Innate immunity of Drosophila

WR-XLM-GC
2023.1月

报告主题：**Innate immunity of Drosophila**

报告内容:

Innate immunity of Drosophila and its mechanisms　　12:00-12:40 WR

Host-parasitoid interaction in Drosophila　　12:40-13:20 XLM师姐

13:20- 讨论 ~

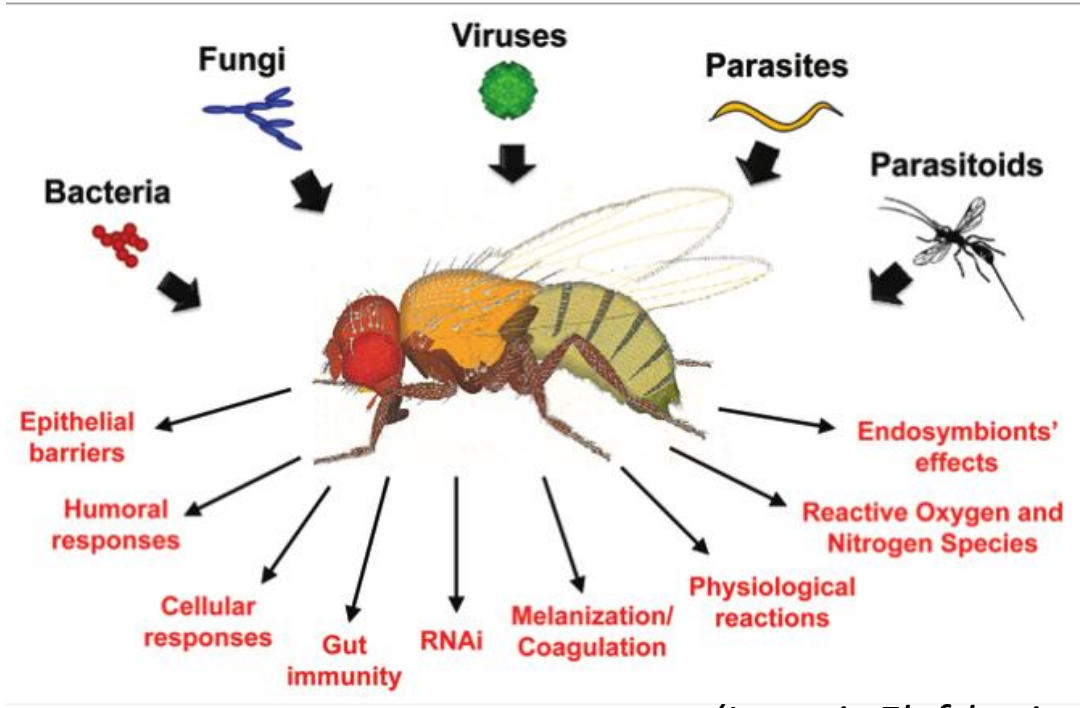
- **The immune system and immune modalities of fruit flies**
- **Mechanisms of innate immunity in fruit flies**

What is innate immunity in fruit flies?

What is innate immunity ?

The immune system ——an important system for the body to perform immune responses and immune functions.
Composition—— immune organs, immune cells and immune molecules.
Function—— recognize and eliminate antigenic foreign bodies, coordinating with other systems of the body, and jointly maintaining the stability of the environment and physiological balance in the body.

What is innate immunity in fruit flies?

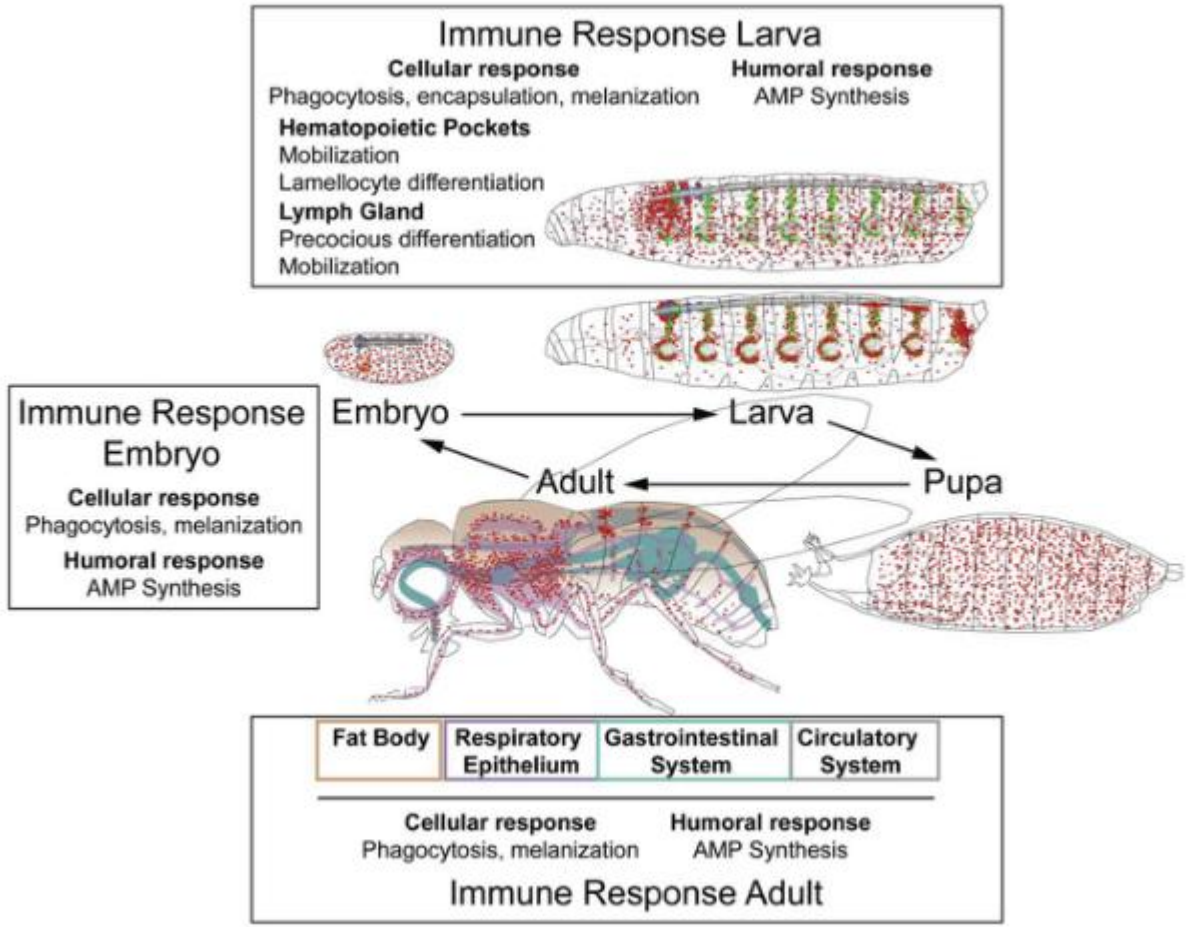


(Ioannis Eleftherianos and David Schneider.*Fly*.2011)

Innate immunity ——Conservative body-defense mechanisms produced earlier;the first line of defense against invading pathogens and plays an essential role in defending the brain against infection, injury, and disease. (**Insect**)

Adaptive immunity——The whole process in which antigen-specific T/B lymphocytes in vivo are activated, proliferated, and differentiated into effector cells after receiving antigen stimulation, resulting in a series of biological effects. (**Mammal**)

Melnogaster's innate immune response



(Katrina S. Gold and Katja Brückner.*Semin Immunol*.2015)

Melnogaster's innate immune response

Innate immune response in fruit flies

Cellular immunity——Plasma cells

- consists of hemocytes that phagocytose, encapsulate, and kill invading microbes, much like vertebrate macrophages.
- The process involved:Phagocytosis, conditioning, encapsulation, coagulation, and blackening

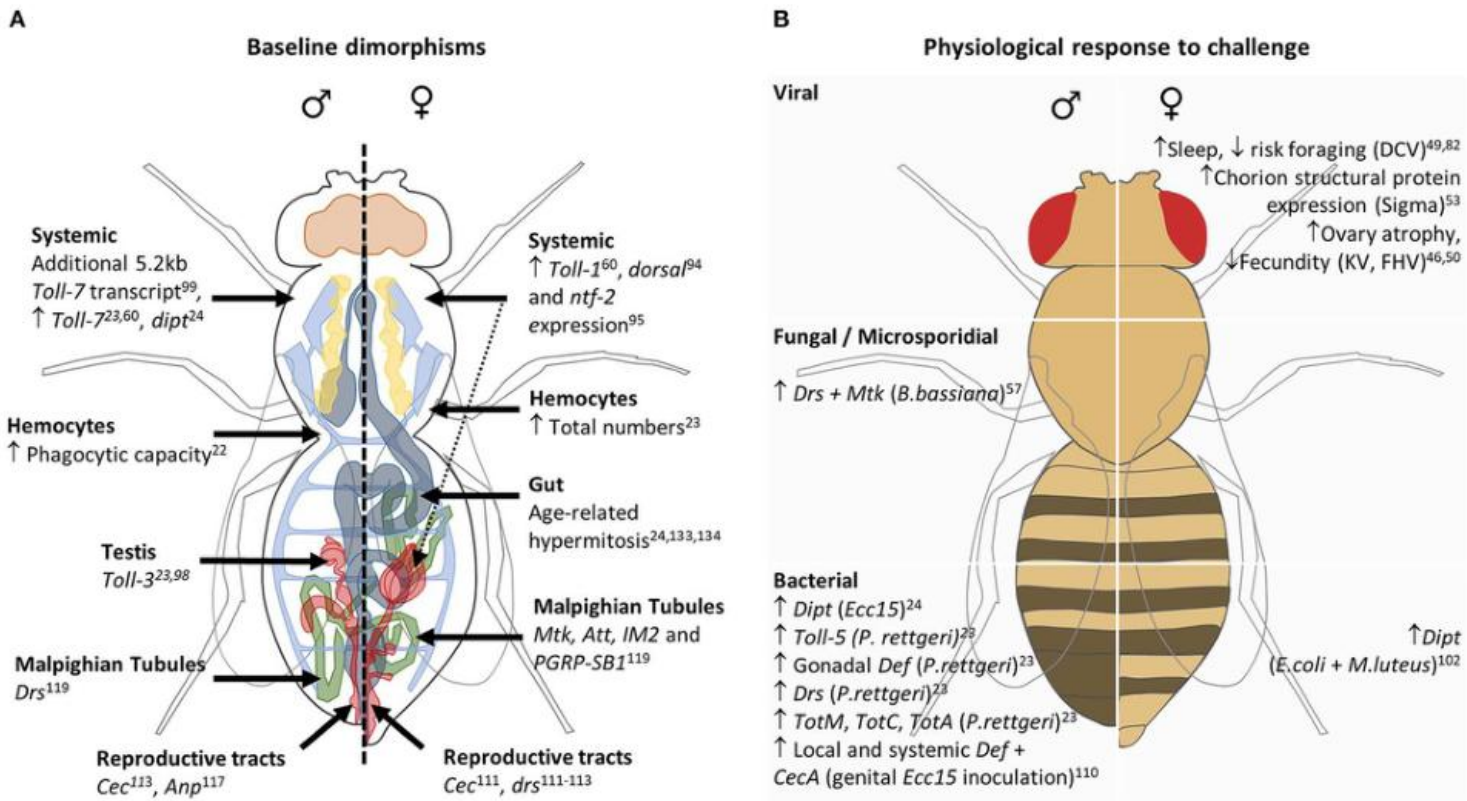
Humoral immunity——Induced in fat body , acting in the blood

- involves the secretion of soluble factors, such as antimicrobial peptides (AMPs), into the hemolymph following immune activation.
- involves **Toll**、**IMD**、JAK-STAT and JNK pathway——systemic immune response.

melanization

- whereby melanin is deposited at wound sites and parasite surfaces, resulting in the release of toxic reactive oxygen species.
- involves phenoloxidase and a series of protein cascades.

Sexual dimorphisms in innate immunity at basal state



(Rebecca L. Belmonte, Mary-Kate Corbally et.al.*Frontiers*.2020)

Summary:

•Fruit flies only have innate immunity, but not vertebrate adaptive immunity, which quickly activates the immune response of fruit flies when infected by pathogens.

•In general, immune reactions in Drosophila can be categorized into systemic, epithelial and cellular immunity . The systemic immune response is characterized by the synthesis of immune effector molecules such as the antimicrobial peptides (AMPs) by the cells of the fat body—a functional equivalent of the mammalian liver—and their release into hemolymph to address infections by microorganisms.

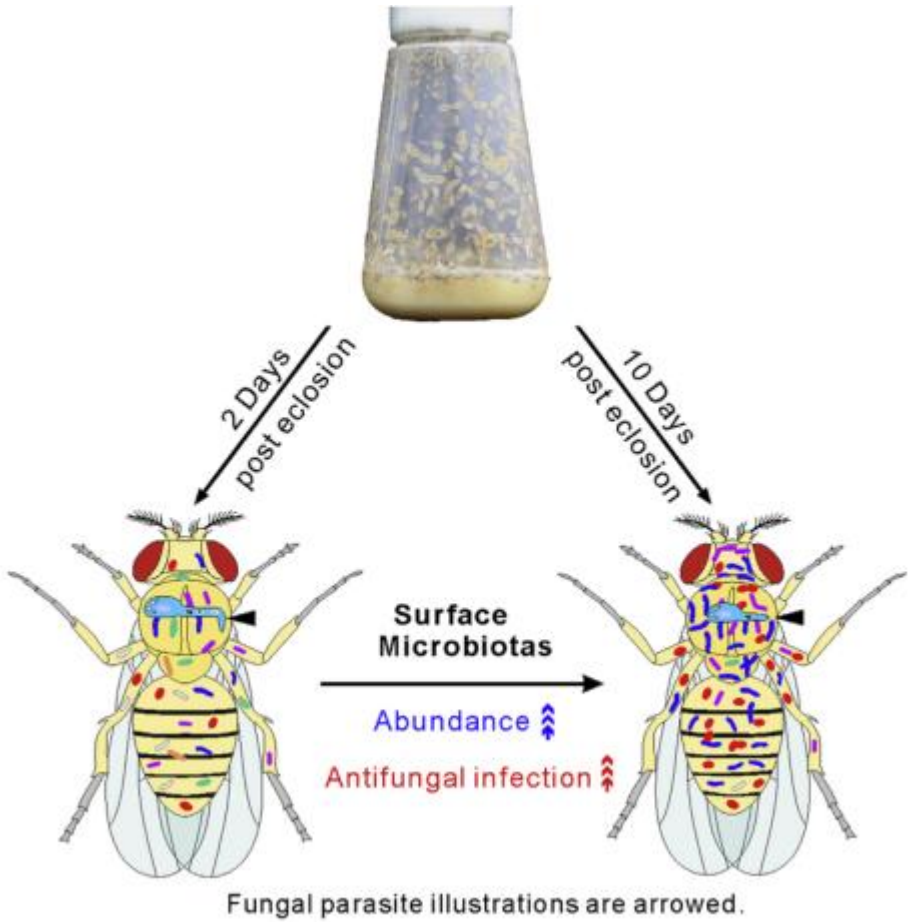
•Epithelial immunity fights against invading microorganisms at the level of the barrier epithelia such as gut and trachea, and significantly contributes to the protection of flies . For instance, in the gut, both the synthesis of AMPs and production of reactive oxygen species (ROS) characterize this response.

• The cellular immune response is centered on the action of hemocytes, which play a major role in the phagocytosis of microorganisms and apoptotic cells .

•The innate immunity of fruit flies is sexually dimorphic, and immune-related genes are upregulated or downregulated during the immune response, and this difference in immune response will lead to different behavioral outputs in the face of different pathogens.

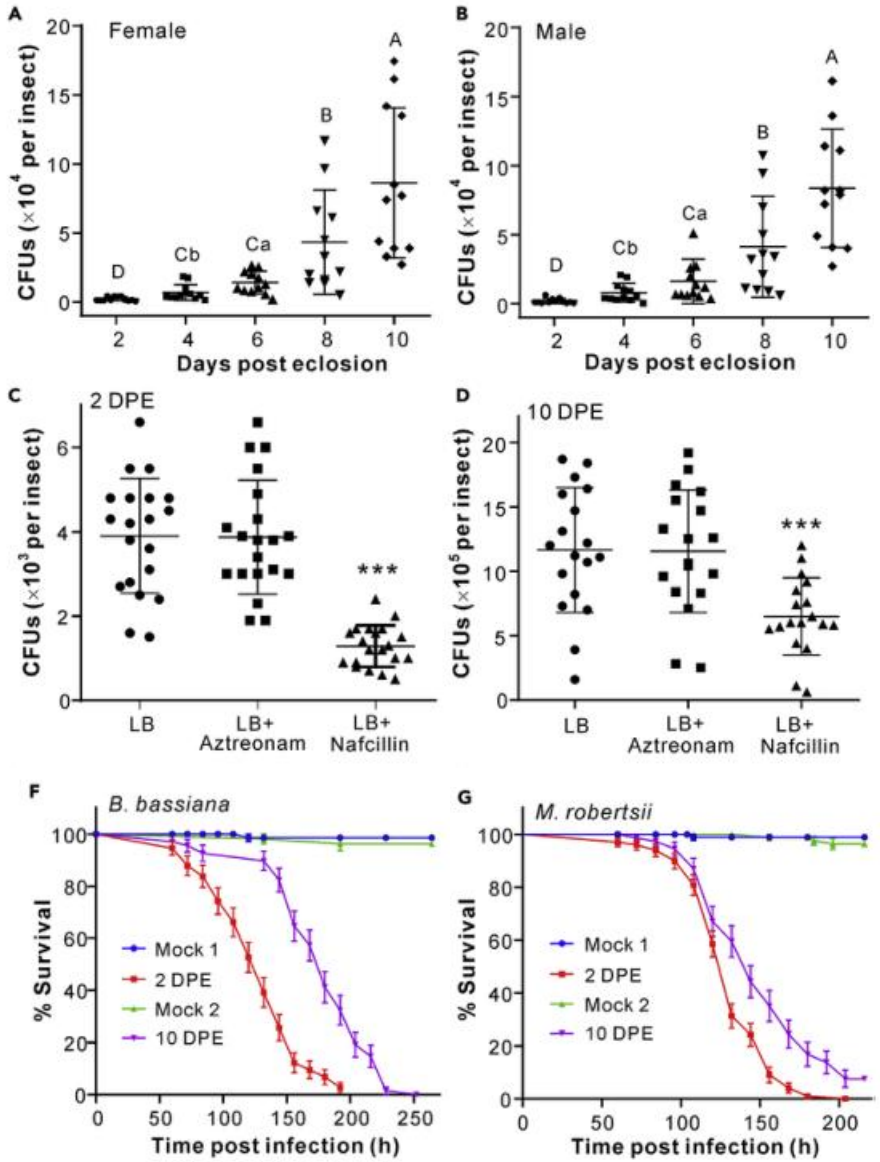
Mechanisms of innate immunity in fruit flies

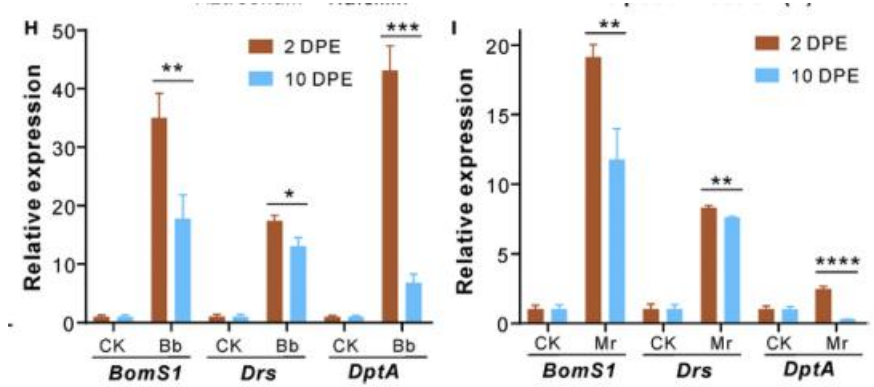
Microbiome assembly on Drosophila body surfaces benefits the flies to combat fungal infections



(Song Hong, Yanlei Sun et.al.*iScience*.2022)

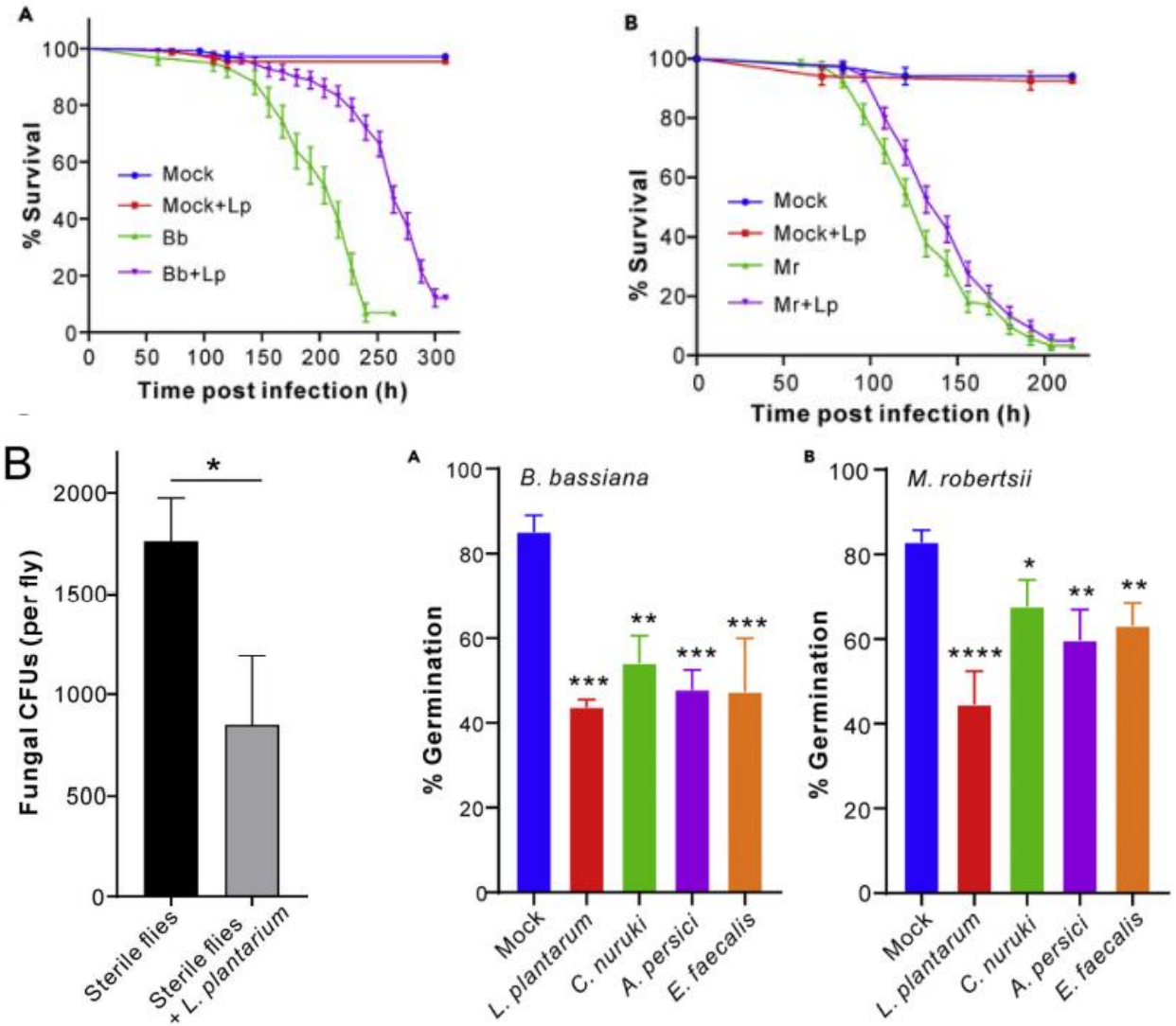
Bacterial load increase on the Drosophila body surfaces after eclosion for different times and variations in fly survival and AMP gene expressions



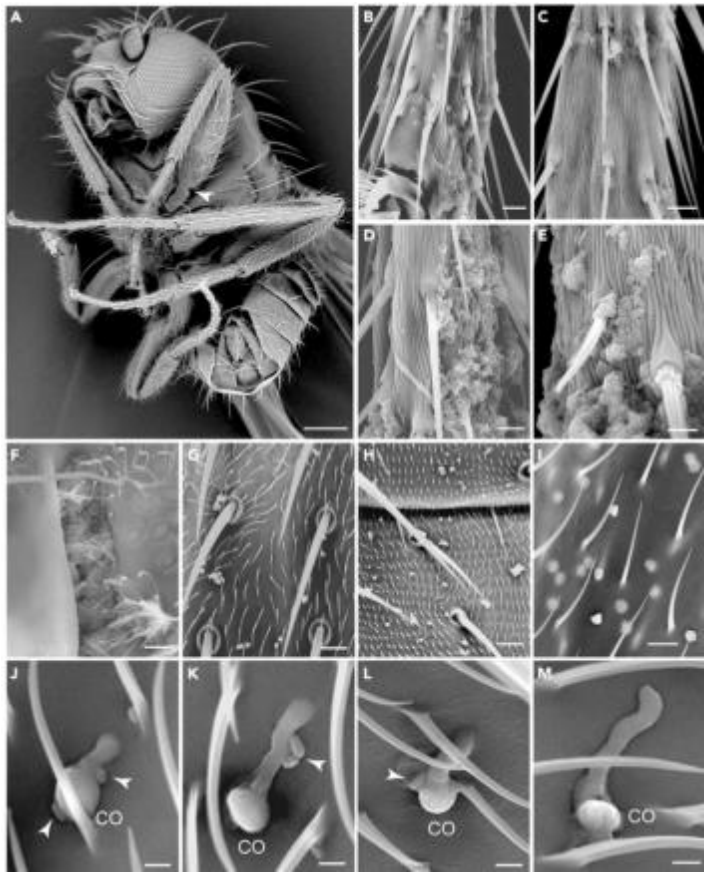


- Bacterial load increases on the body surface of Drosophila after eclosion;
- When challenged by fungal parasites, fruit fly immunity can be stimulated.

