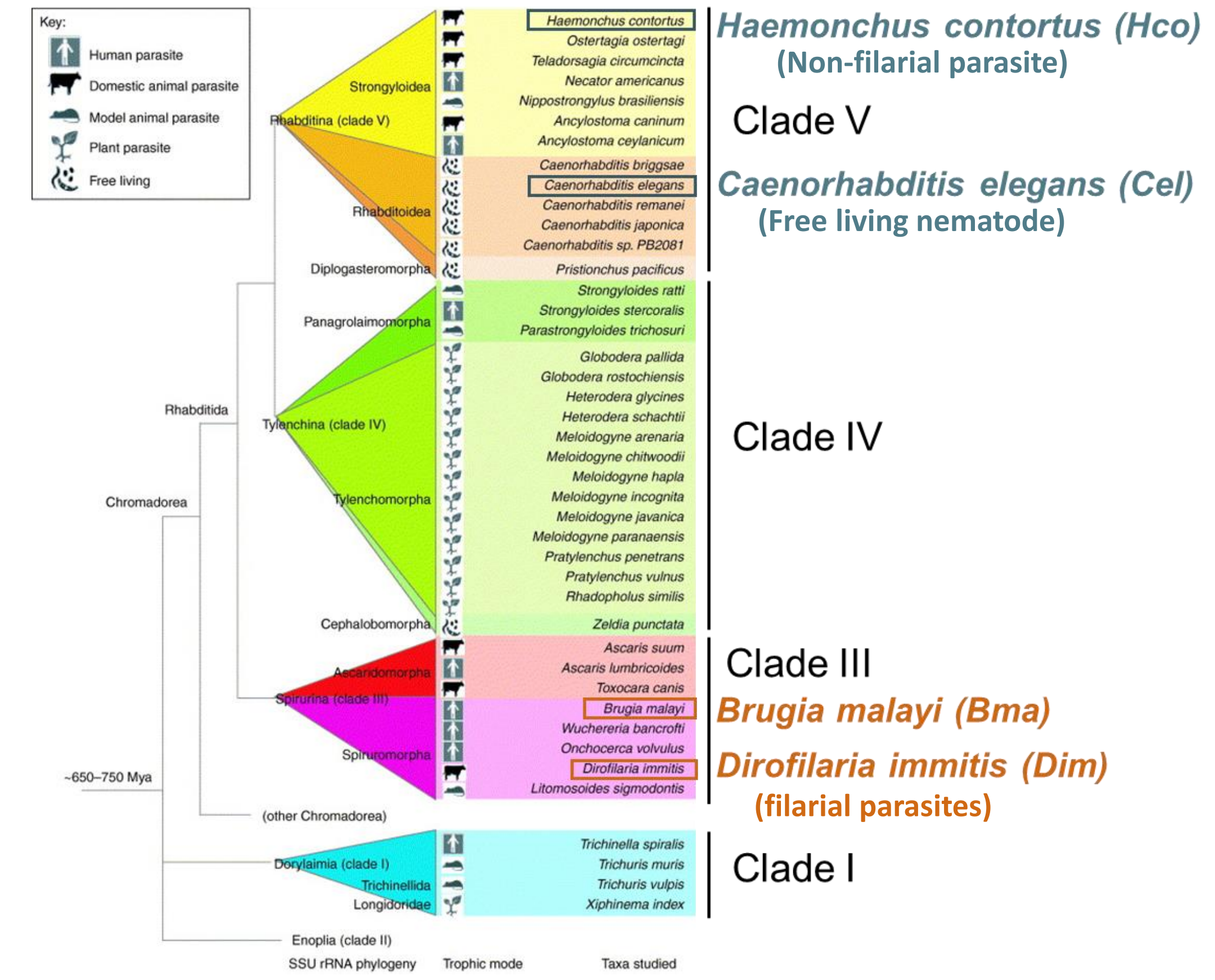
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## INTRODUCTION

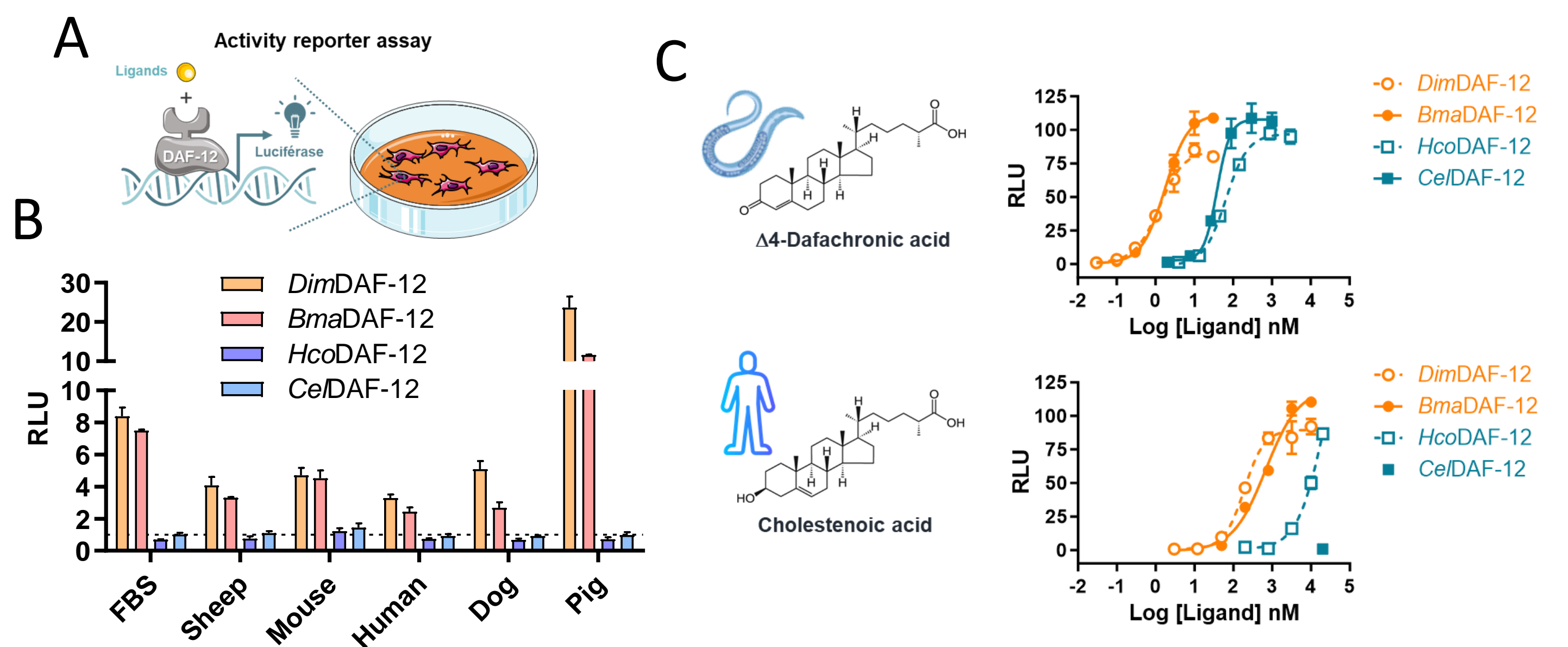
- The nematode model *Caenorhabditis elegans* harbours **284 Nuclear Receptor**
- DAF-12 is the only *C. elegans* NR with known **ligands, the dafachronic acids**.
- DAF-12 is structurally and functionally related to the mammalian FXR
- DAF-12 controls:
  - The expression of reproducible development genes
  - Entry to and exit from the dauer stage (*C. elegans*), an alternative quiescent stage more resistant to degraded environments and the infective larval stage (parasitic nematodes)