The bacterial loads on flies could deter fungal topical infections by inhibiting fungal spore germinations.

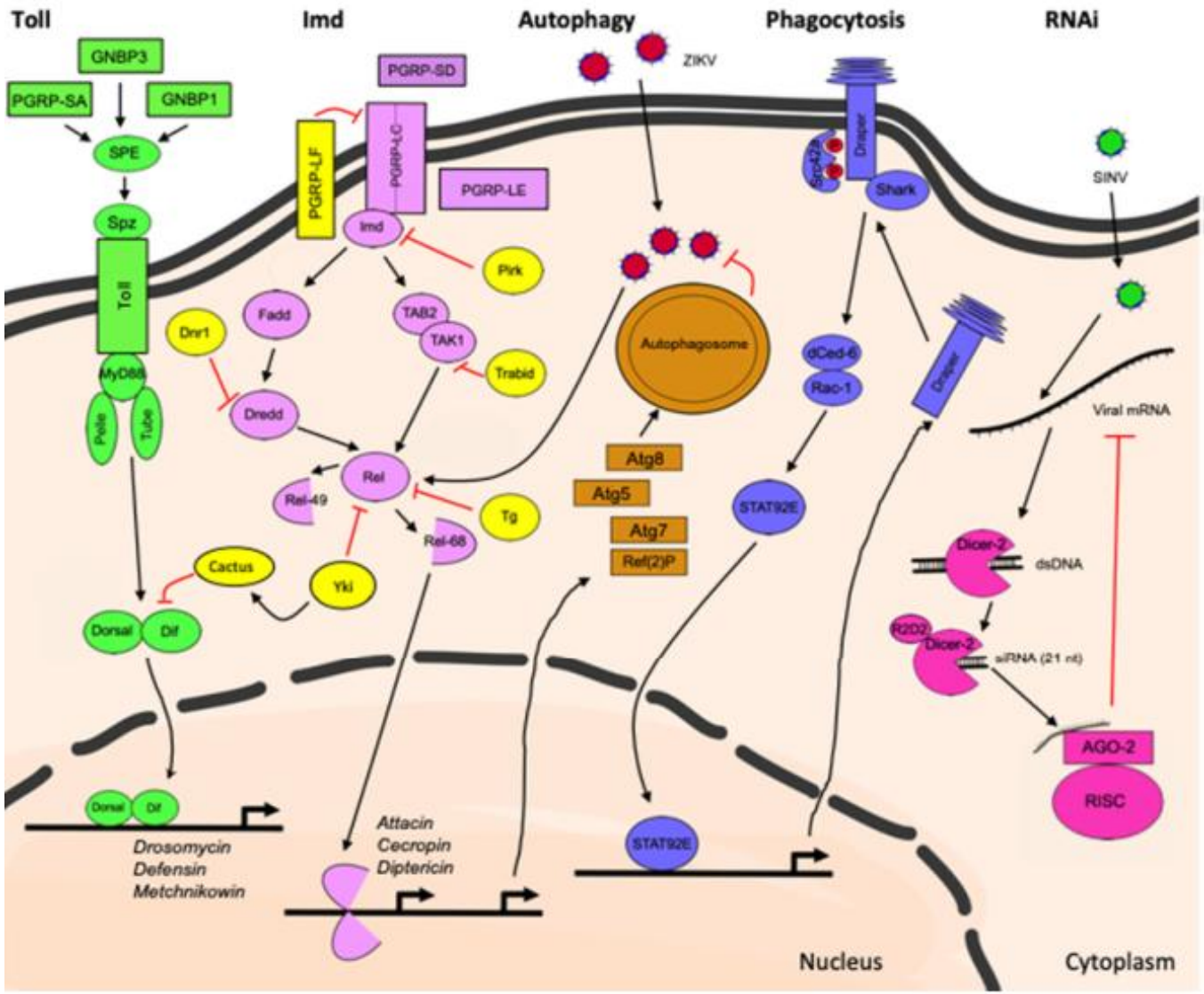


The bacterial load increase in flies after eclosion and that the surface bacteria could inhibit fungal spore germination.



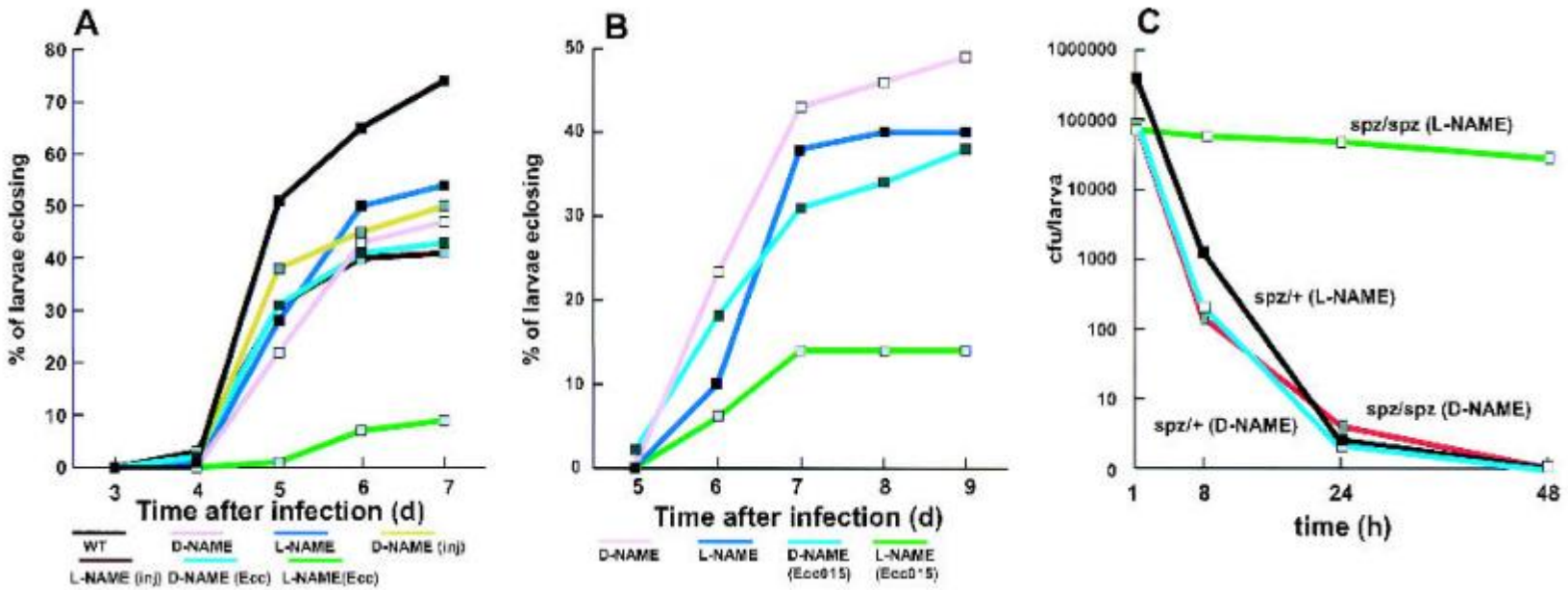
- The bacterial loads quickly increased on fly surfaces within 10 days of eclosion, which could benefit the flies to battle fungal infections by the inhibition of spore germinations.
- Besides the recessed area of body parts , the tarsal segments were found to be densely accumulated with bacterial cells probably owing to the contact and contaminations with food nutrients and fecal bacteria.

Innate immune pathways activated in the Drosophila brain following injury, infection and neurodegenerative disease



(Shu Hui Lye and Stanislava Chtarbanova.*Int. J. Mol. Sci. 2018*.)

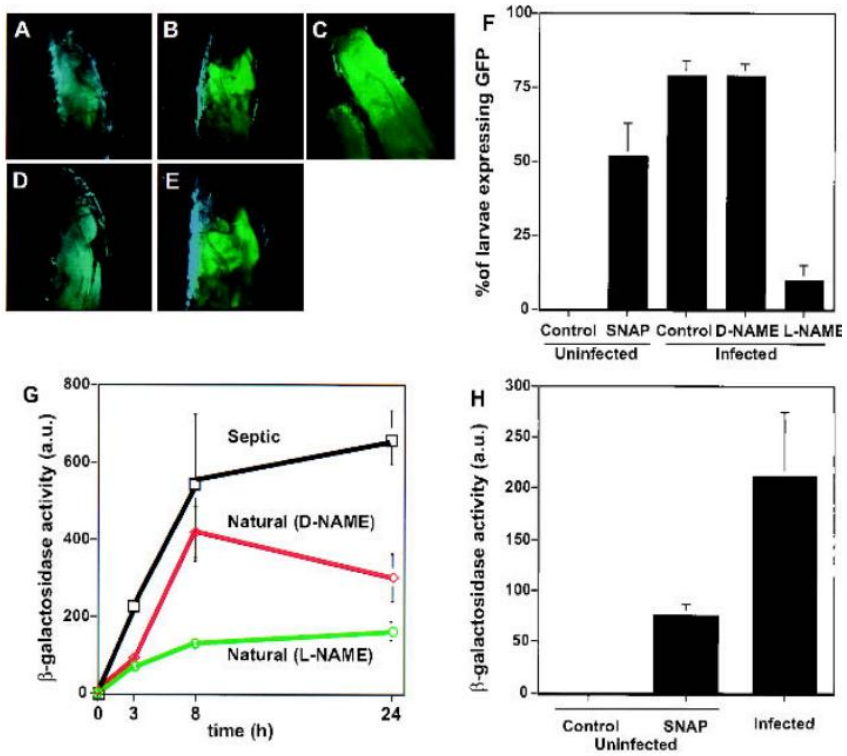
NOS contributes to pathogen destruction



(Edan Foley and Patrick H. O' Farrell.*GENES &DEVELOPMENT* .2003)

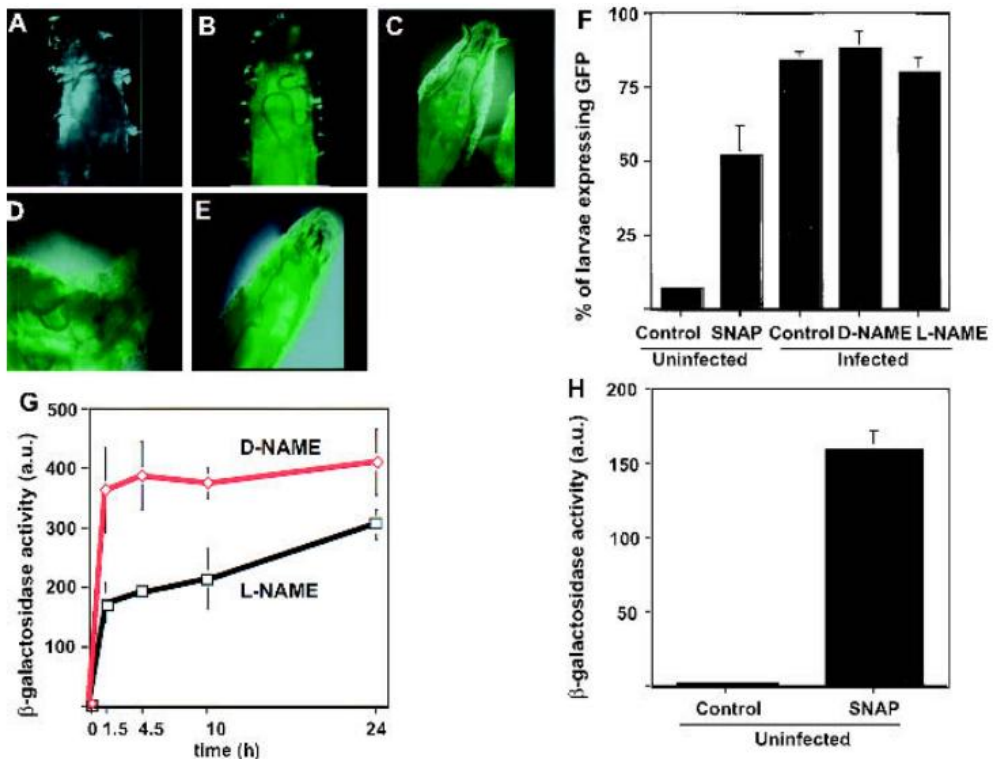
- Inactivation of NOS impairs the ability of Drosophila to combat subsequent infections by two different routes.
- L-NAME severely compromises Spz-independent host defenses. The major defense against gram-negative bacteria such as Ecc is thought to be mediated via the Spz-independent Imd pathway.

NO is a signaling molecule in the Imd/Rel pathway



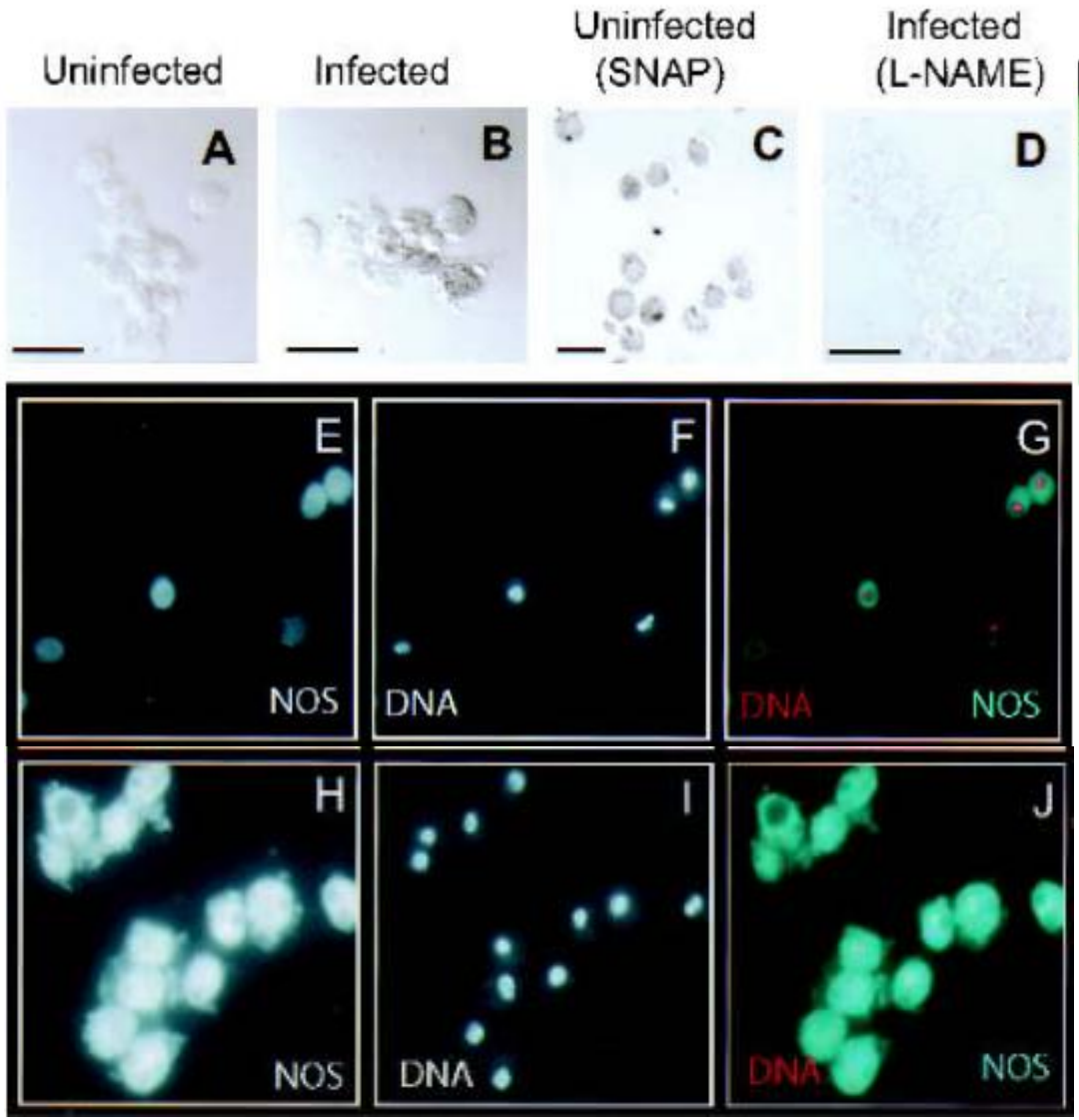
NOS activity is required for Dipt expression after natural infection with gram-negative bacteria,and that NO is sufficient to activate Dipt expression in the absence of infection.

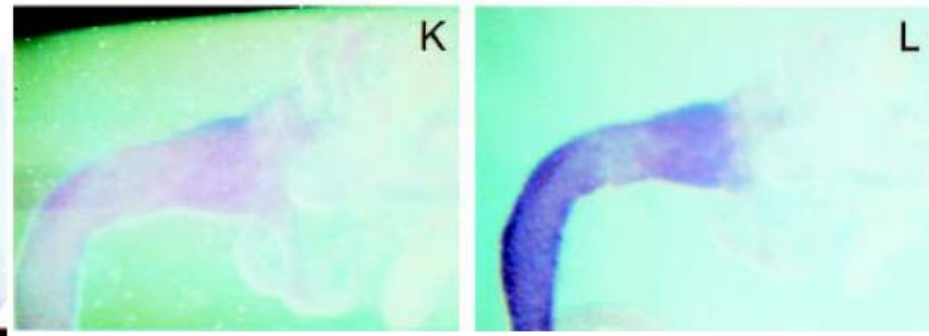
NO effects on Drosomycin expression



- It appears that inhibition of NOS does not prevent infection-dependent Drs induction.
- Infection-mediated induction of Drs may occurs via two pathways —— a NOS dependent and independent one.

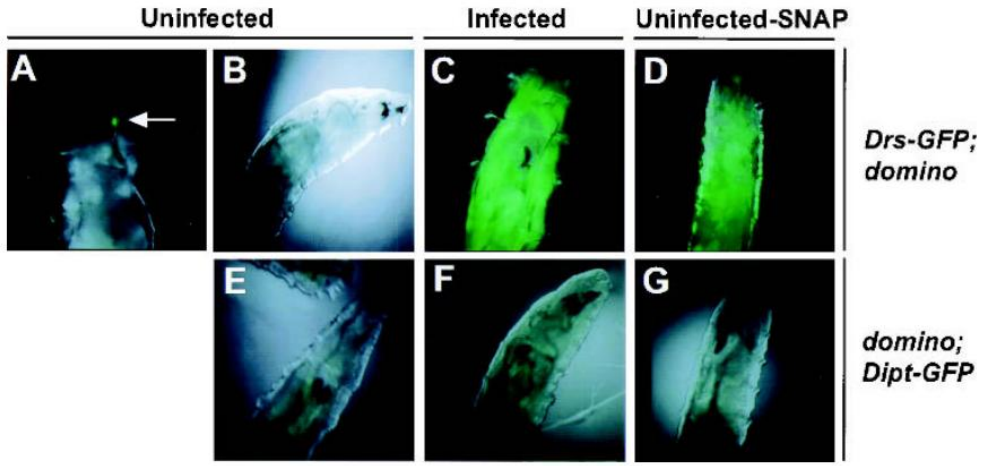
NOS involvement in hemocyte responses to infection

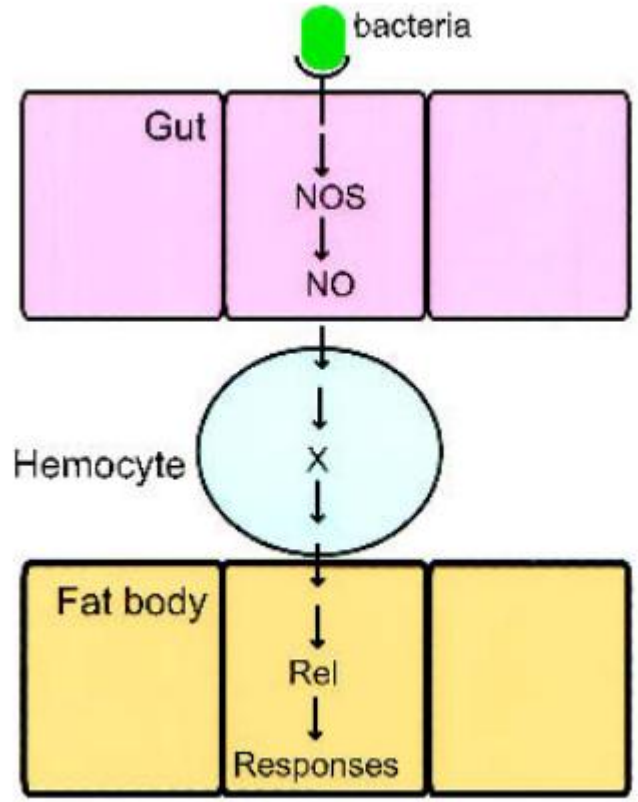




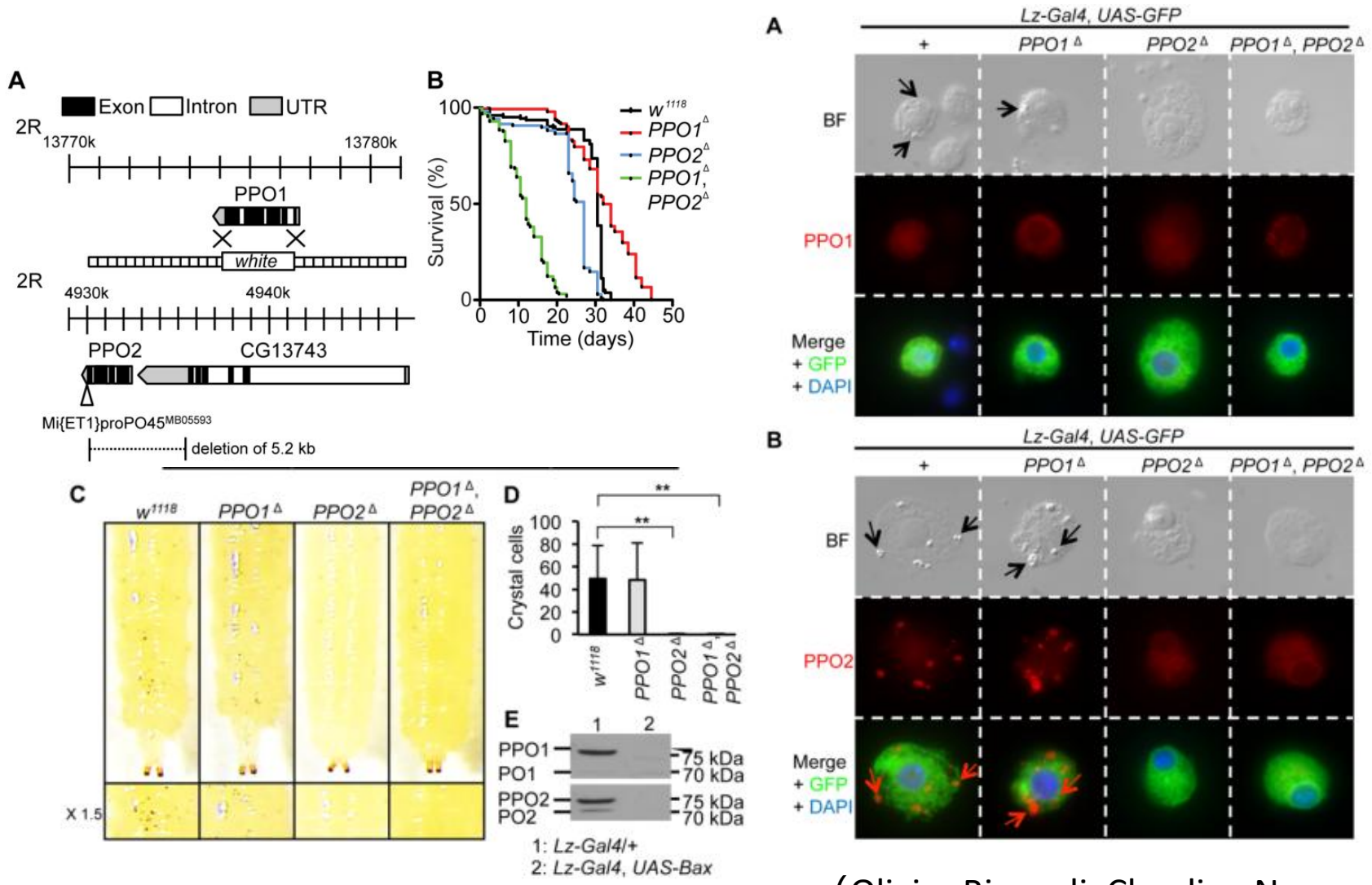
NO is necessary for efficient induction of Dipt in larval hemocytes following natural infection.

The domino mutant interferes with NO induction of Dipt, but not induction of Drs.