## OBJECTIVE: Compare DAF-12 activity and function in filarial and non-filarial nematodes

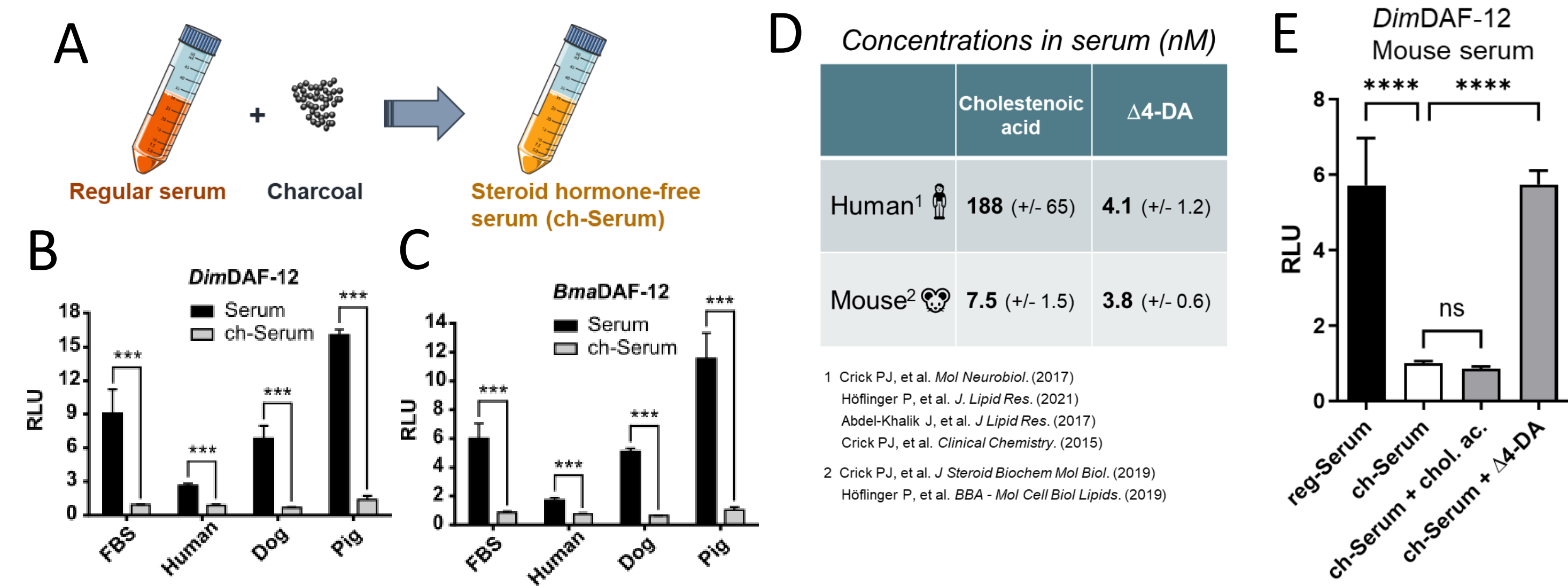


## SPECIFICITIES OF FILARIAL DAF-12 ACTIVATION



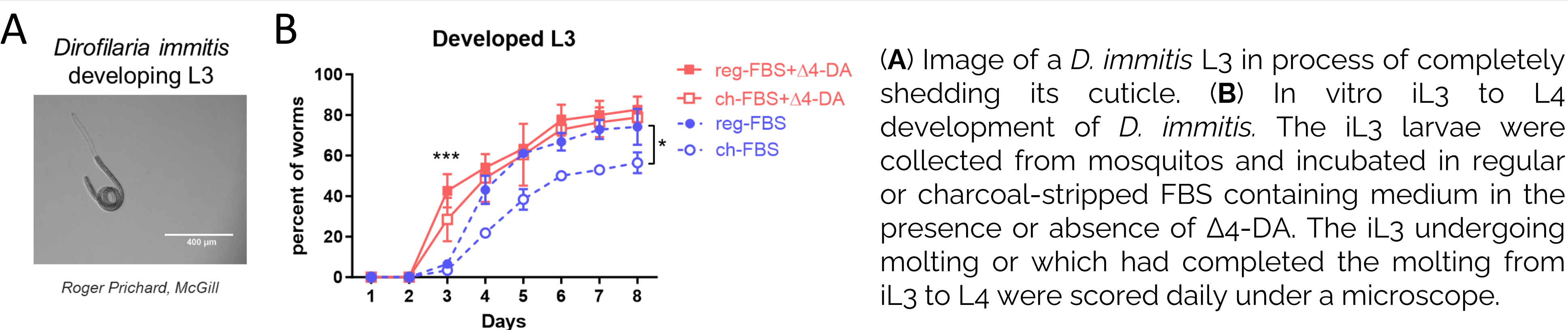
(A) Schematic representation of the DAF-12 reporter assay. (B) Activation of DAF-12 from *Dim*, *Bma*, *Hco* or *Cel* by regular sera. (C) Dose-response curves for  $\Delta 4$ -dafachronic acid and cholestenic acid on the activation of *Dim*, *Bma*, *Hco* or *Cel*DAF-12.