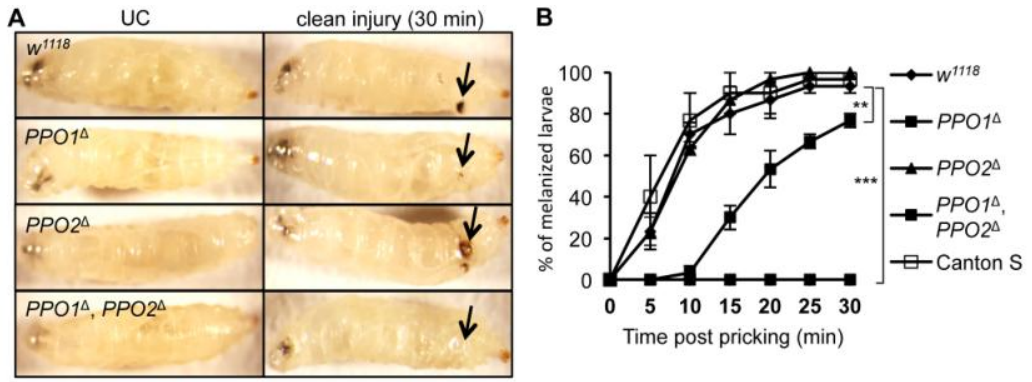
PPO2 is stored in the crystals of crystal cells

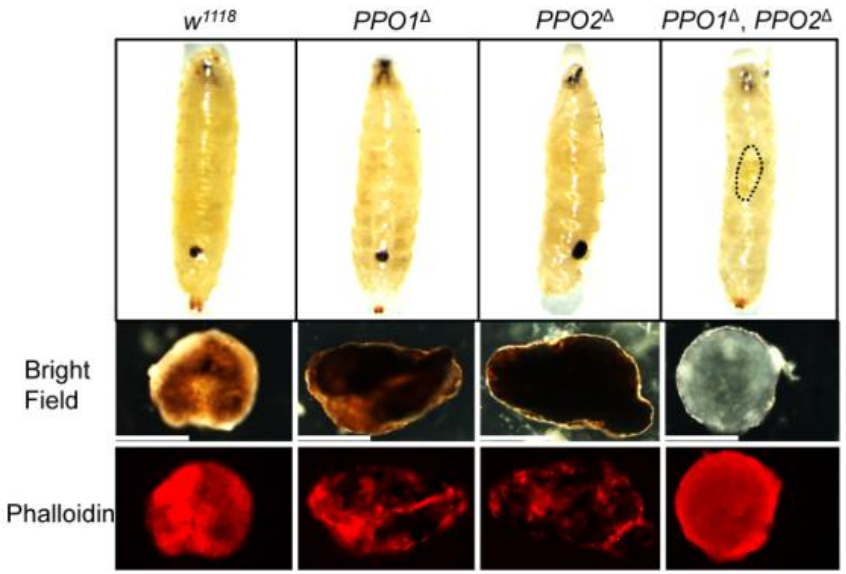


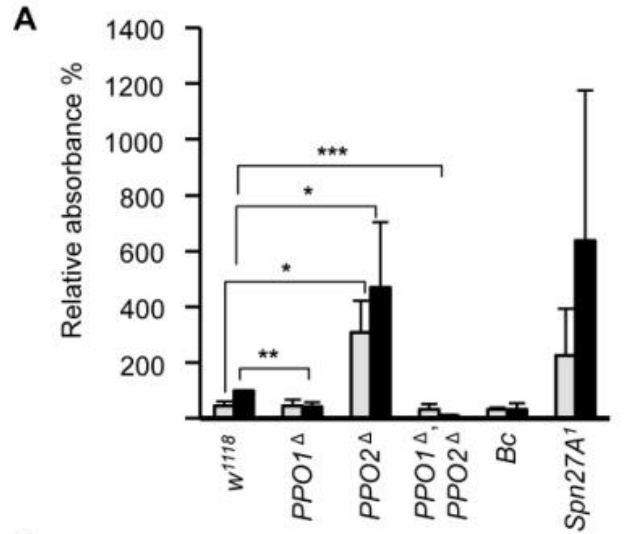
(Olivier Binggeli, Claudine Neyen et.al.*PLOS Pathogens*.2014)

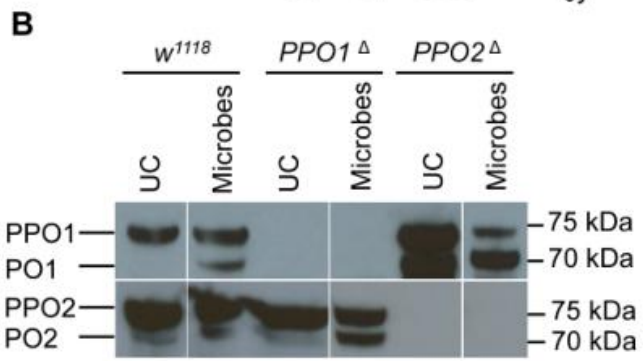
PPO2 is stored in crystal cells while PPO1 is either a minor component of the crystal or most probably released from crystal cells into the hemolymph.

PO1 and PO2 both contribute to injury-mediated melanization in larvae and adults



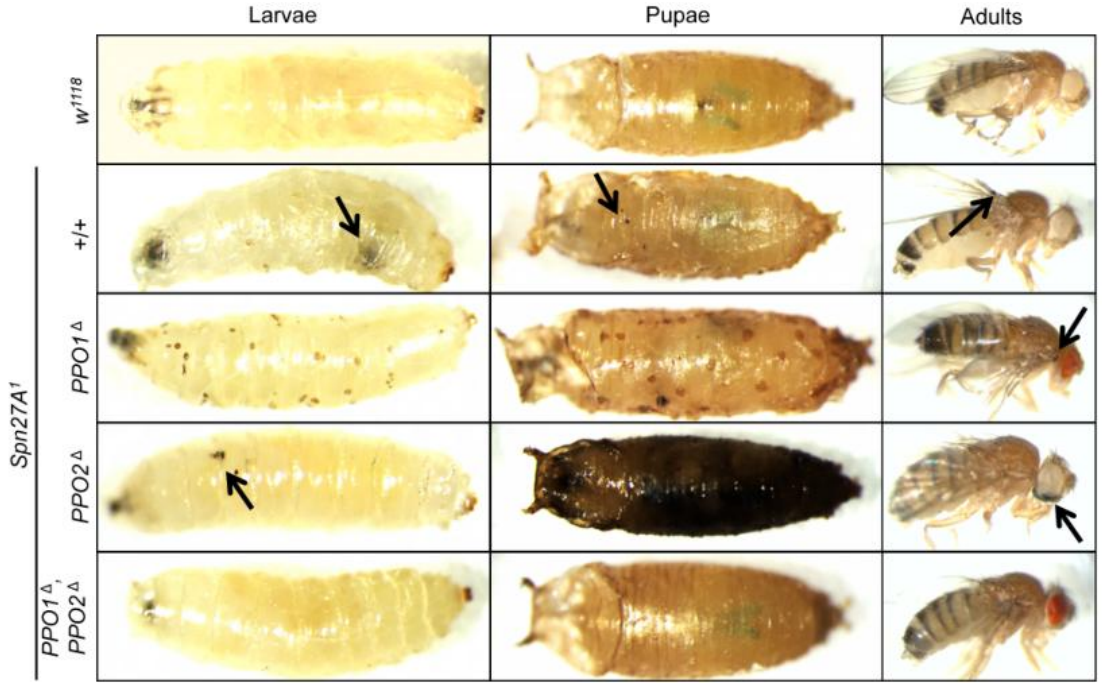




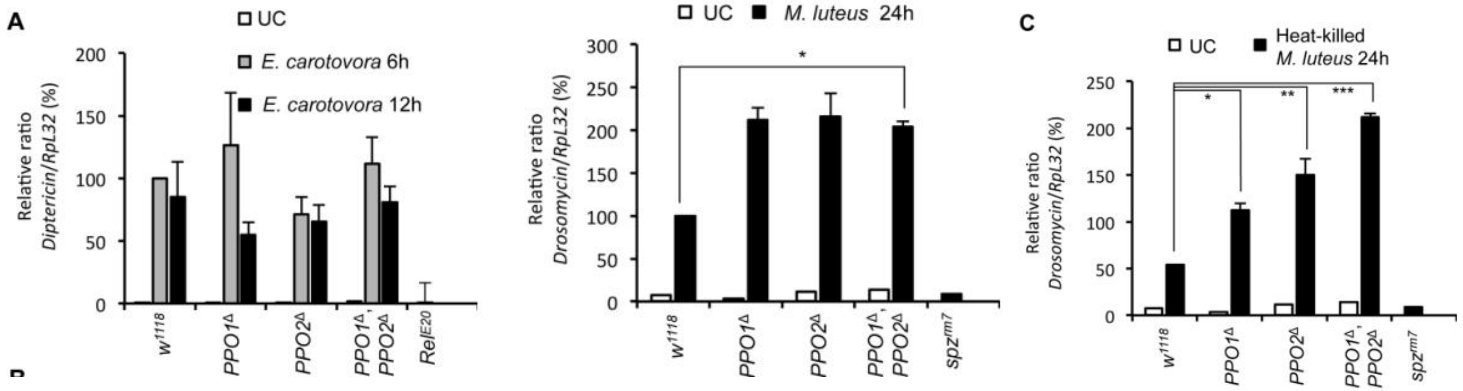


Both PPO1 and PPO2 contribute to the melanization observed in the hemolymph or at the wound site in flies upon injury.

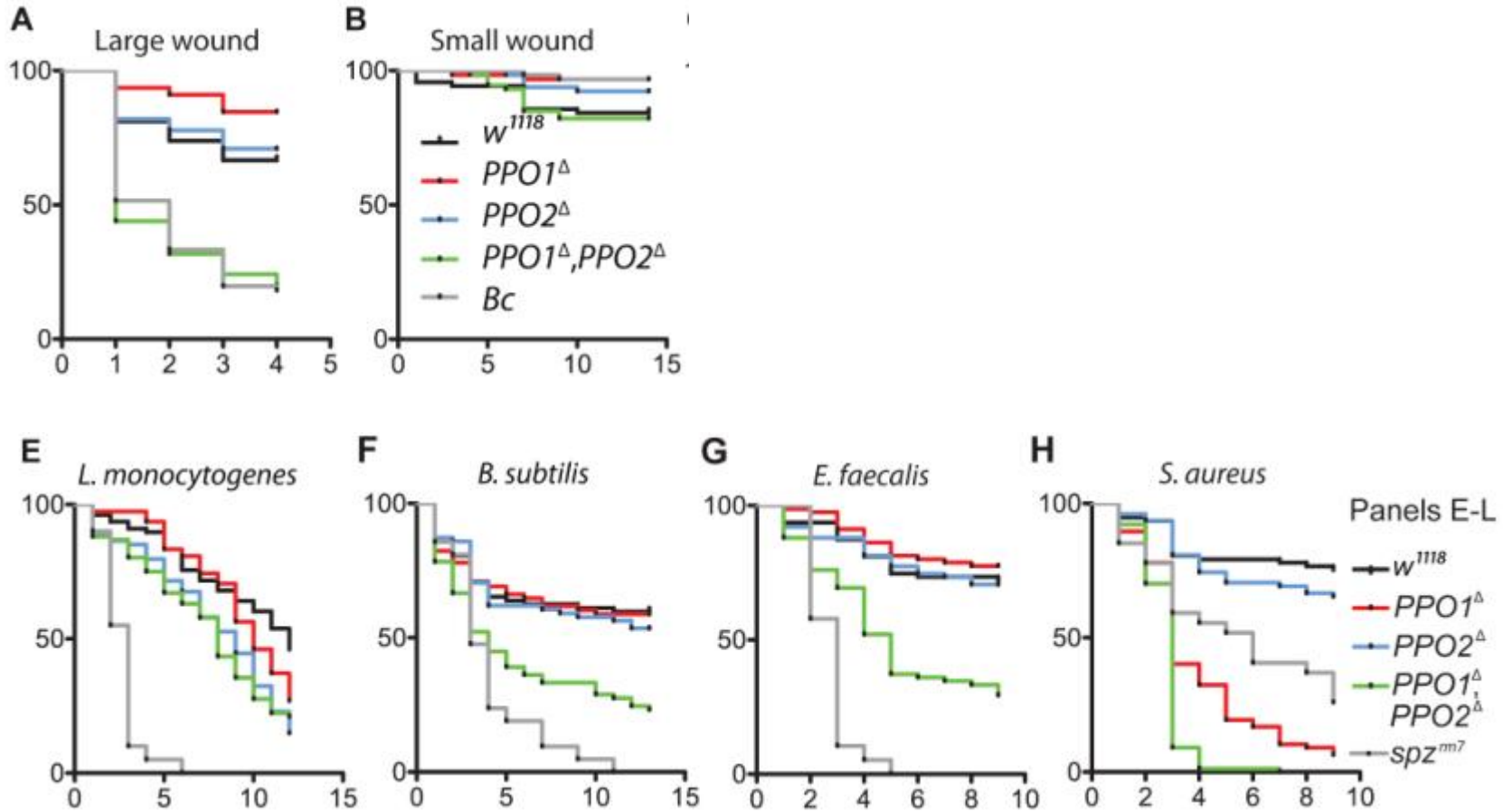
Melanization is dispensable for Toll and Imd pathway activation



Although PPOs are not required for Toll and Imd pathway activation, absence of melanization specifically enhances Toll activation.

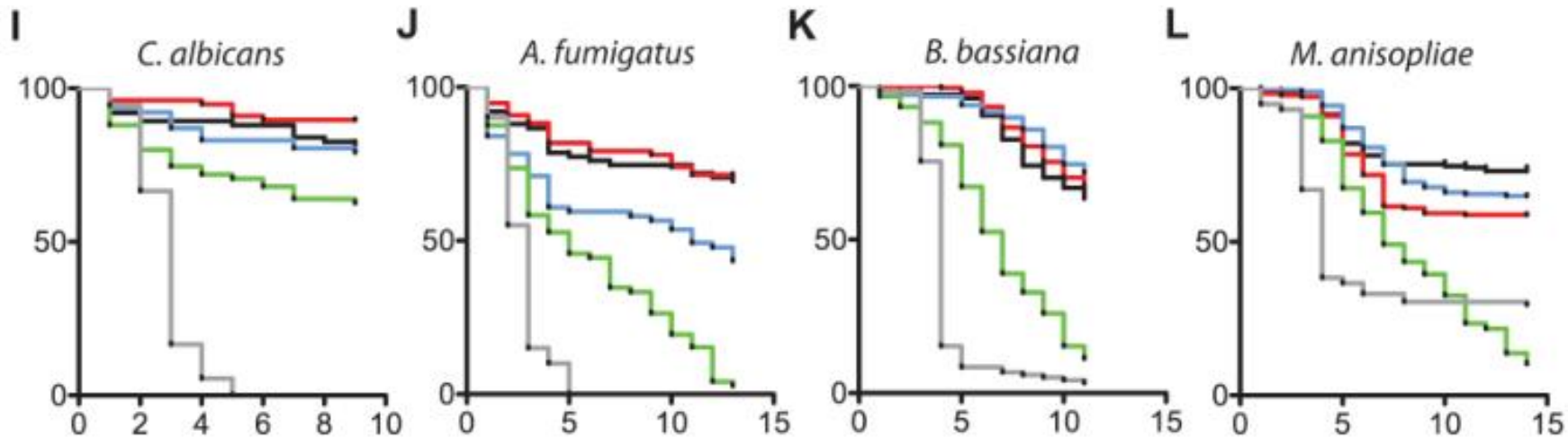


Melanization contributes to survival to wounding and to infection with Gram- positive bacteria



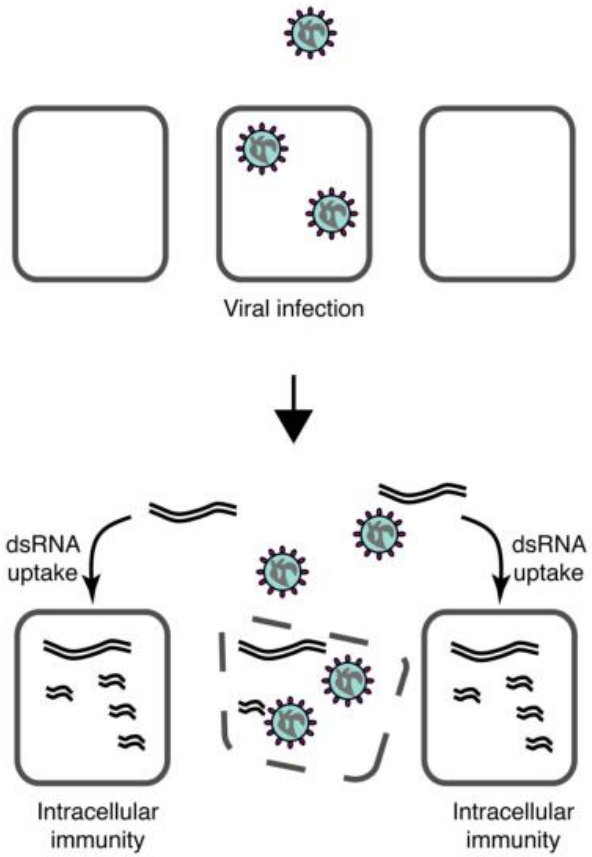
PPOs cooperate with the Toll pathway in promoting host defense against Gram-positive bacteria, notably Lysine-type strains.

PPOs contribute to survival to infection with entomopathogenic fungi



melanization significantly contributes to the survival to fungal and Gram-positive bacterial infections.

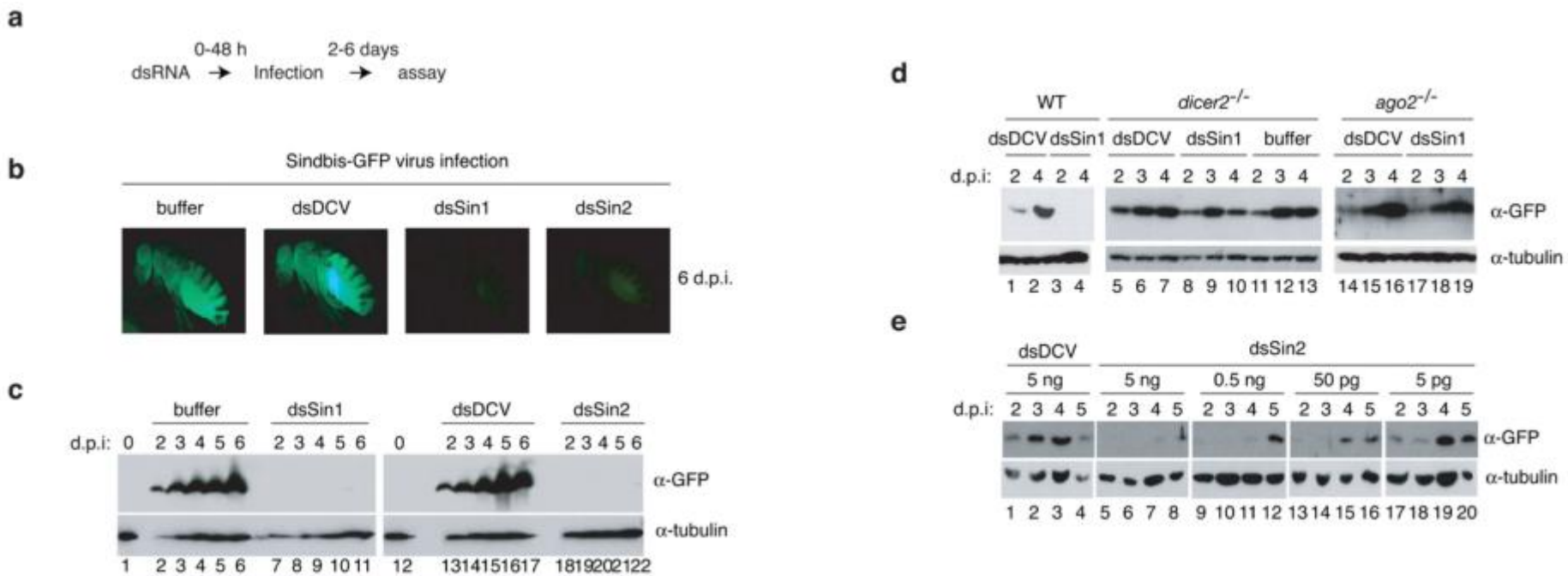
Model for systemic RNAi viral immunity in Drosophila melanogaster.



Upon viral infection, virus-specific dsRNAs (eg., replication intermediates) are generated during the initial rounds of virus replication. Following cell death or lysis, dsRNAs are taken up and processed by uninfected cells to protect them from subsequent infection, thereby preventing virus spread.

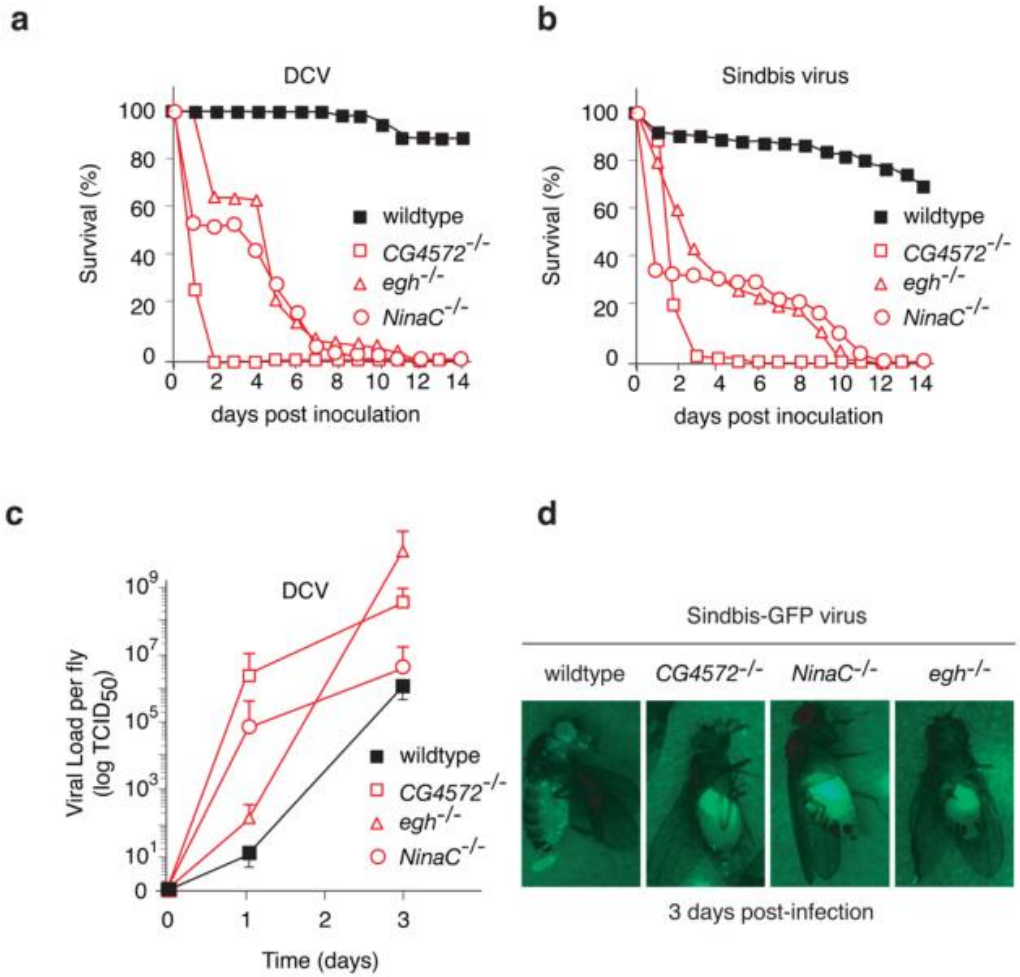
(Maria-Carla Saleh, Michel Tassetto et.al.*Nature*. 2009)

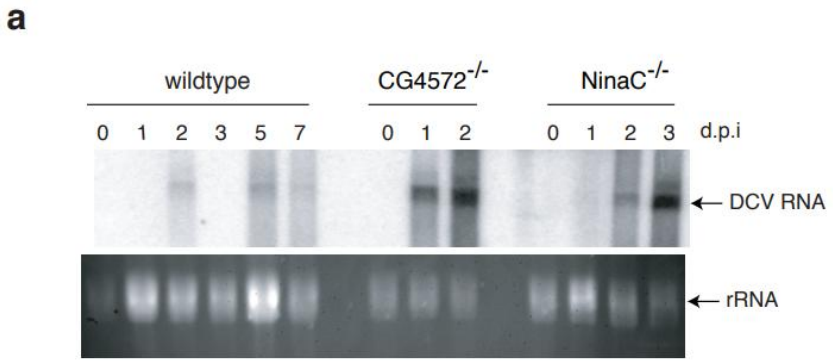
In vivo dsRNA immunization provides sequence-specific antiviral protection in D. melanogaster.



- Inoculation of dsRNA initiates a bona-fide, specific RNAi response that protects flies against virus infection.
- The efficiency and persistence of the dsRNA mediated antiviral immunity in Drosophila, and supports the idea that exogenous dsRNA can initiate an RNA silencing response in flies.