## MAMMALIAN SERA CONTAIN DAF-12 LIGANDS

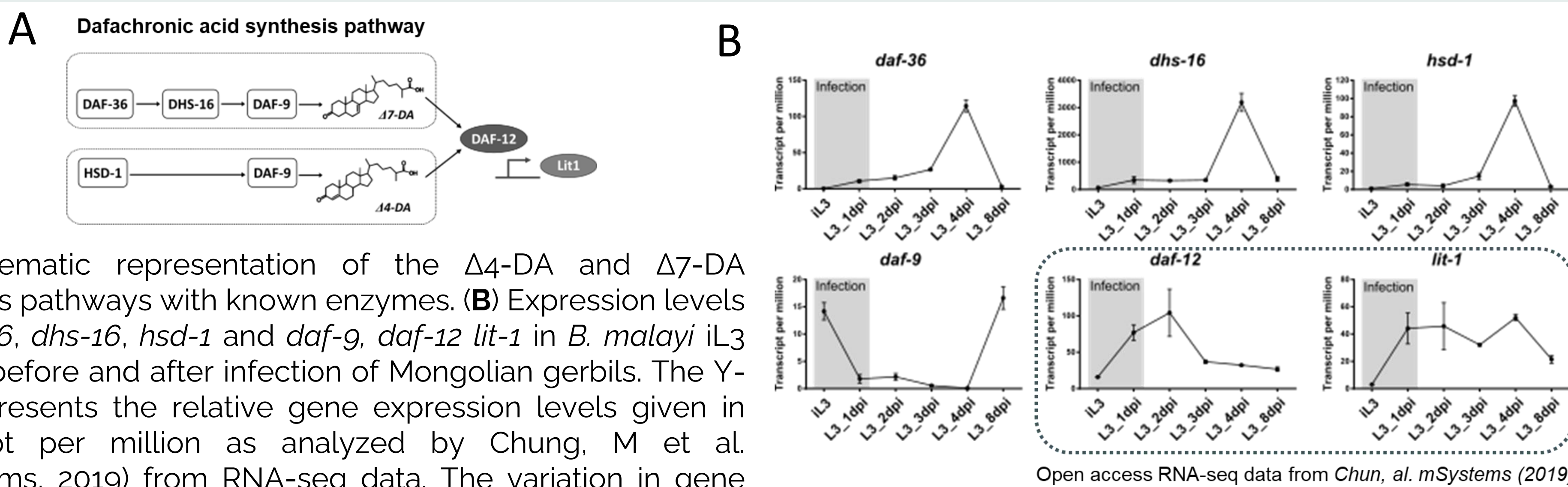


(A) Serum charcoal stripping procedure. (B) Activation of DAF-12 from *Dim* and (C) from *Bma* by regular or charcoal-stripped sera from different mammalian species. (D) Concentrations of  $\Delta 4$ -dafachronic acid ( $\Delta 4$ -DA) and cholestenic acid in human and mouse serum. (E) Supplementation of charcoal stripped mouse serum with cholestenic acid (chol. ac.) or  $\Delta 4$ -dafachronic acid ( $\Delta 4$ -DA) at their concentrations found in mouse sera