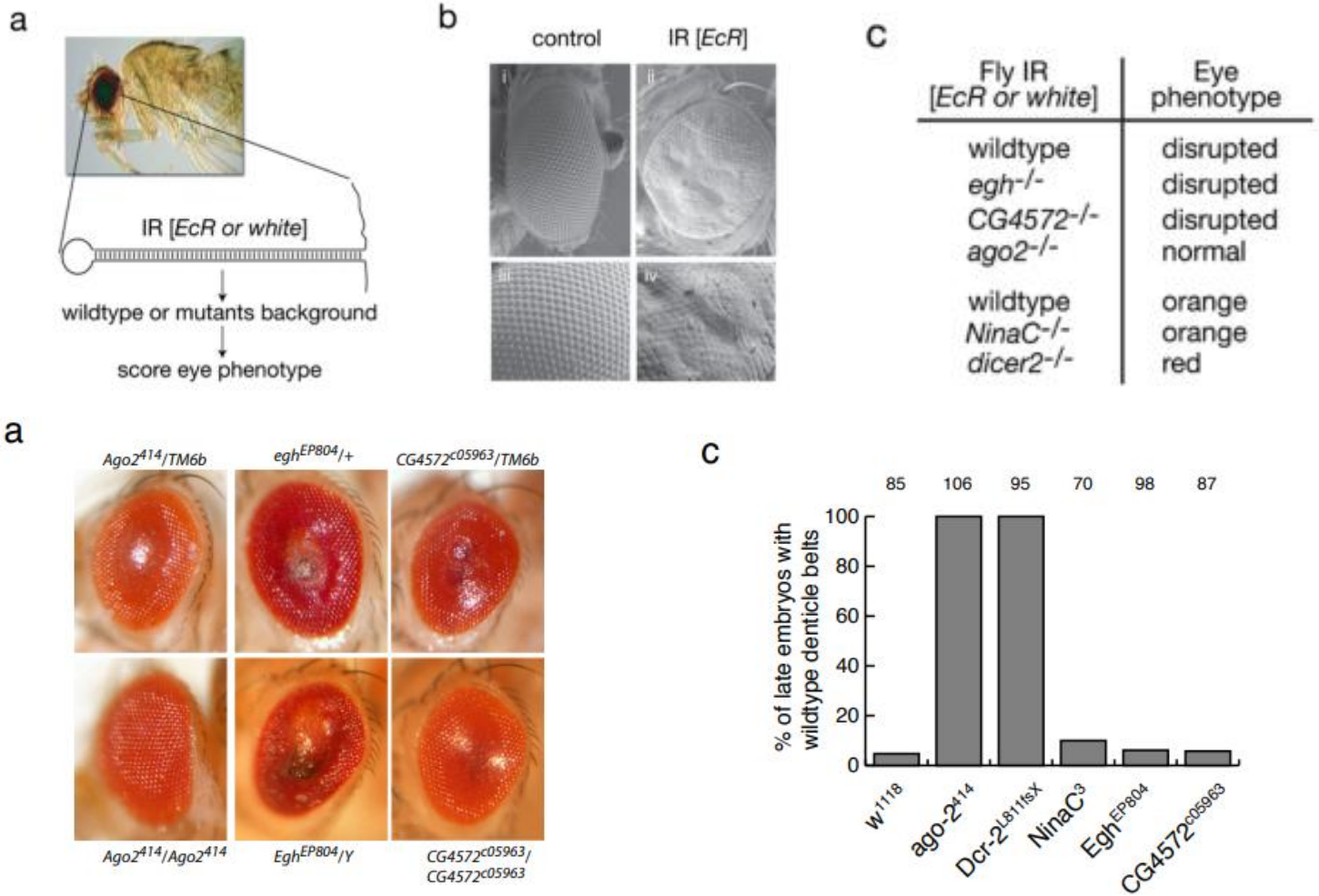
Increased viral susceptibility of dsRNA uptake deficient mutants.





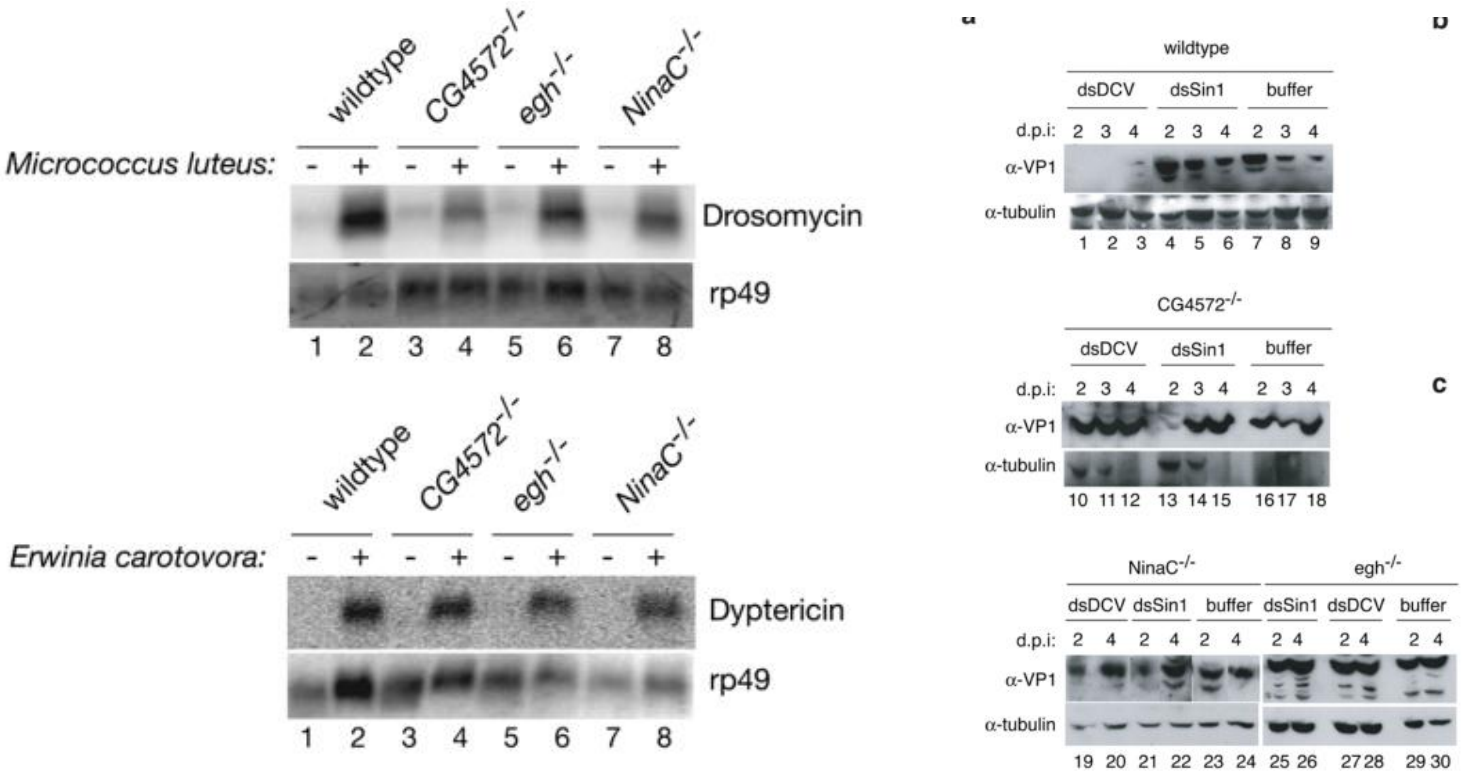
The enhanced viral susceptibility of egh, NinaC and CG4572 mutant flies is due to their inability to control virus replication.

Core RNAi machinery and antibacterial immunity are intact in dsRNA uptake mutants.



Mutant flies support efficient RNAi silencing if dsRNA uptake is bypassed through expression of dsRNA hairpins intracellularly or by injecting dsRNA into syncytial embryos.

Systemic spread of dsRNA follows virus infection and it is essential for effective antiviral immunity



- Defects in cellular components that abrogate dsRNA uptake and its ensuing antiviral immunity do not generally impair other arms of the fly innate immune system.
- Infected cells released viral dsRNA that is subsequently taken up by uninfected cells through the dsRNA uptake pathway thereby eliciting an antiviral RNAi response.
- A virus specific derived RNAi signal spread from the thorax to the head early after infection.

Summary:

- In Drosophila, systemic infections of bacteria and fungi trigger the synthesis of AMPs, mediated by NF-κB pathway **Toll** and **IMD**. The **Toll** pathway is primarily activated against gram-positive bacteria and fungi, while the **IMD** pathway, which is primarily directed at gram-negative bacteria, is activated. Activation of these two pathways relies on the recognition of microbial cell wall components or virulence factors by Drosophila pattern recognition receptors (PRRs), leading to nuclear translocations of NF-kB transcription factors leading to the expression of hundreds of genes .

- Autophagy goes through a series of defined stages that ultimately lead to the isolation and degradation of cytoplasmic components, a process that involves vesicles subsequently fusing with lysosomes to form autolysosomes, which undergo acidification to activate lysosomal enzymes, thereby degrading the engulfed contents.

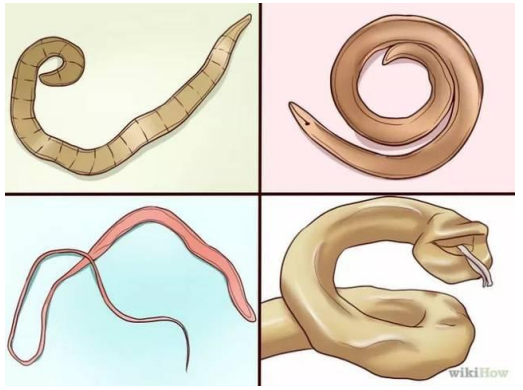
- Phagocytosis is a powerful way for fruit flies to clear apoptotic bodies or bacterial infections. This complex cellular process begins with the identification of particles to be ingested, followed by cytoskeletal remodeling and signaling events leading to the engulfment and destruction of particles.
- RNA interference (RNAi) is the main defense mechanism of fruit flies against viruses and mobile genetic elements. This pathway relies on the perception of double-stranded RNA (dsRNA) from external or endogenous sources.
- The melanization reaction involves the rapid synthesis of melanin at the site of infection or injury to contain microbial pathogens and promote wound healing. A key enzyme in melanin biosynthesis is phenol oxidase (PO), which catalyzes the oxidation of phenolic compounds to hydroquinone and subsequent polymerization into melanin. PO is normally synthesized as an inactive proenzyme (PPO), which is activated by the proteolytic cascade to produce active PO.

Host-parasitoid interactions in Drosophila

邢丽敏

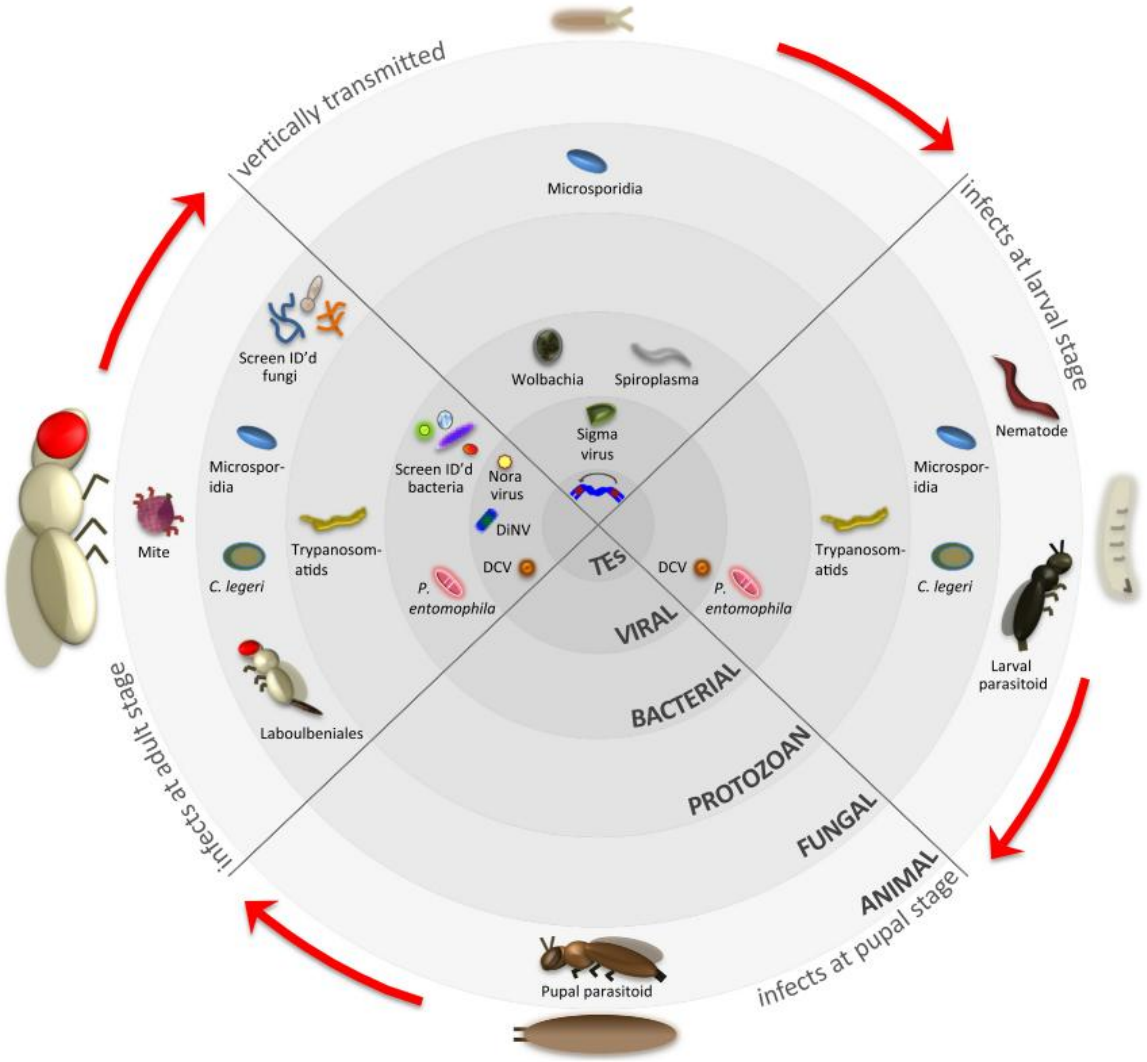
2022-12-31

Parasitic manifestations are prevalent in living organisms



What are the typical parasites that fruit flies are related to?

Insights from natural host–parasite interactions: The *Drosophila* model

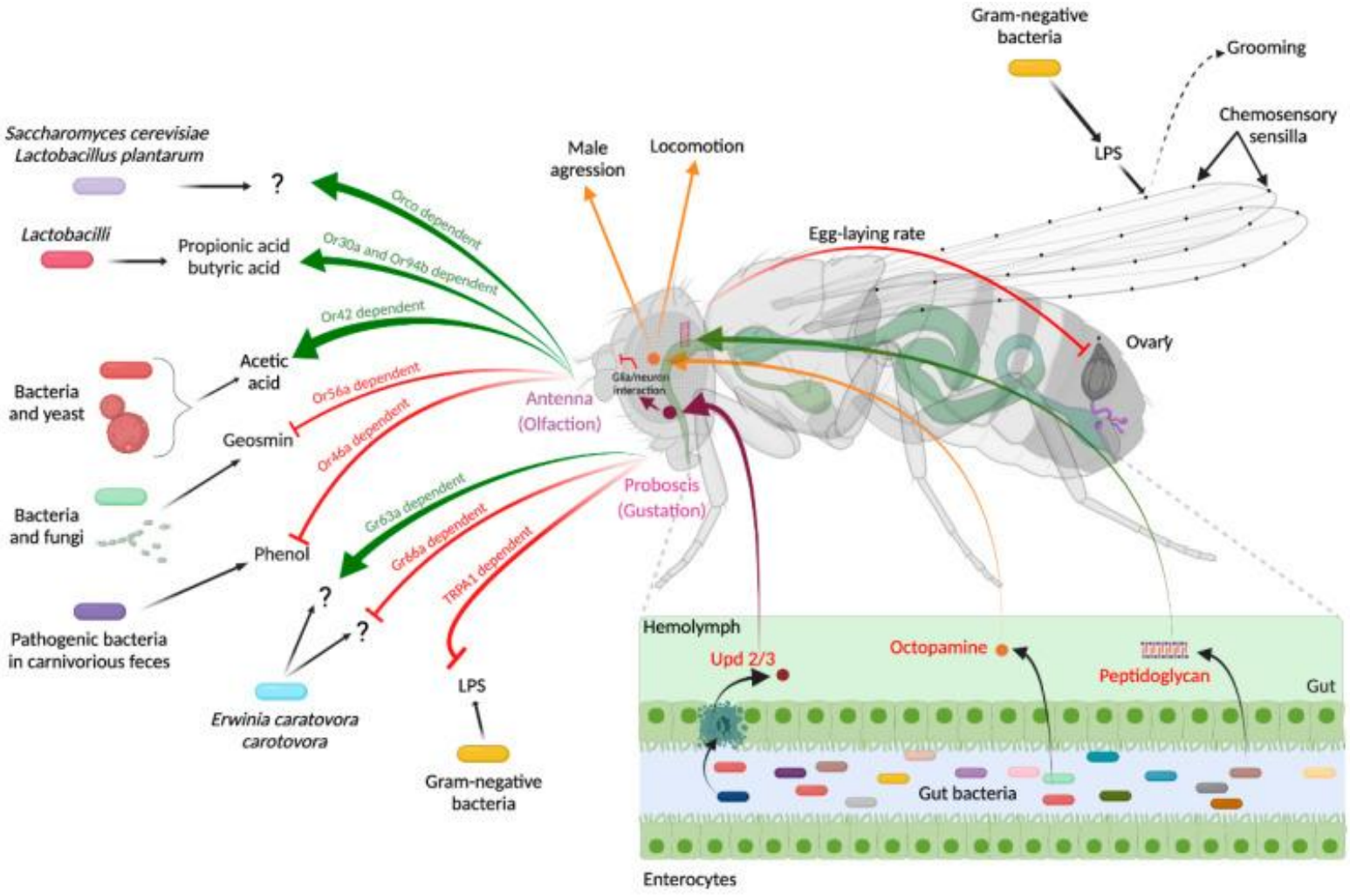


the **only** other natural *Drosophila*-parasite interactions studied at the genetic level are fruit fly interactions with **endo-parasitoid wasps** that lay eggs in fly larvae.

Keebaugh, E. S. & Schlenke, T. A. *Dev Comp Immunol.* 2014.

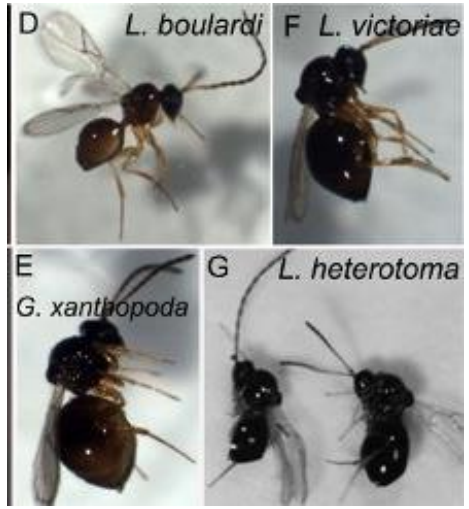
How Are Bacteria Sensed by the Nervous System?

Mechanisms of interactions between microbes and the *Drosophila* nervous system



Montanari, M. & Royet, J. *Cells.* 2021

Some typical parasitic wasp species:
L. boulardi* and *L. heterotoma is particularly well studied
低毒力：*L. boulardi*
高毒力：*L. heterotoma*



- What are the interactions between a parasitic wasp and its host?
- Defense-protection mechanisms in fruit flies and parasites?

From the parasitic wasp

Two main factors in finding hosts: food - pheromones

Journal of Chemical Ecology, Vol. 10, No. 5, 1984

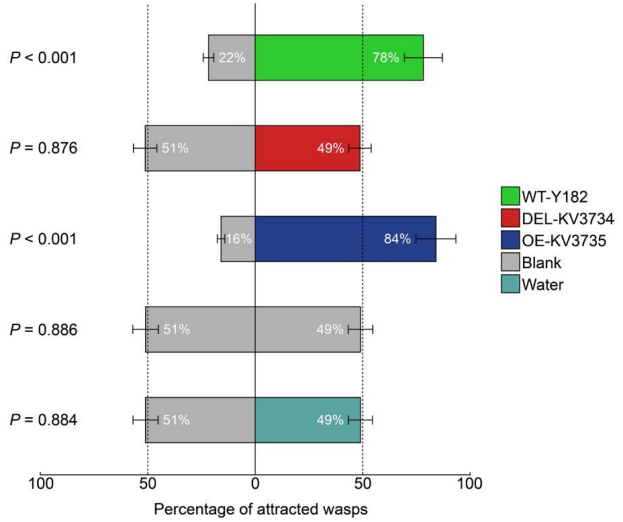
CHEMICAL STIMULI IN HOST-HABITAT LOCATION BY *Leptopilina heterotoma* (Thomson) (Hymenoptera: Eucoilidae), A PARASITE OF *Drosophila*

M. DICKE,[1] J.C. VAN LENTEREN,[1]
G.J.F. BOSKAMP, and E. VAN DONGEN-VAN LEEUWEN

Department of Ecology
University of Leiden
The Netherlands

(Received May 18, 1983; revised August 4, 1983)

Ethanol, ethyl acetate, and acetaldehyde, all metabolic products of baker's yeast



Đurović, G. *et al. Journal of Chemical Ecology.* 2021

Oecologia (1993) 93:145–148

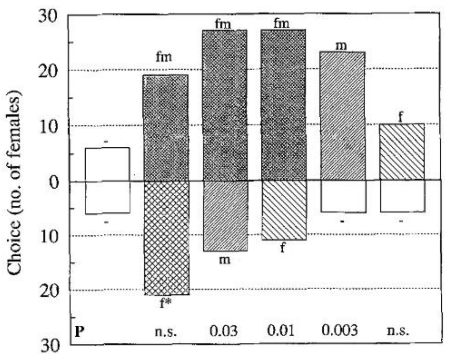
Oecologia

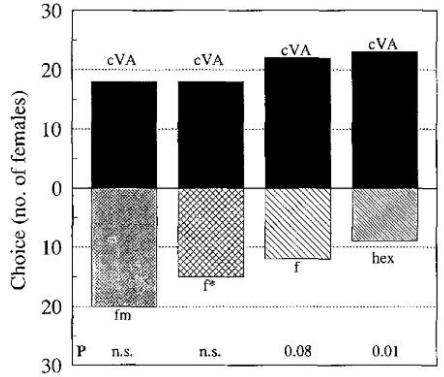
Larval parasitoid uses aggregation pheromone of adult hosts in foraging behaviour: a solution to the reliability-detectability problem

J.S.C. Wiskerke, M. Dicke, L.E.M. Vet

Department of Entomology, Wageningen Agricultural University, P.O. Box 8031, 6700 EH Wageningen, The Netherlands

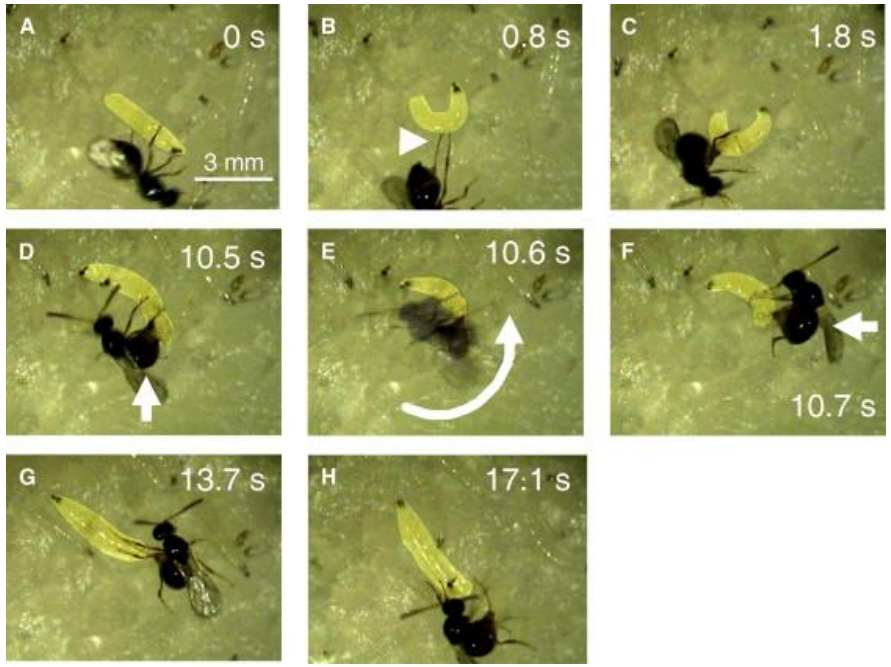
Received: 15 June 1992 / Accepted: 21 August 1992





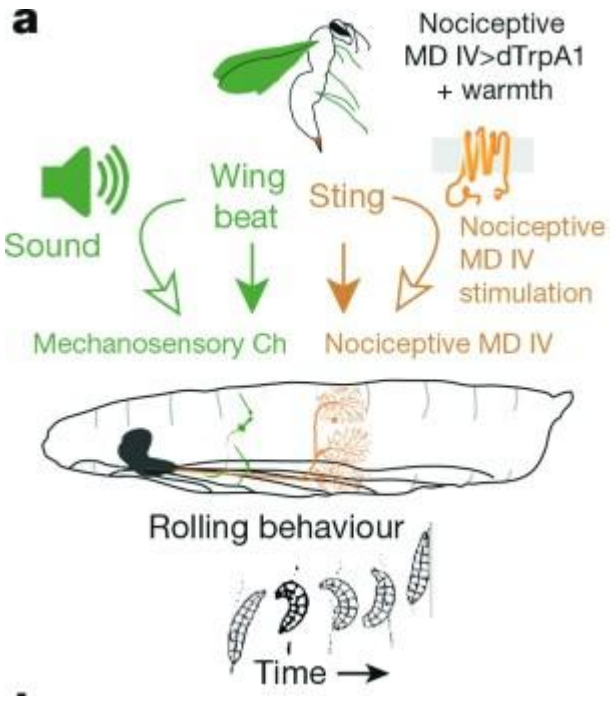
From the fruit flies

Larvae exhibit escape behavior when infected by parasitic wasps



md class IV neurons

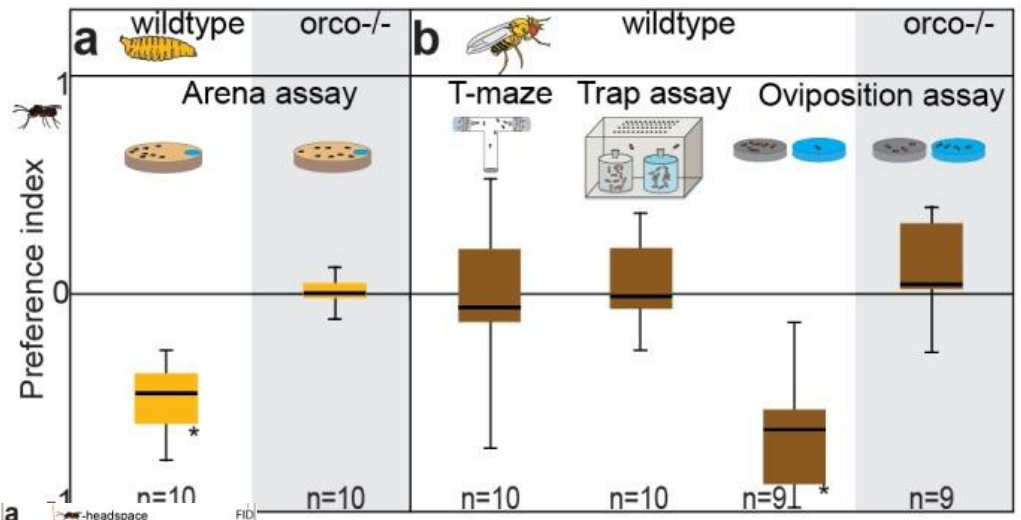
Hwang RY, et al,. *Curr Biol.* 2007

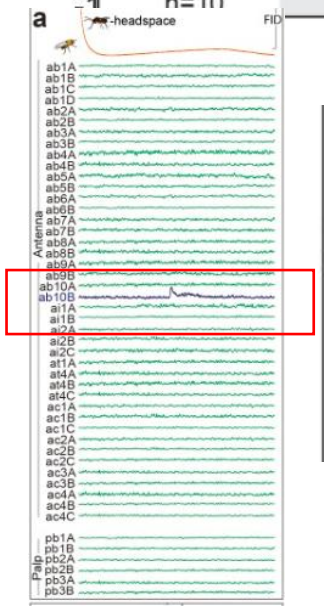


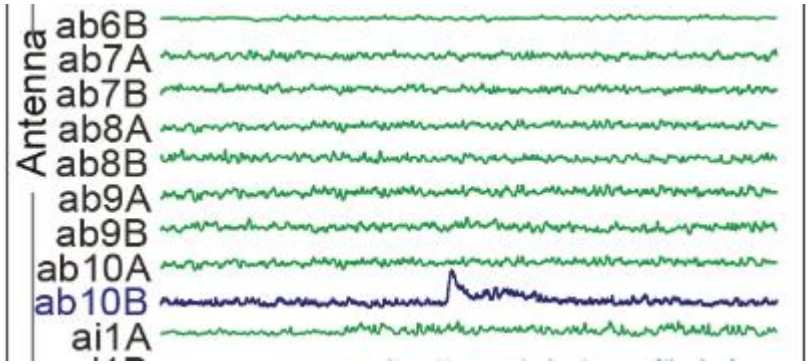
Ohyama, T. *et al. Nature* 2015

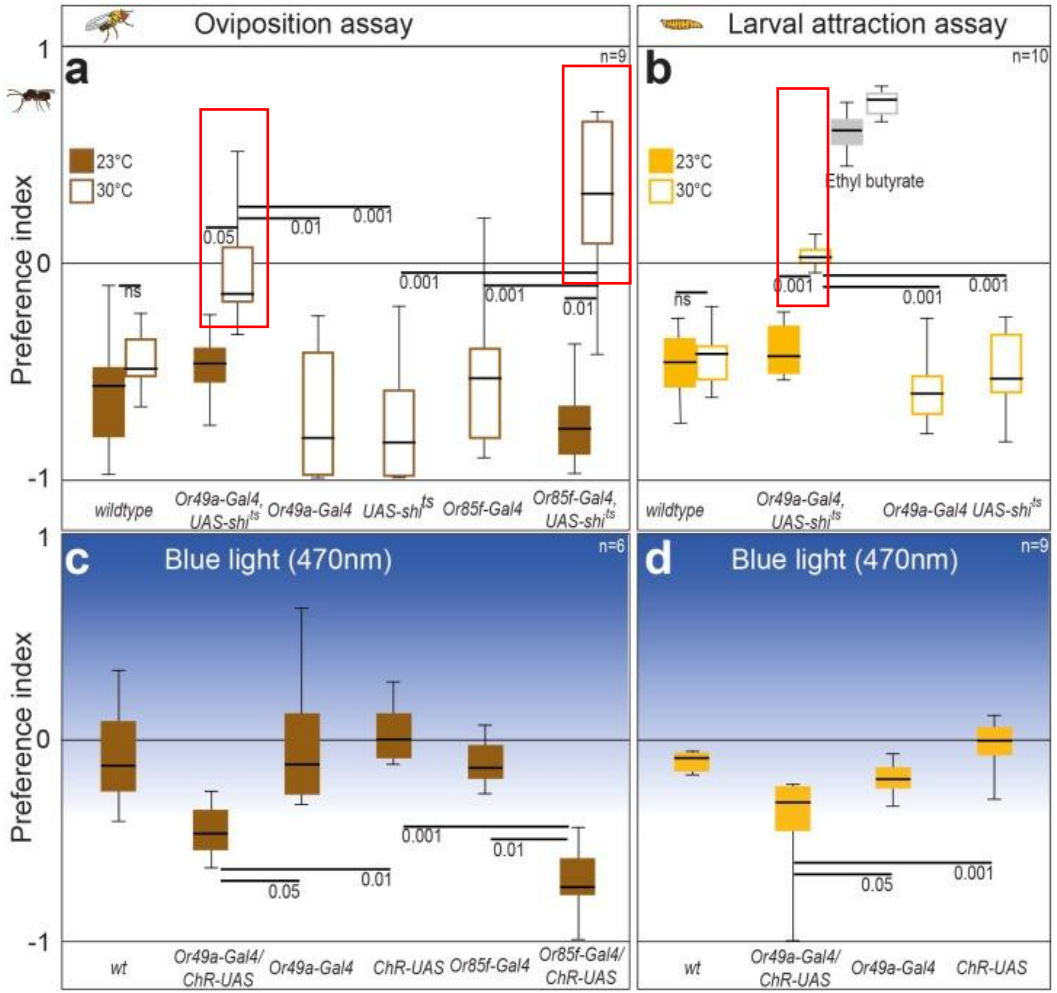
From the fruit flies

Drosophila avoids parasitoids by sensing their semio-chemicals via or49a and or85f





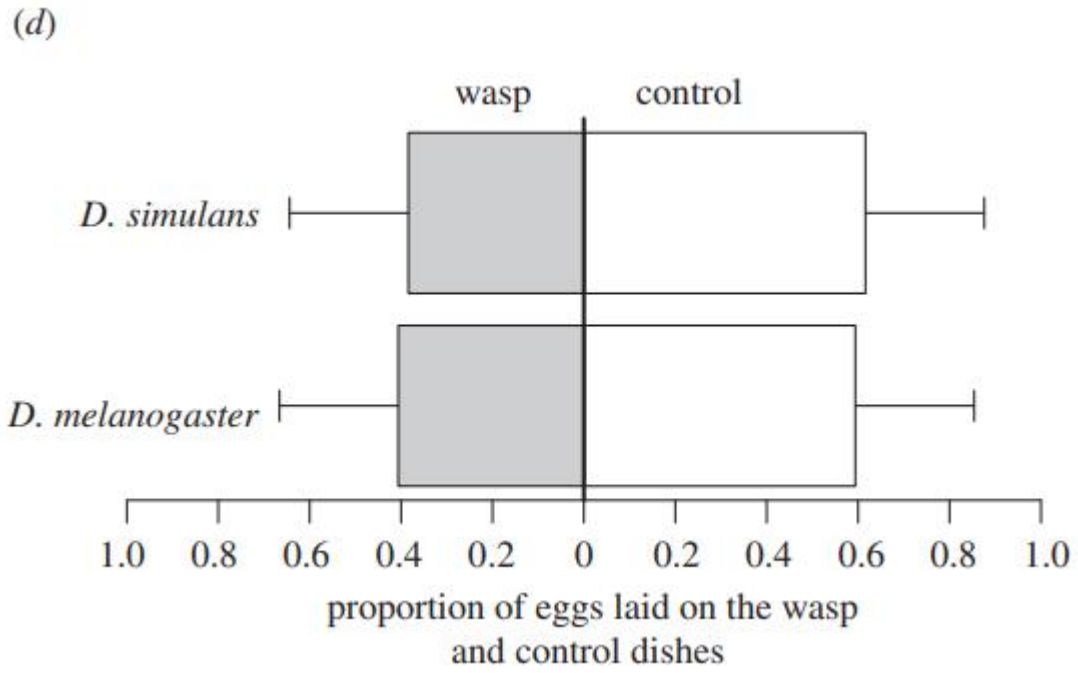


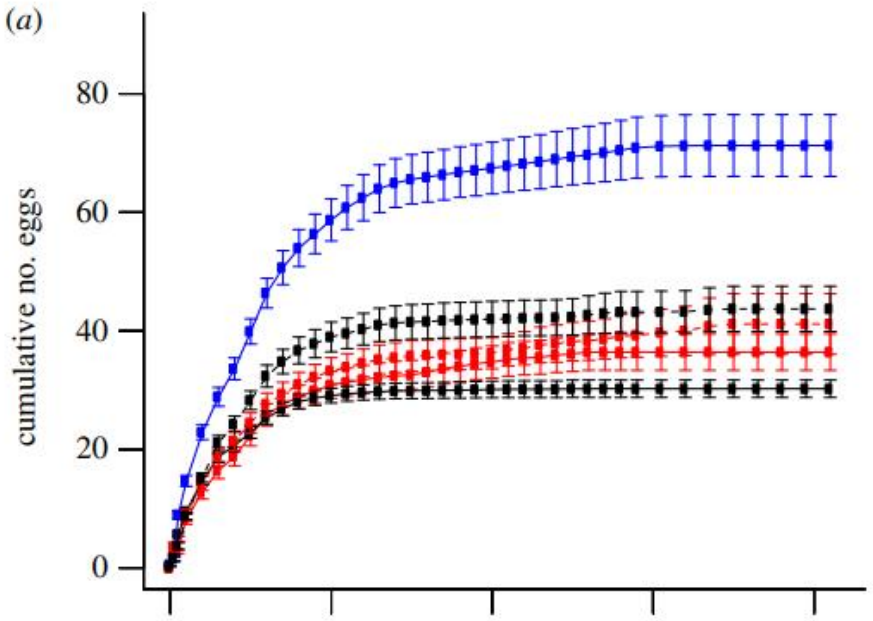


Ebrahim, S. A. M. *et al.*. *PLoS Biol*. 2015

From the fruit flies

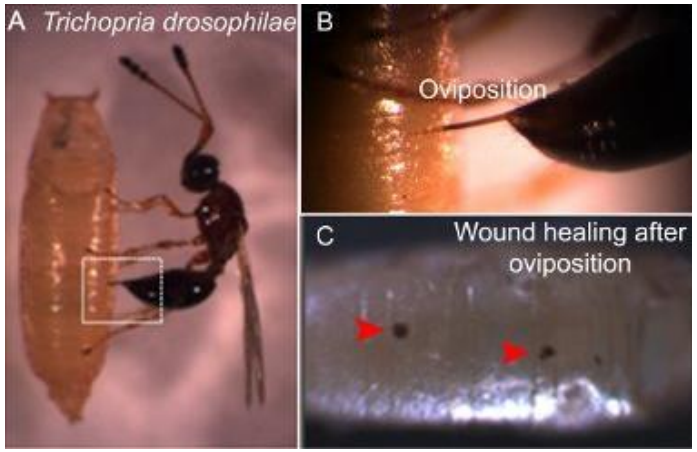
Wasps reduce the number of eggs laid by females

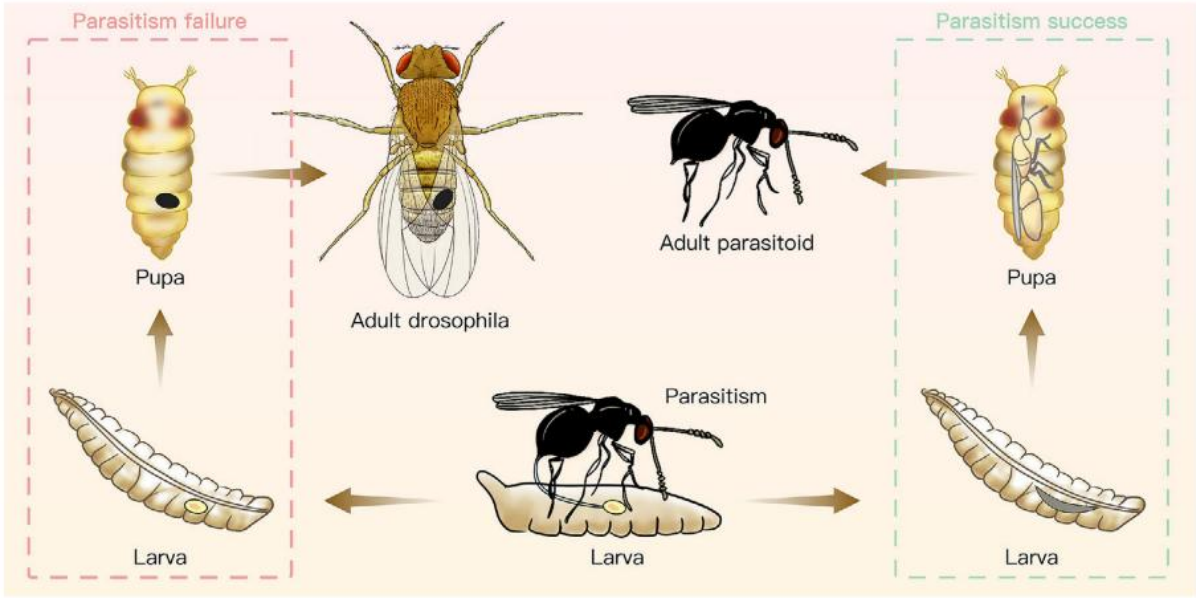


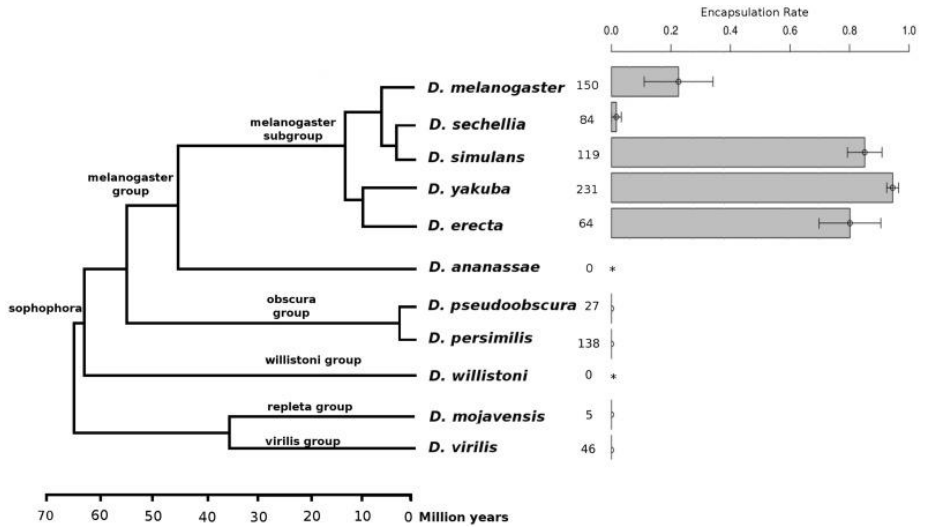


T. Lefe`vre et al., Biol. Lett. 2012

Two outcomes of parasitic wasps infecting larvae





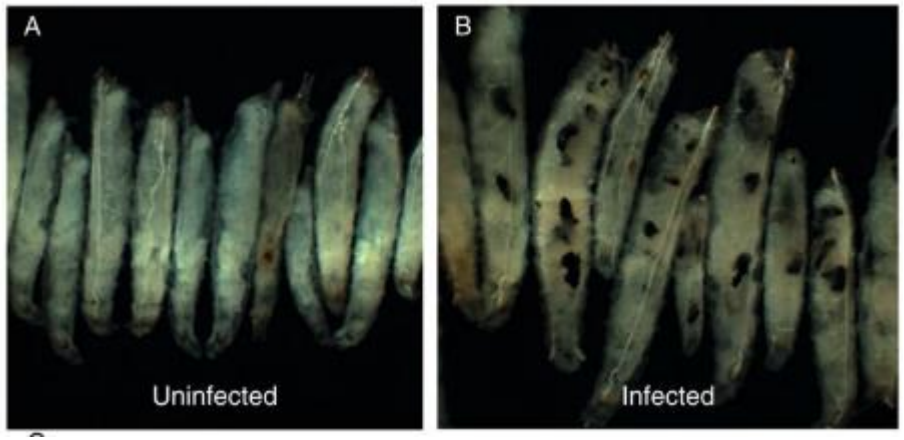


Lei Yang., et al. *Insect Science*. 2021

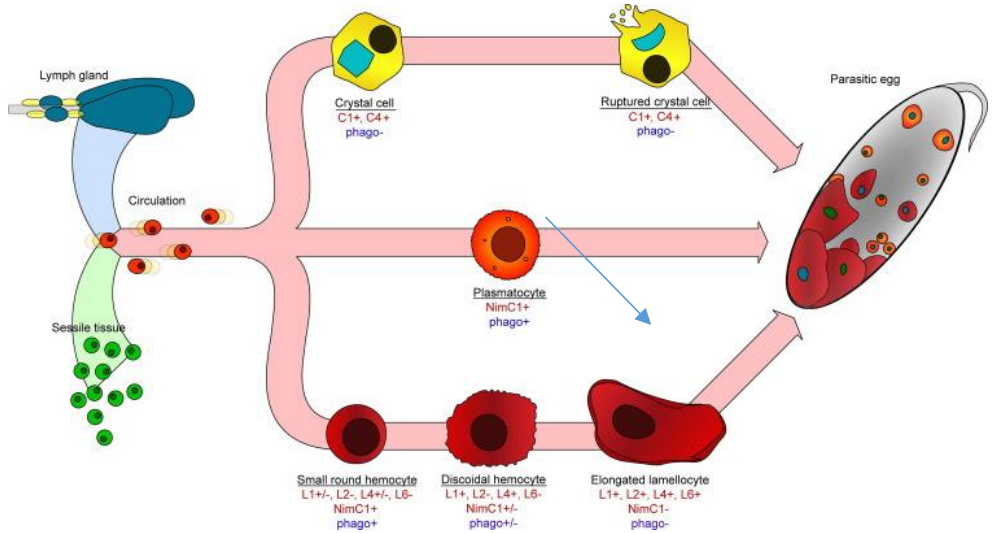
Successful encapsulation involves activation of immune cells within the hemolymph and lymph gland（LG淋巴结）

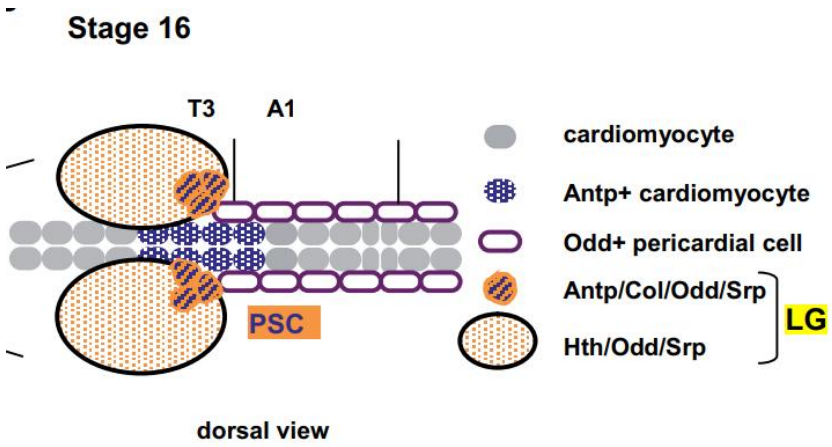
one avirulent strain L. boulardi

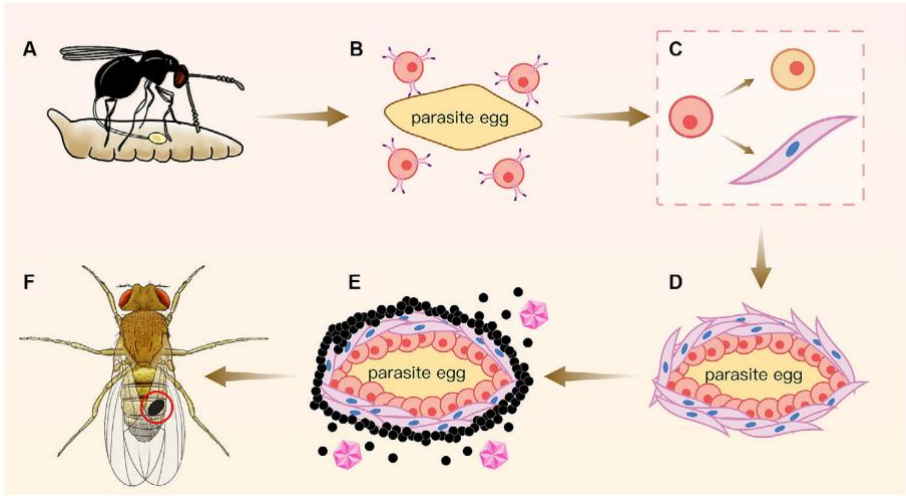
The encapsulation reaction



Lee et al. Adv Parasitol. 2012

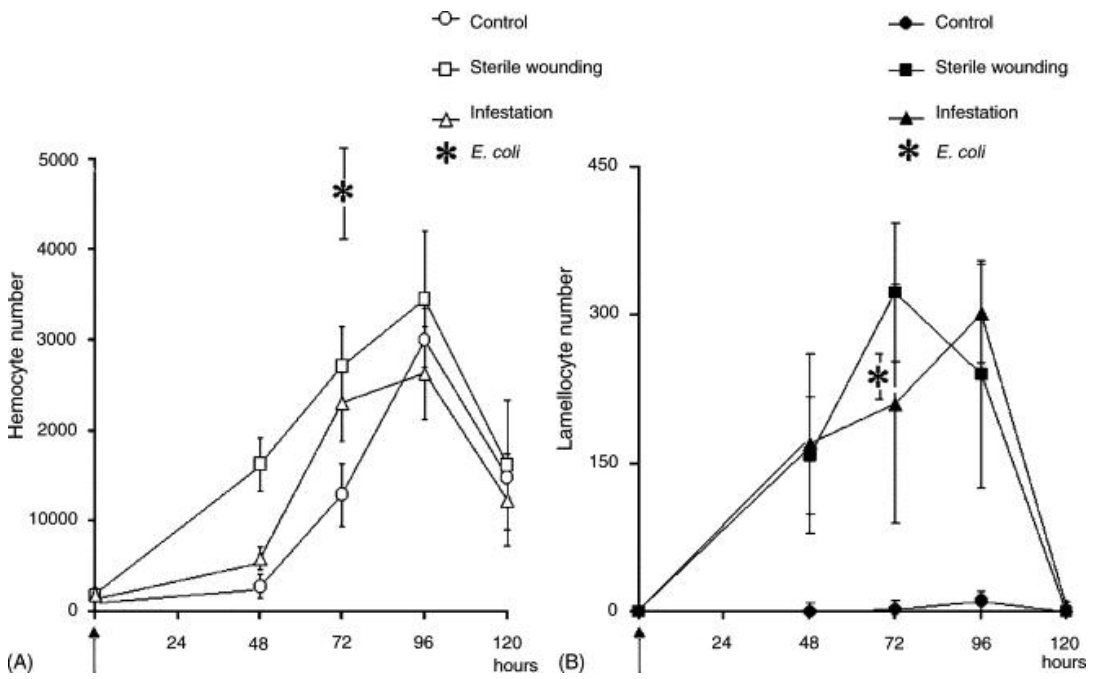


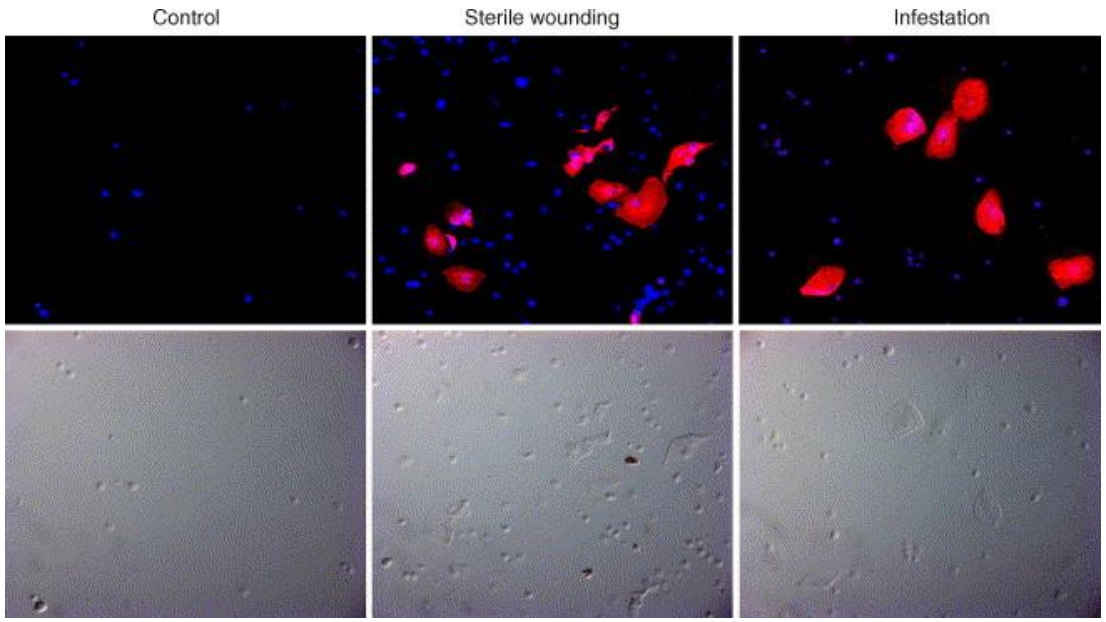




Lei Yang., et al. Insect Science. 2021

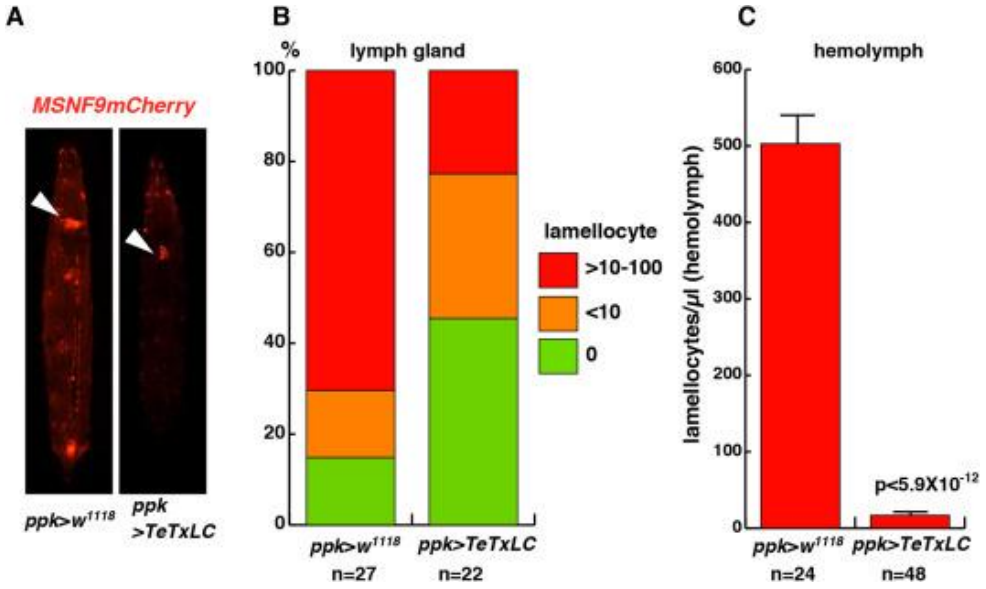
Sterile wounding is a minimal and sufficient trigger for a cellular immune response in *Drosophila melanogaster*