## DAF-12 ACTIVATION STIMULATES *D. IMMITIS* IL3 DEVELOPMENT



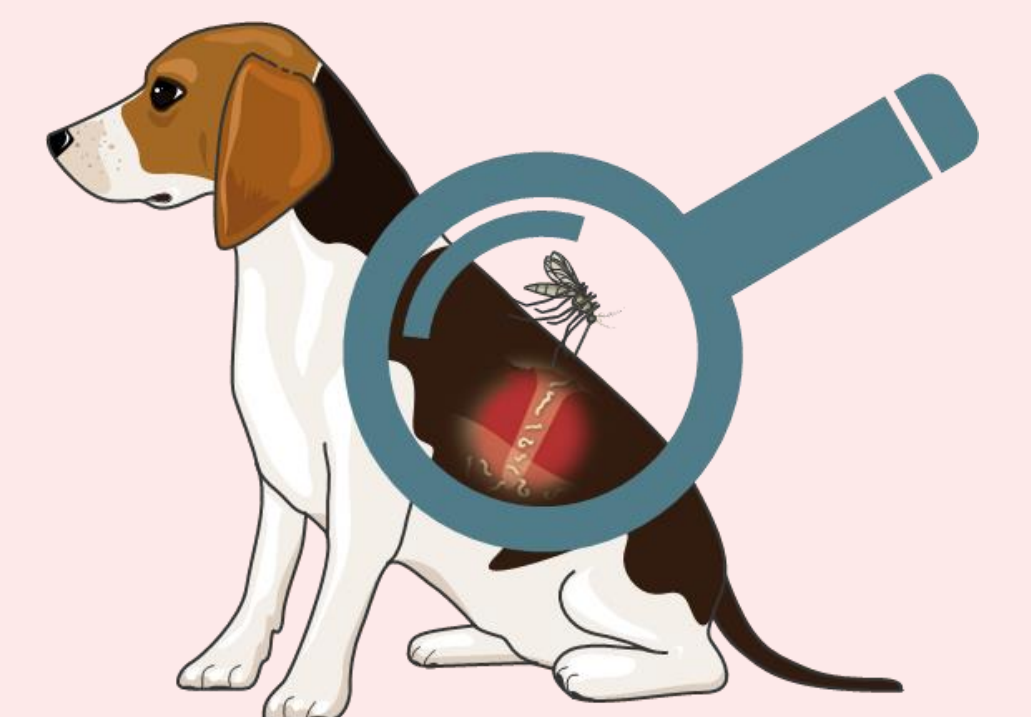
## DAF-12 LIGANDS BIOSYNTHESIS ENZYMES ARE DOWN-REGULATED IN THE FILARIAL NEMATODE BRUGIA MALAYI AT THE TIME OF INFECTION



(A) Schematic representation of the  $\Delta 4$ -DA and  $\Delta 7$ -DA synthesis pathways with known enzymes. (B) Expression levels of *daf-36*, *dhs-16*, *hsd-1* and *daf-9*, *daf-12* *lit-1* in *B. malayi* iL3 and L3 before and after infection of Mongolian gerbils. The Y-axis represents the relative gene expression levels given in transcript per million as analyzed by Chung, M et al. (mSystems, 2019) from RNA-seq data. The variation in gene expression at time infection is highlighted in grey.

## CONCLUSIONS

- Filarial DAF-12s are hypersensitive to their ligands
- Host serum contains DAF-12 ligands, including  $\Delta 4$ -dafachronic acid
- These DAF-12 ligands support *D. immitis* larval development
- The expression of genes involved in DA biosynthesis is very low during the early days of infection



**daf-12 may have evolved in filarial parasites to sense the host environment through its ligands and promptly trigger parasite development and growth upon infection.**