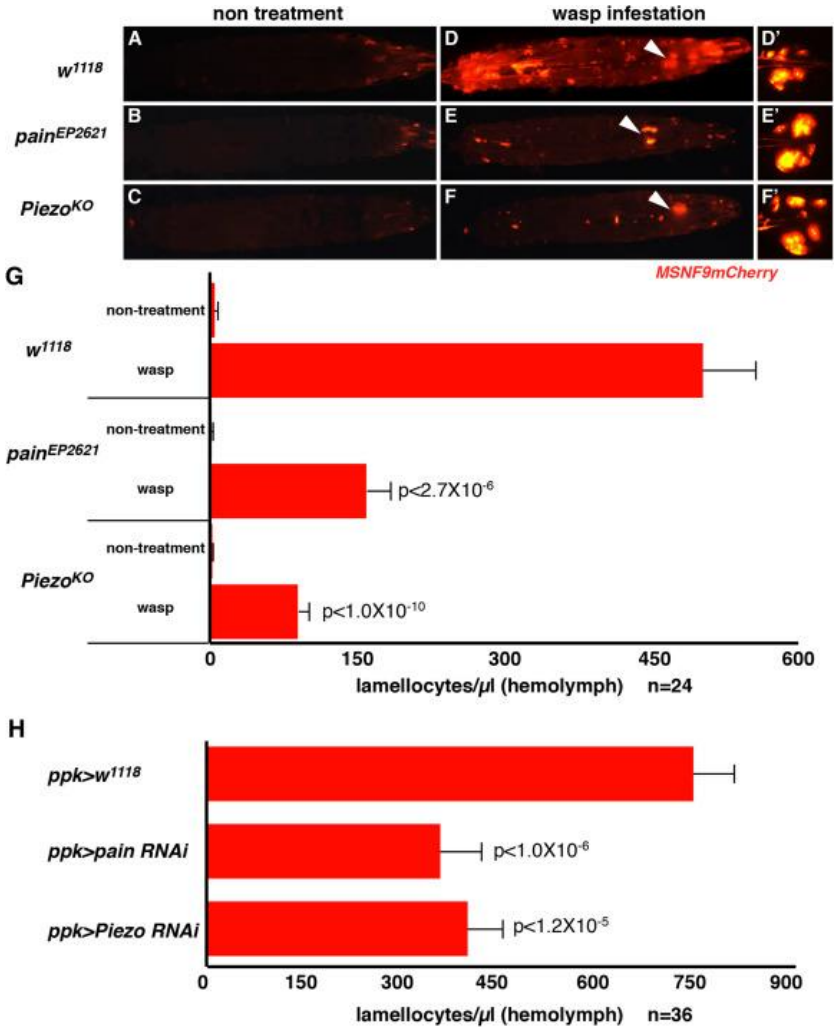




Markus, R., et al. *Immunol Lett* .2005

The nociception genes painless and Piezo are required for the cellular immune response of *Drosophila* larvae to wasp parasitization

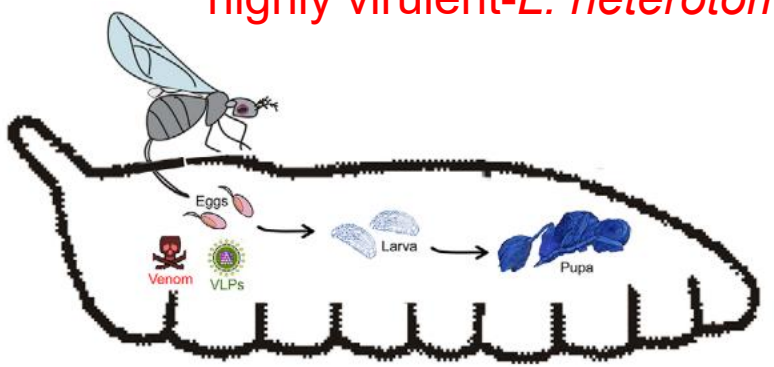




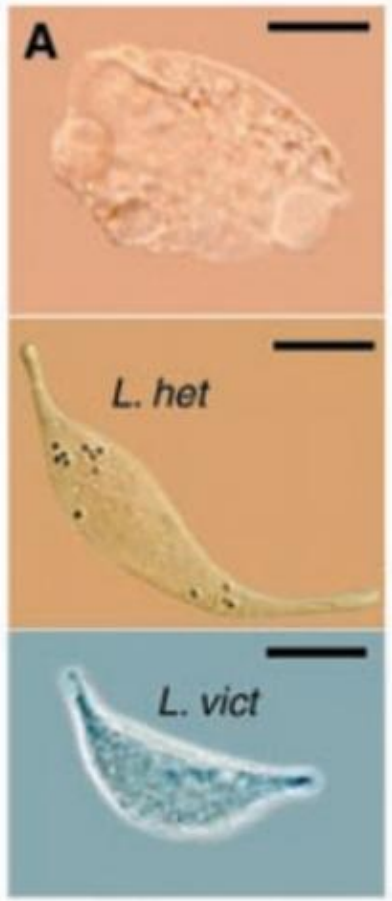
Tokusumi, Y., et al.,*Biochemical and Biophysical Research Communications.* ***2017***

Successful parasitism: by destroy lamellocytes and specifically deleting a significant proportion of hematopoietic precursors

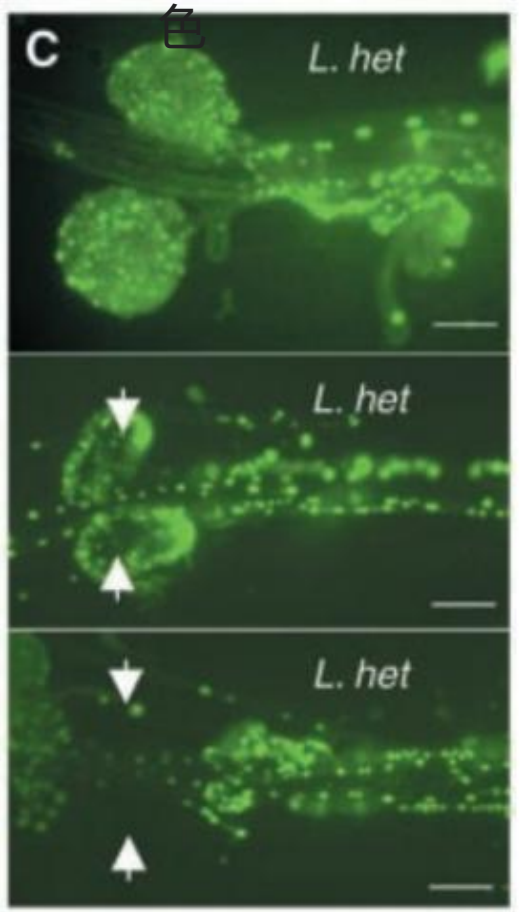
highly virulent-*L. heterotoma*



Live parasitoid



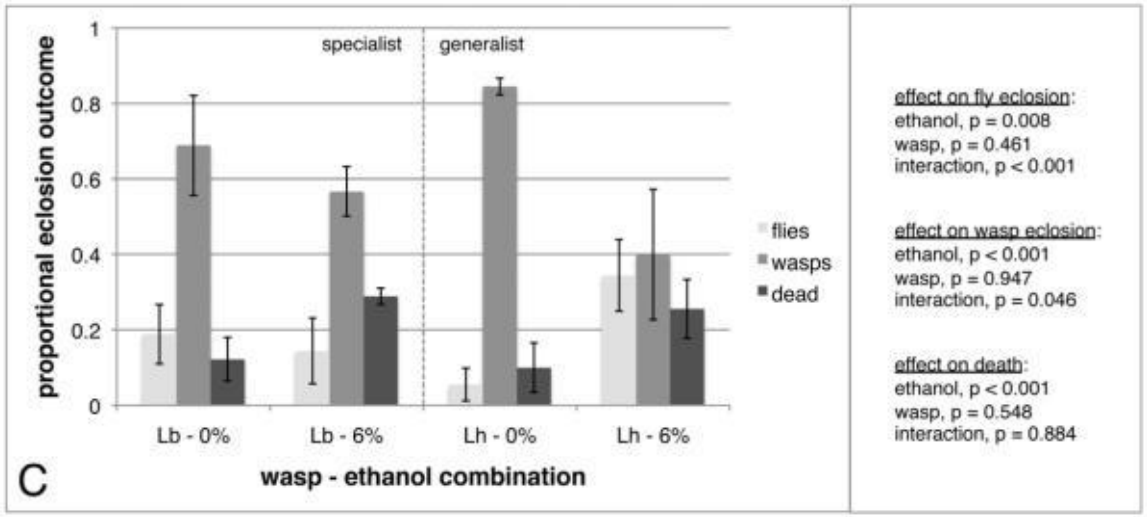
TUNEL染色

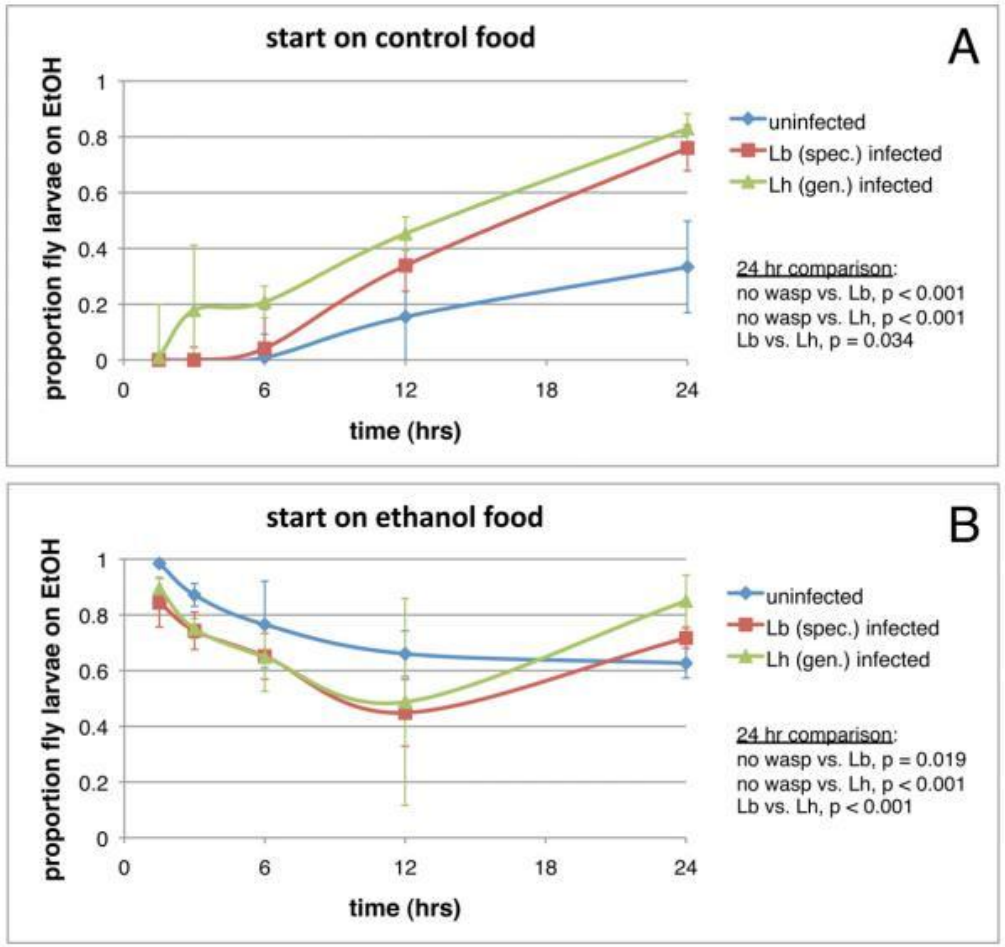


Lei Yang., et al. Insect Science. 2021 A. Nappi, . et al., Advances in Parasitology., 2009 Chiu, H. & Govind, S. *Cell Death & Differentiation* 2002

Behavioral Immunity toward Parasitoid Wasps

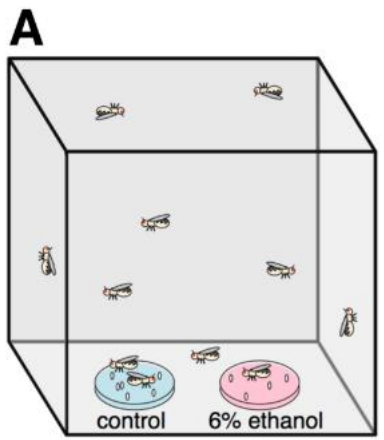
Consumption of ethanol by *D. melanogaster* can protect them and also kills internal wasp parasites

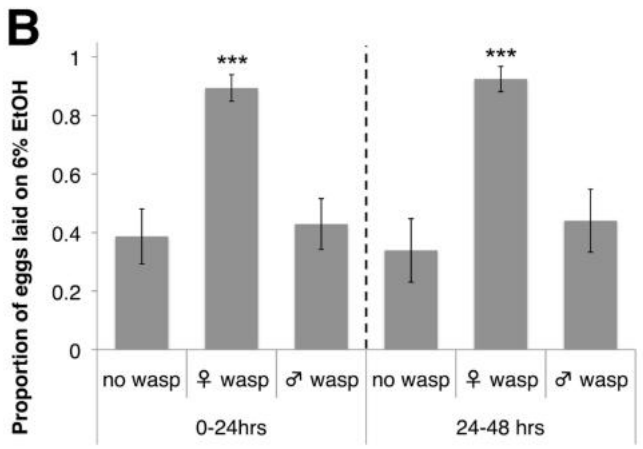


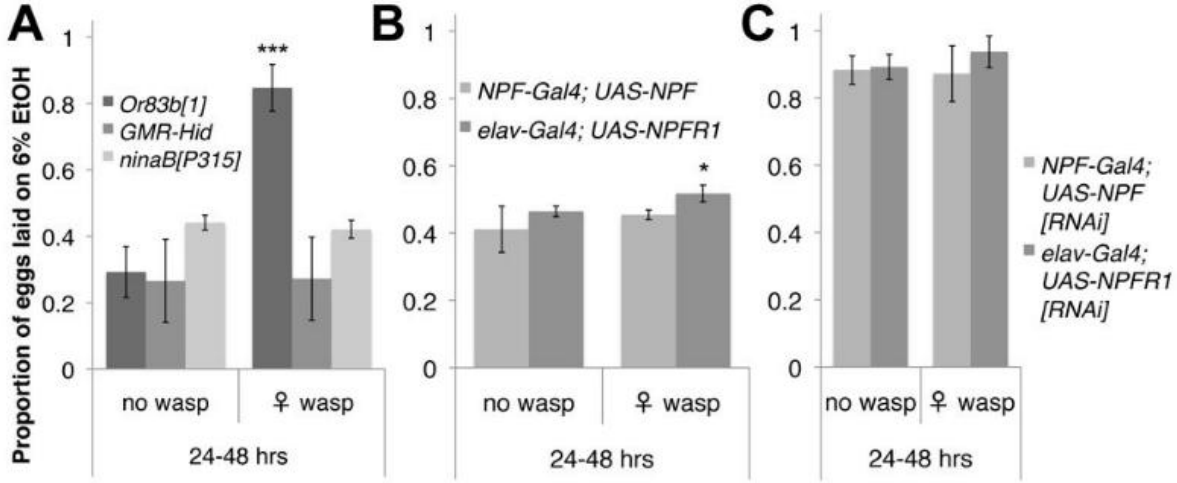


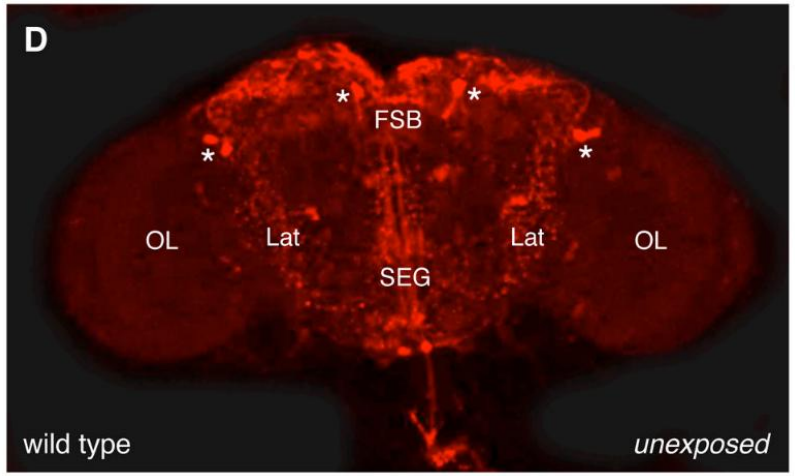
Milan NF, et al. Curr Biol. 2012

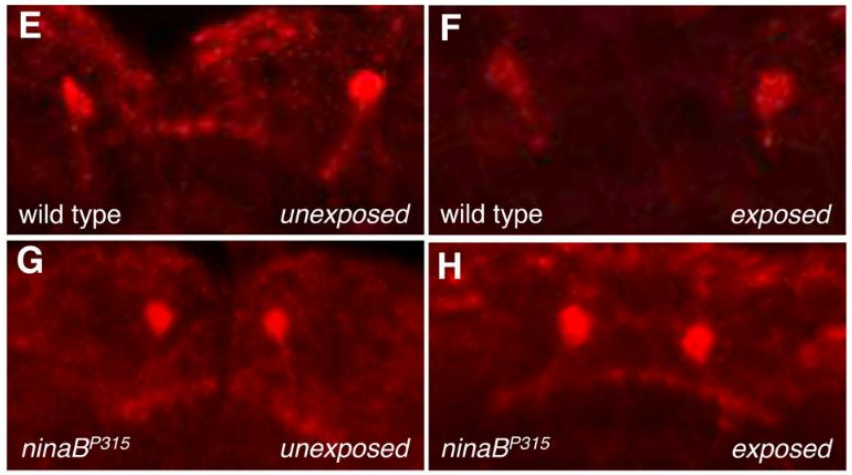
D. melanogaster medicates offspring with alcohol after exposure to wasps, with participation of vision and NPF





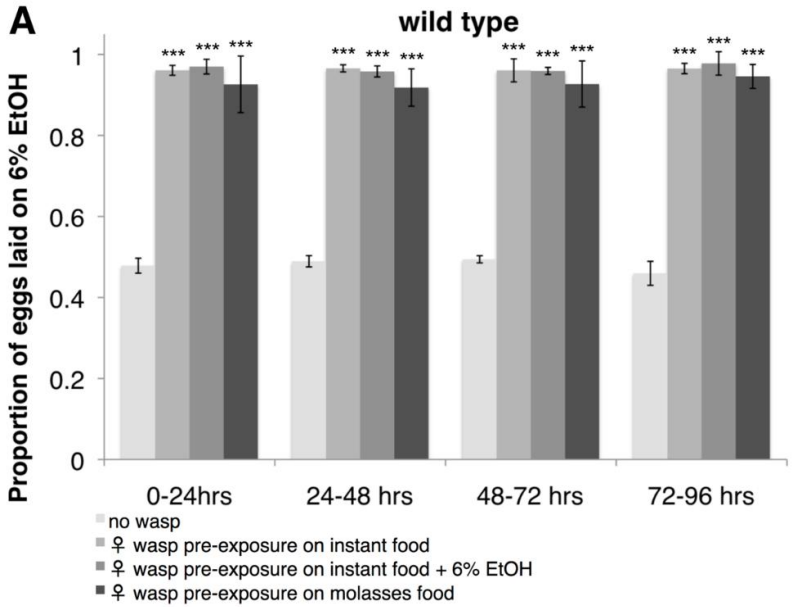






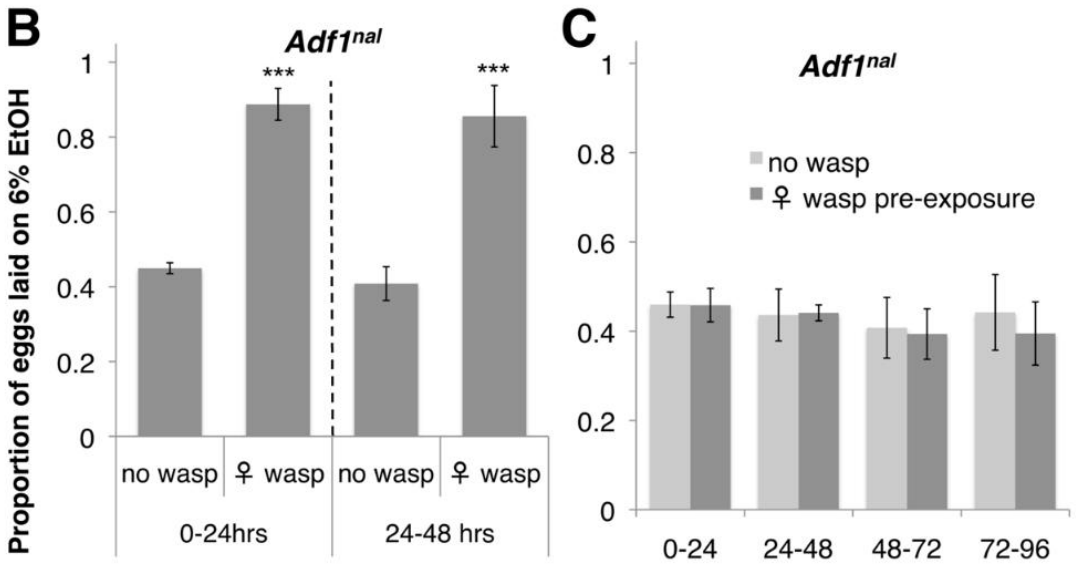
Kacsoh et al. *Science.* 2013

Flies form long-term memories of seeing wasps



in the presence of wasps

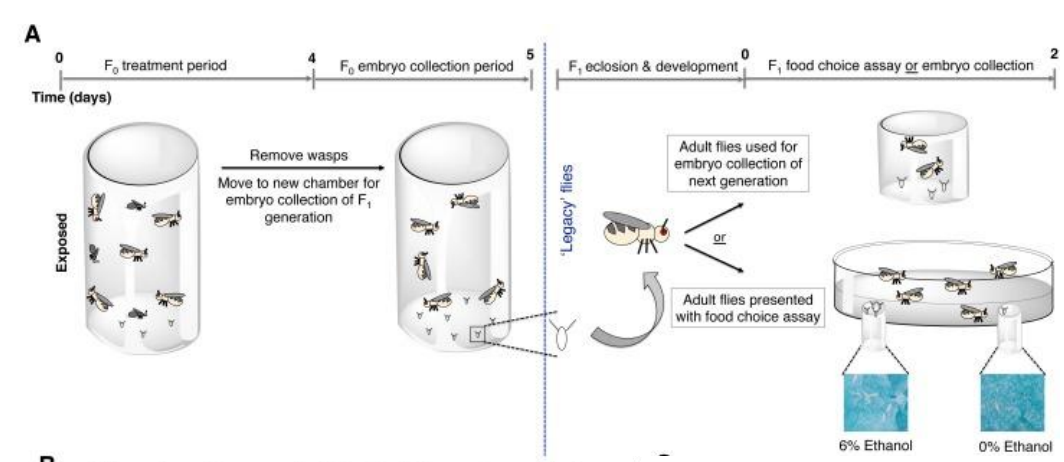
after wasp pre-exposure

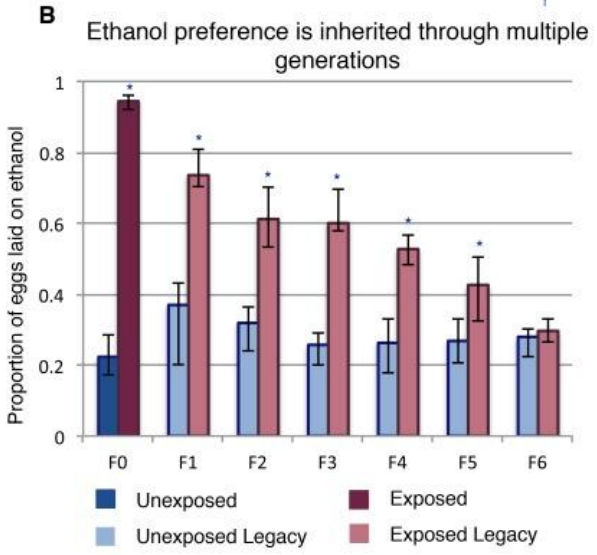


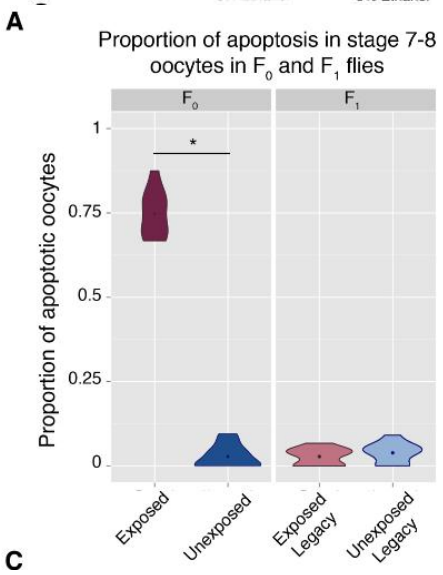
Adf1^{nal}, a mutant that has normal early memory but lacks long-term memory

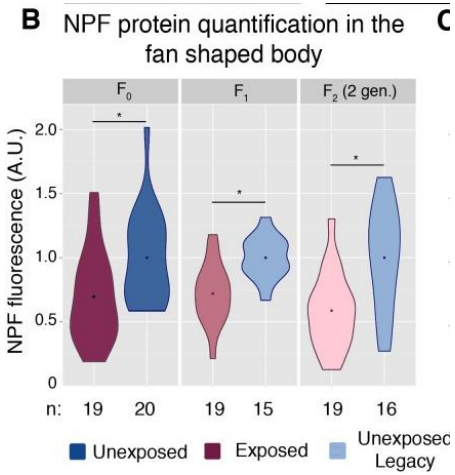
Kacsoh et al. *Science*. 2013

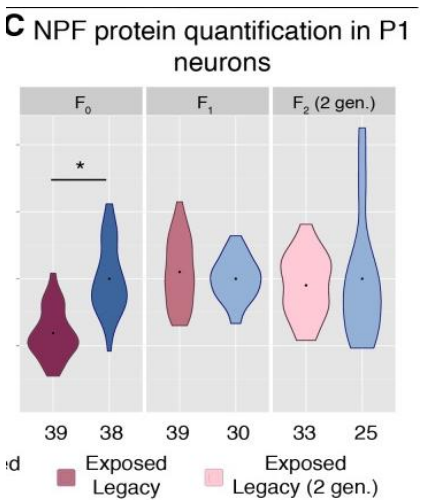
Genetic inheritance of ethanol preference is caused by maternal NPF inhibition

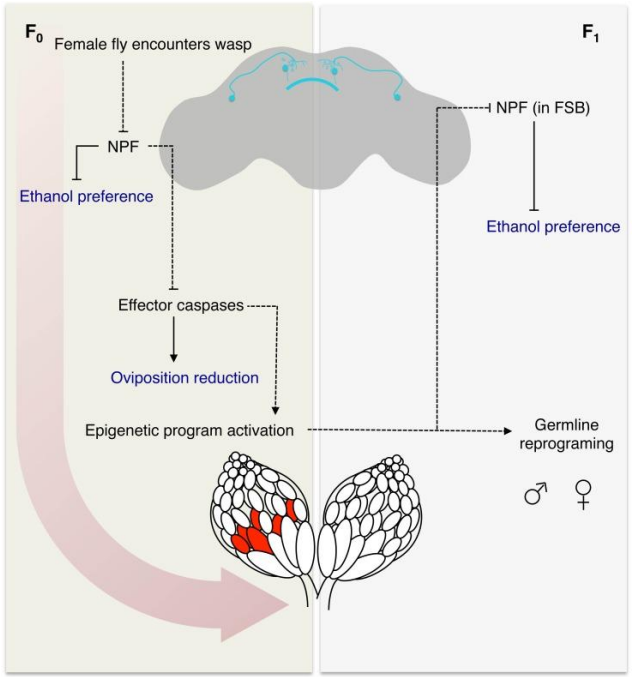






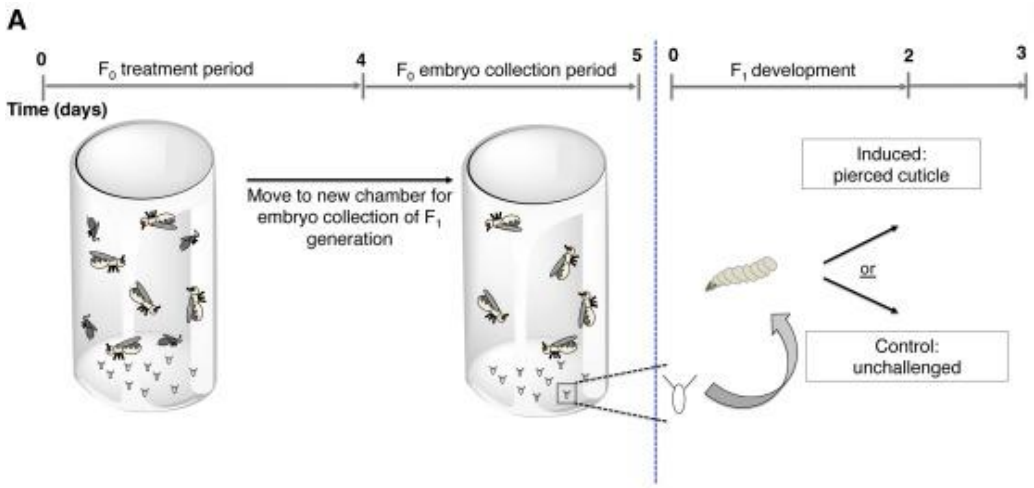


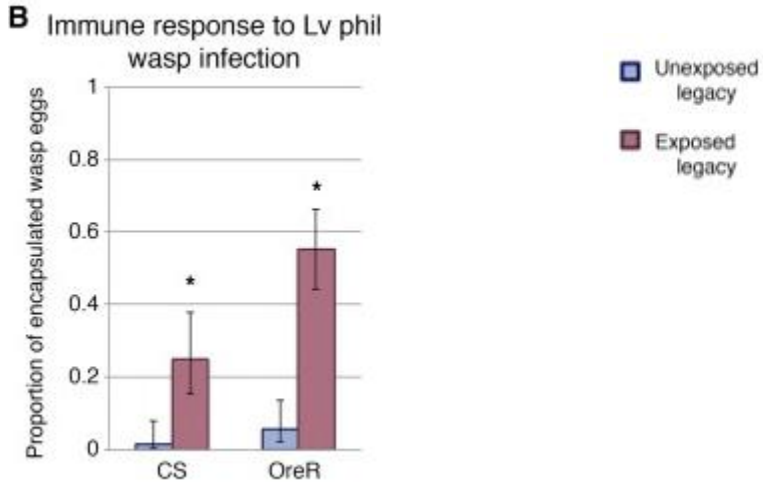


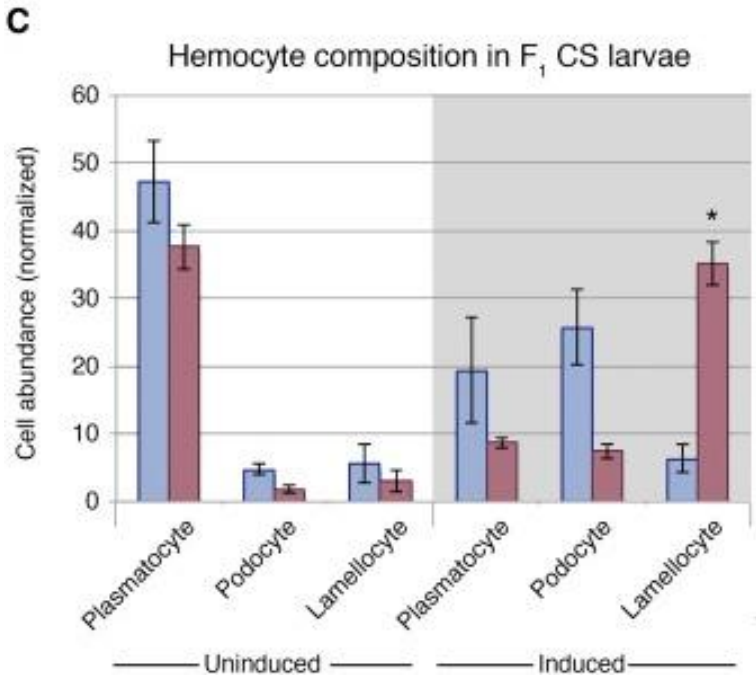


Bozler, J., et al., *eLife.,* 2019

Exposed legacy offspring have enhanced cellular response following immune induction

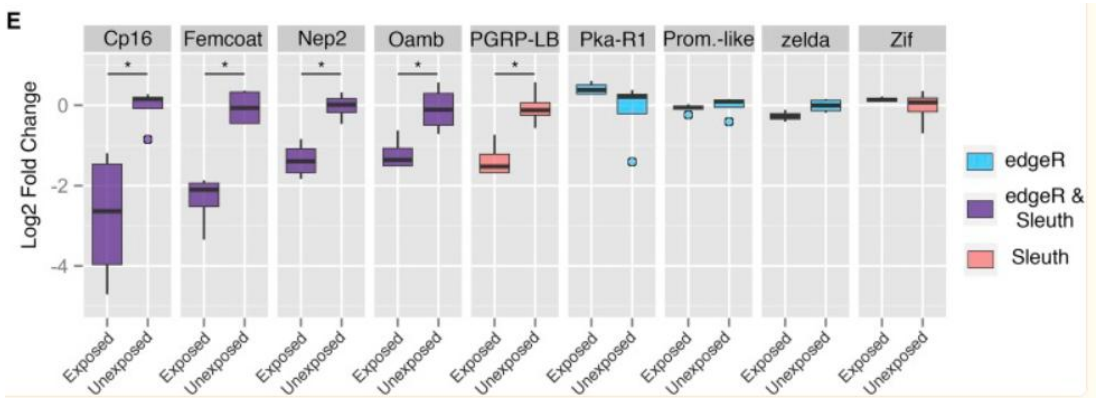




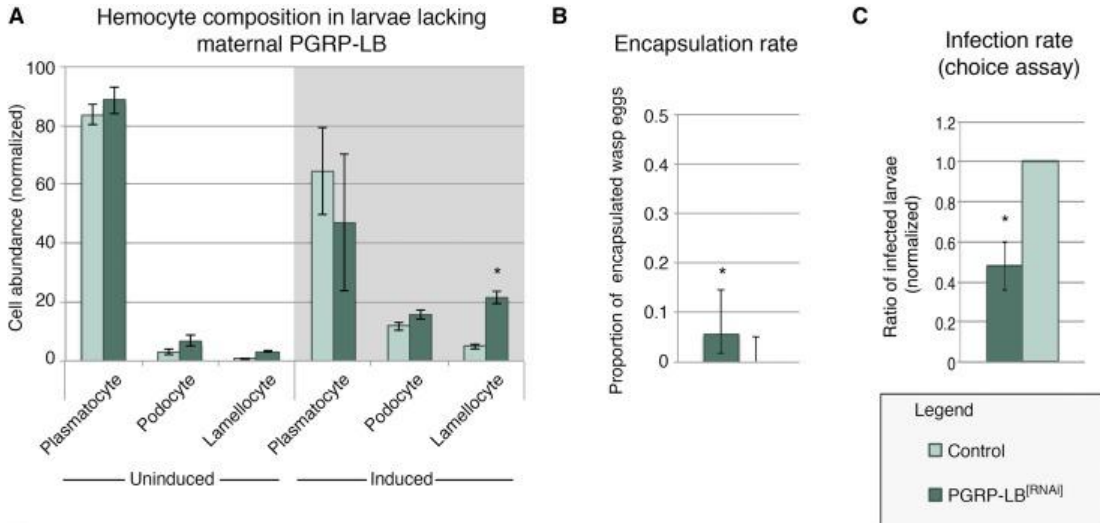


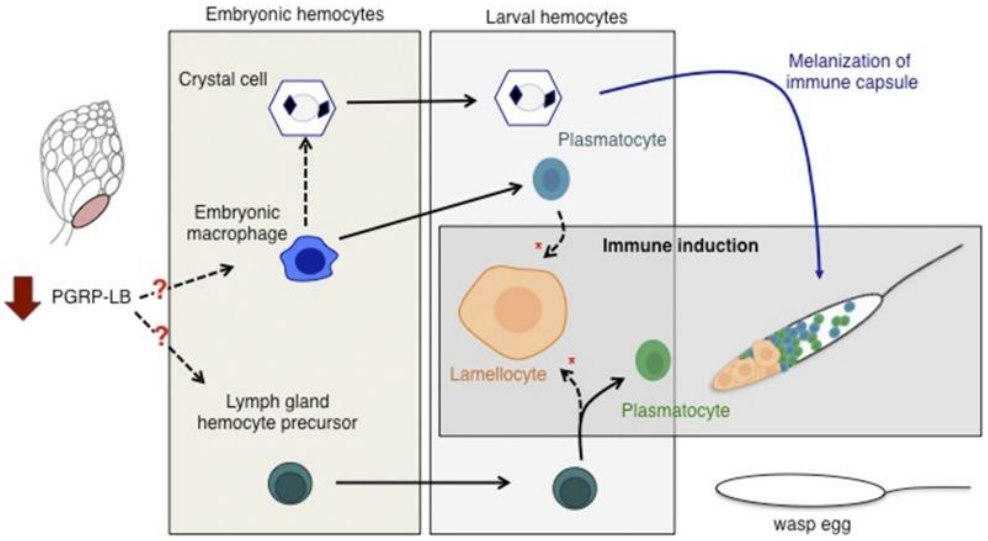
Bozler, J., et al., *G3.* 2020

Larvae lacking maternal *PGRP-LB* have enhanced cellular response following immune induction



Kallisto/Sleuth & CLC/edgeR pipeline：
两种RNA-seq分析方法

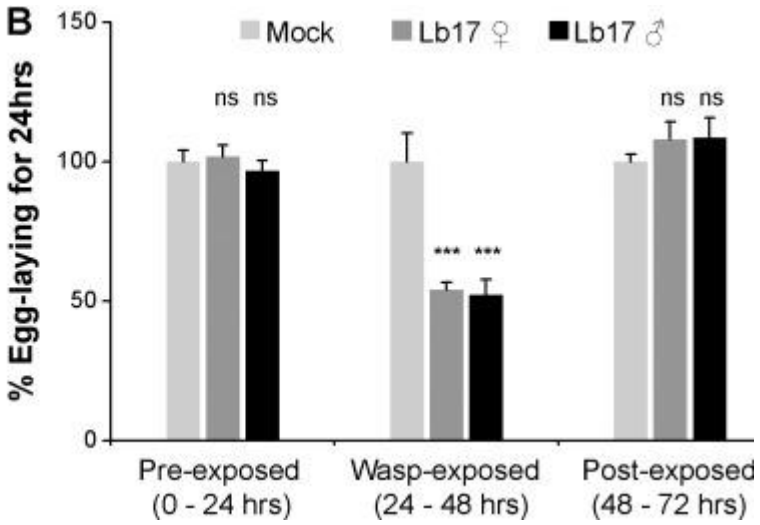


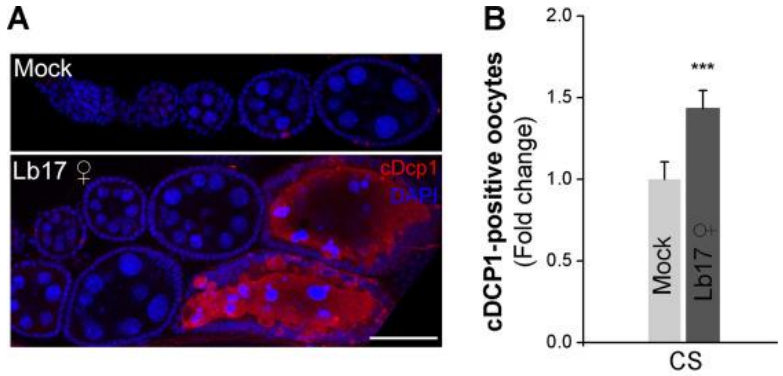


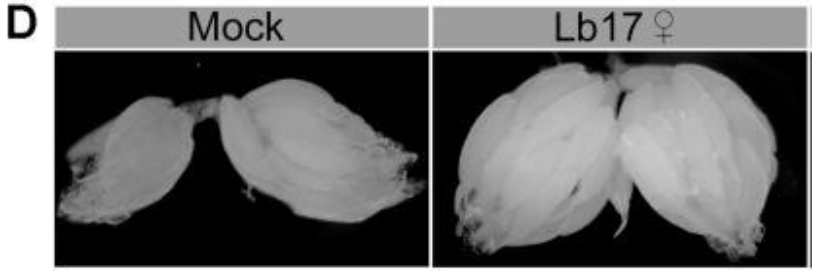
Peptidoglycan recognition protein LB （PGRP-LB）是 immune d效率途径 （IMD） 的负调节因子和对细菌感染免疫反应的调节因子。果蝇中的IMD途径作为细菌感染的介质，在先天免疫反应中起重要作用。

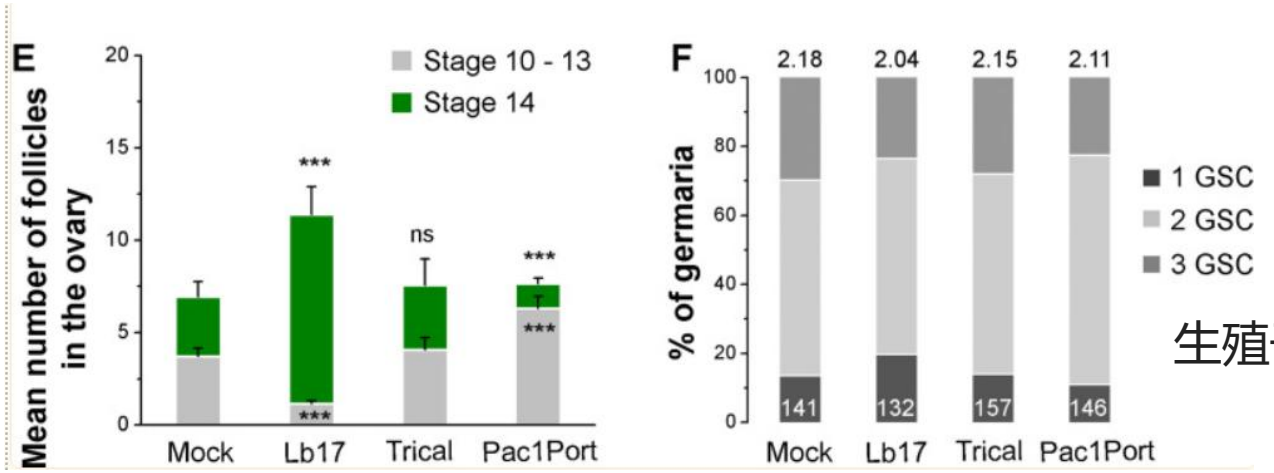
Bozler, J., et al., *G3.* 2020

Egg-lay reduction : matured oocyte retention and increased apoptosis in the ovaries





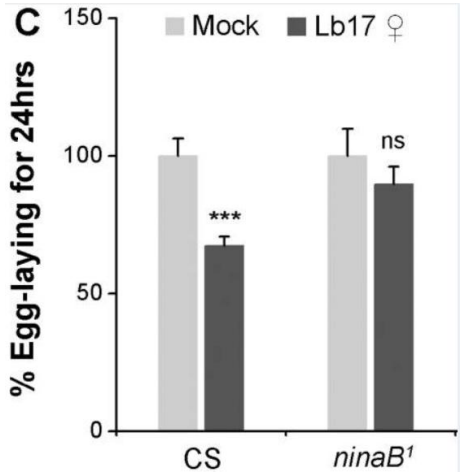


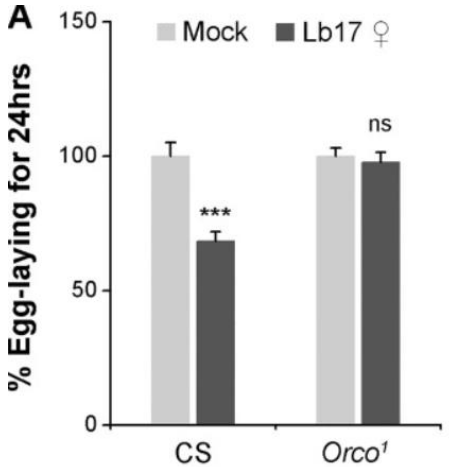


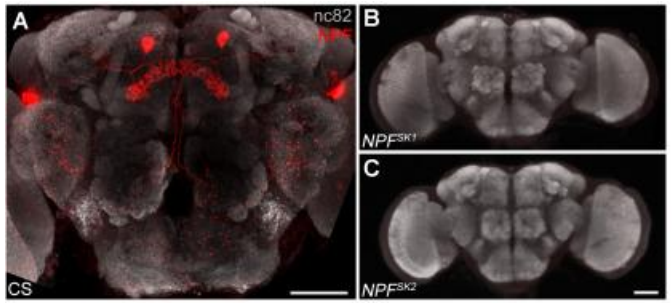
生殖干细胞（GSCs）

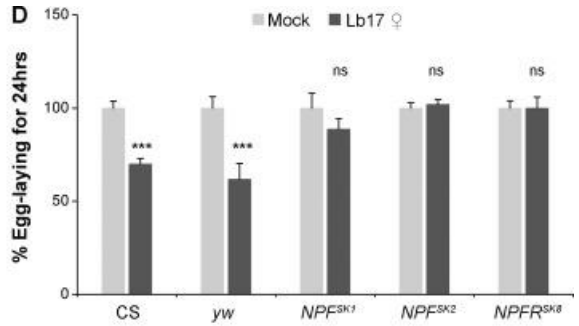
Sadanandappa, M. K., et al., *PLOS Genetics .,* 2021

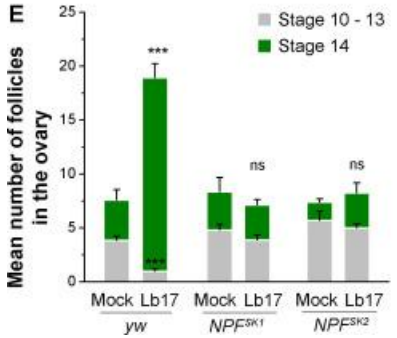
Parasitoid-induced egg-lay depression is innate and regulated by vision、olfactory 、NPF-NPFR signaling

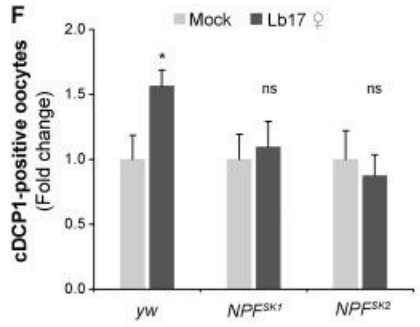


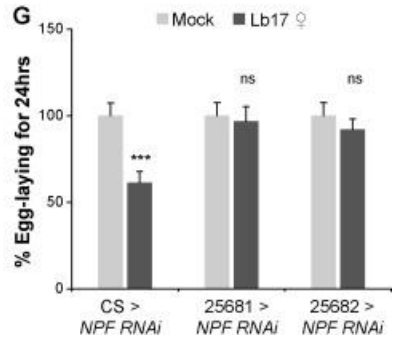


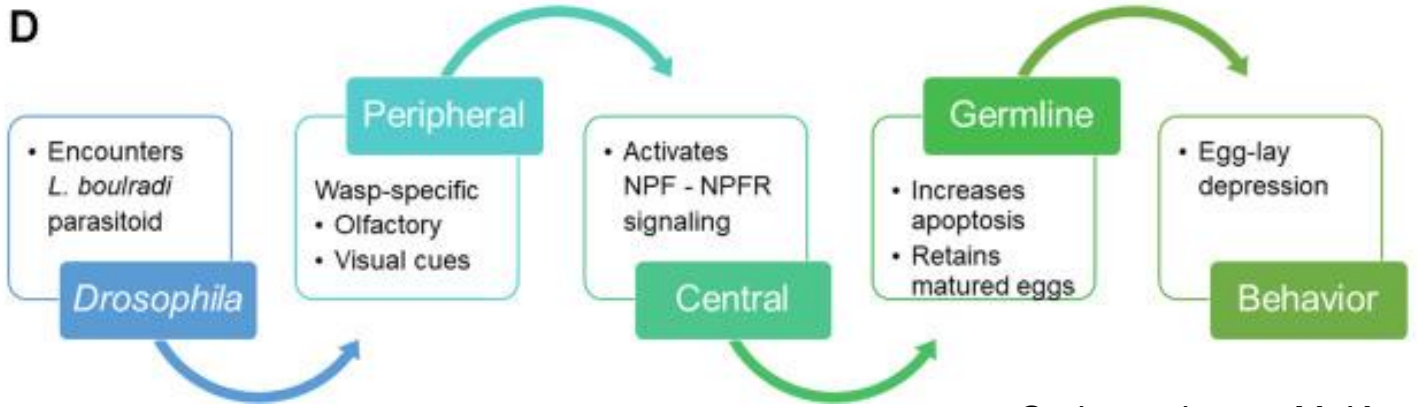






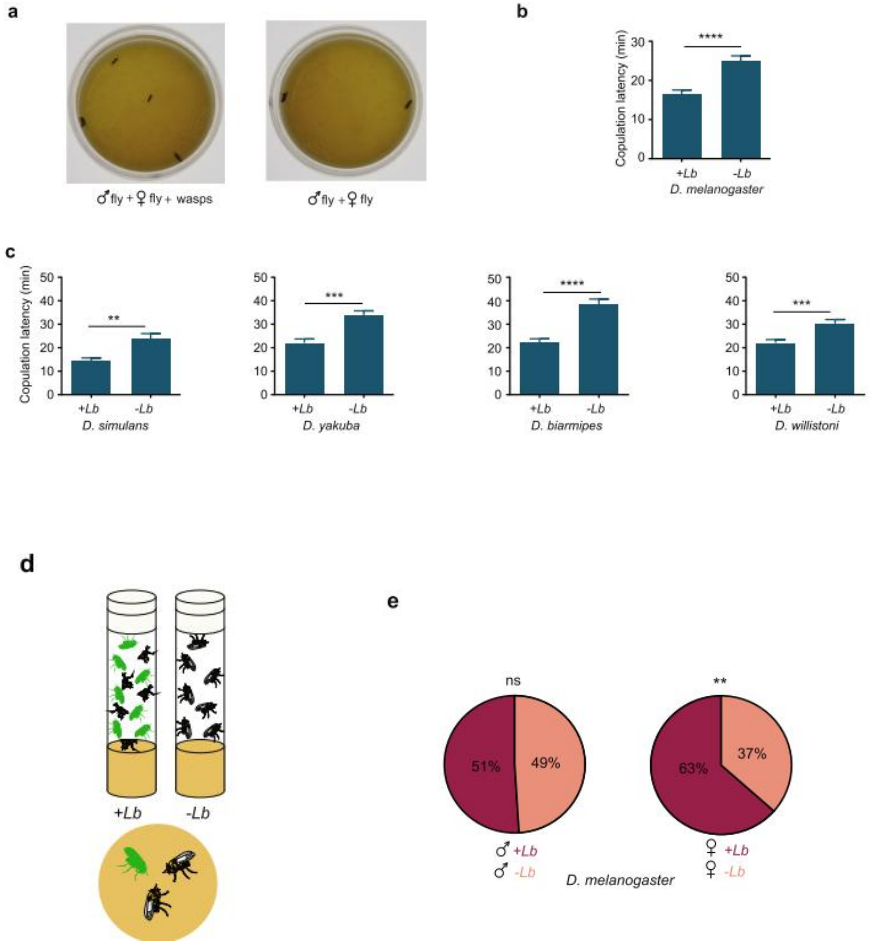


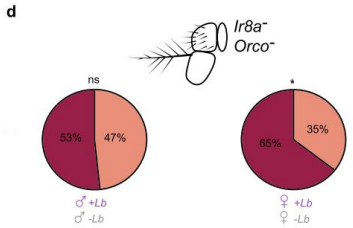


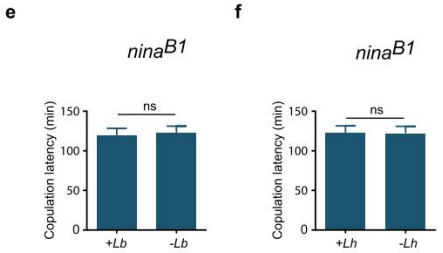


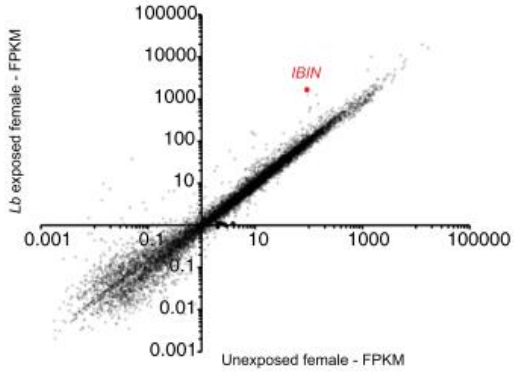
Sadanandappa, M. K., et al., *PLOS Genetics.* 2021

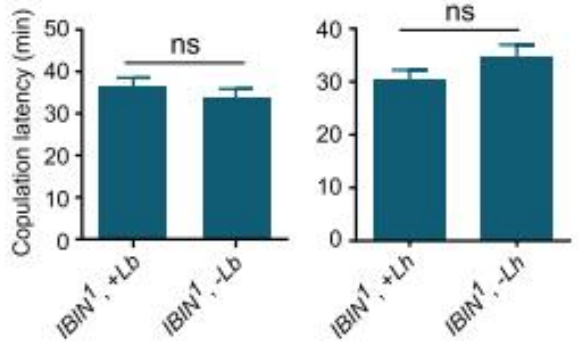
Sight of parasitoid wasps accelerates sexual behavior in female *Drosophila*

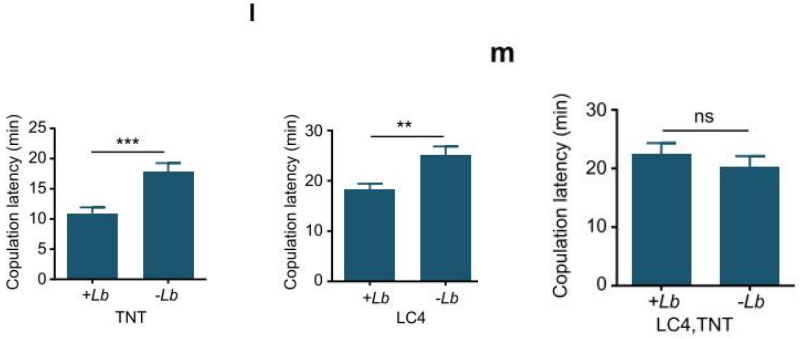








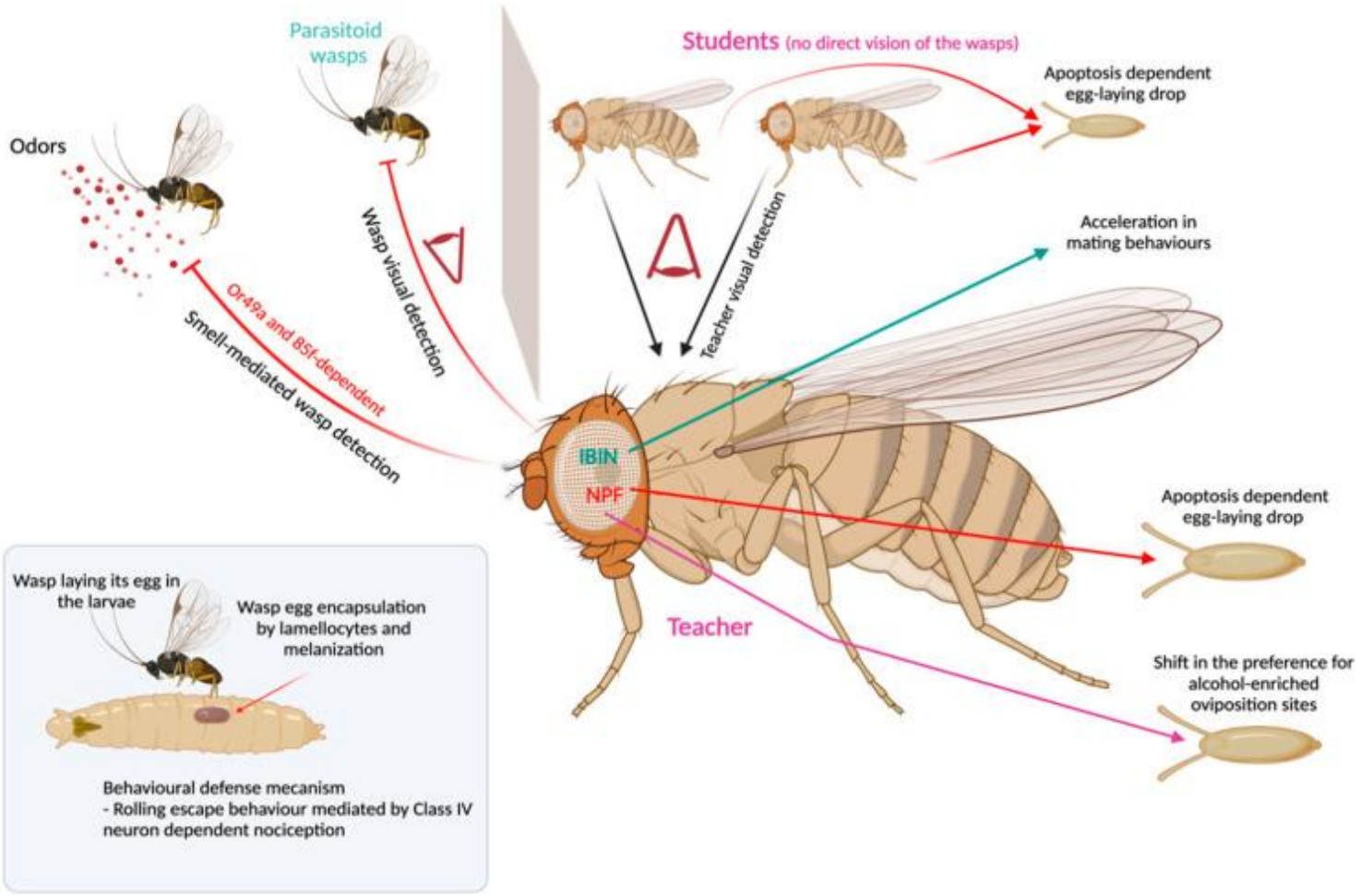




IBIN (Induced by Infection, a gene that encodes a micropeptide)

Ebrahim, S. A. M., et al.,. Nature Communications. 2021

Conclusions:



Neurobiological and genetic control strategies for avoidance or avoidance behavior in Drosophila adults and larvae during host-sensing, as well as immune defenses involving different types of blood cells

Thanks

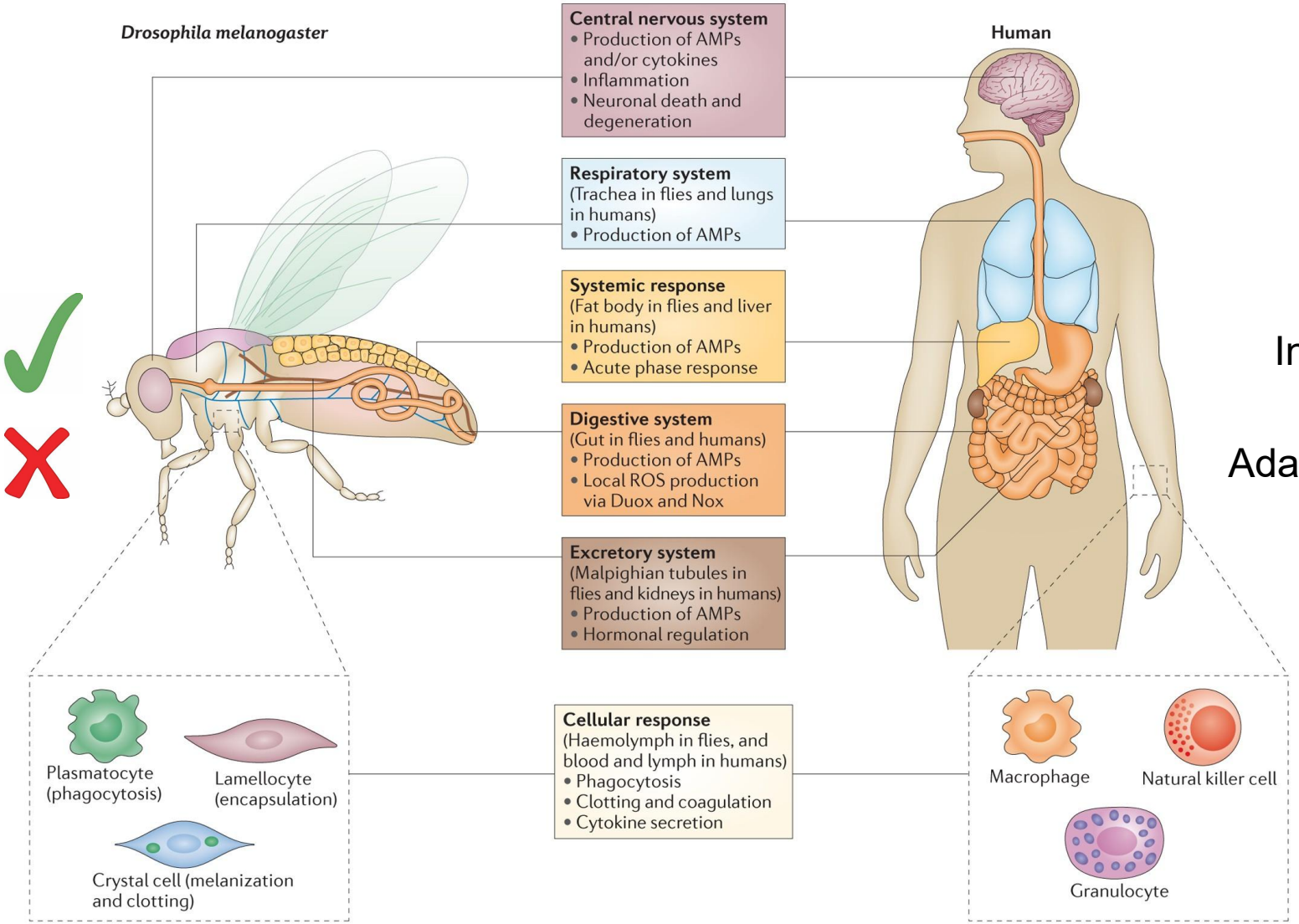
Overview of *Drosophila* immune response and its relation with sleep

Gao Can
2023.1.9

Innate immunity in *Drosophila melanogaster*

Innate immunity ✓

Adaptive immunity ✗

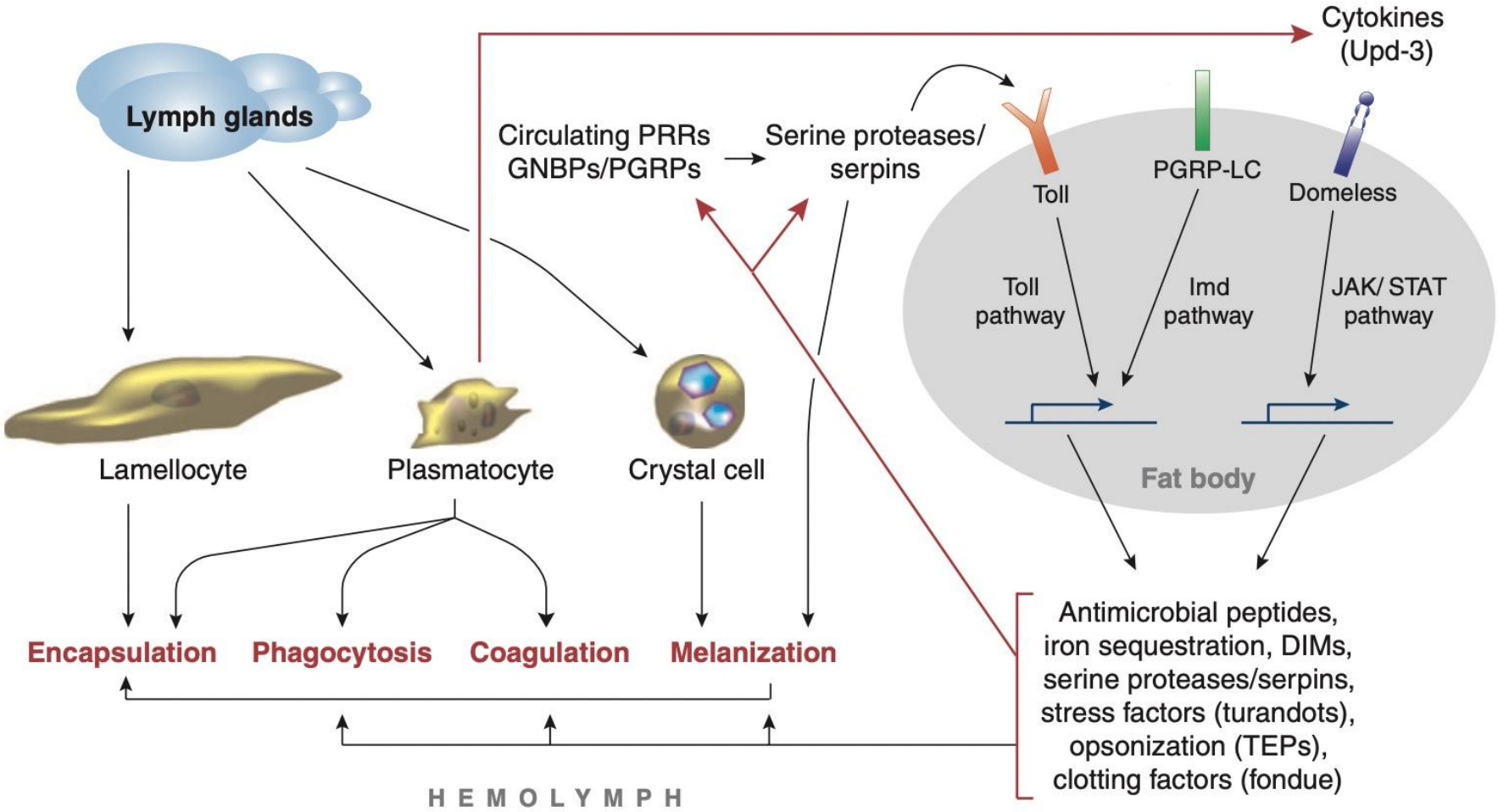


Innate immunity ✓

Adaptive immunity ✓

Nicolas Buchon, 2014

Schematic overview of *Drosophila* host defense



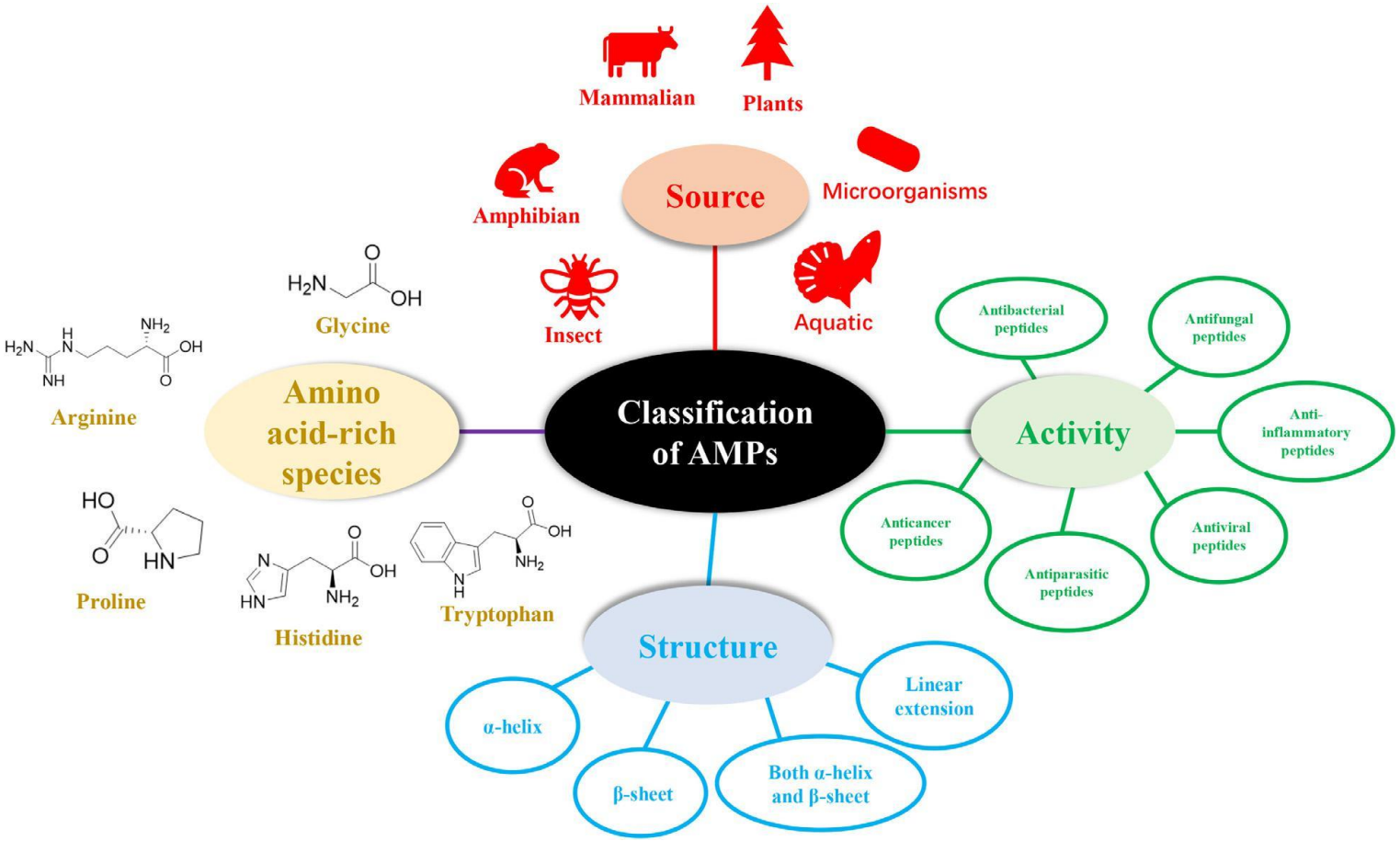
Cellular Response

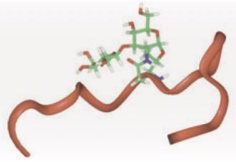
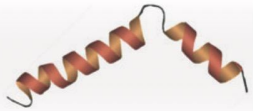
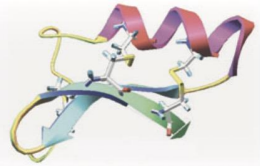
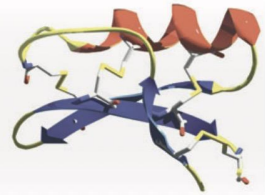
The Systemic Immune Response

Drosophila innate immunity

Bruno Lemaitre, 2007

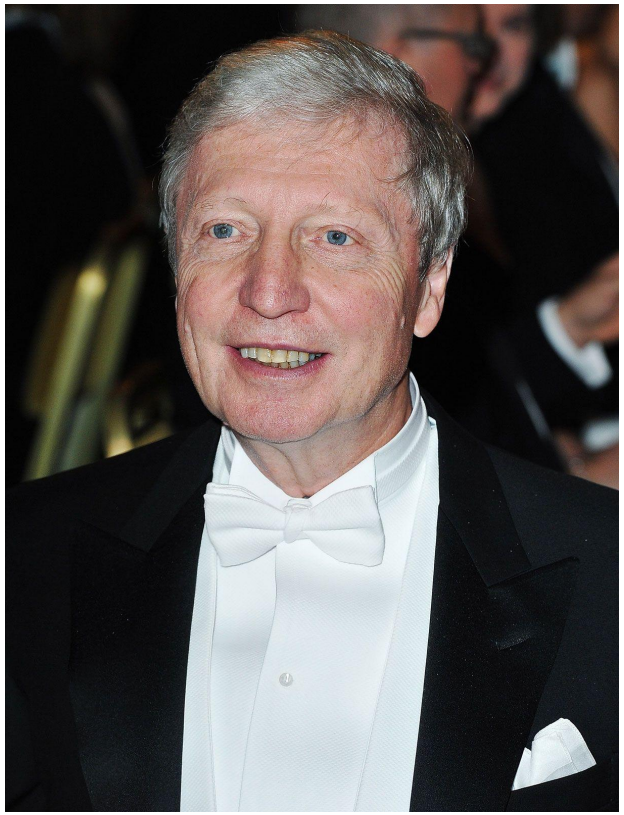
Antimicrobial peptides(AMPs) in different animals



Peptides	# of genes	Main activity	Concentration	3-D structure
Diptericin	2	Gram-negative bacteria	0.5 μM	nd
Attacin	4	Gram-negative bacteria	nd	nd
Drosocin	1	Gram-negative bacteria	40 μM	
Cecropin	4	Gram-negative bacteria	20 μM	
Defensin	1	Gram-positive bacteria	1 μM	
Drosomycin	7	Fungi	100 μM	
Metchnikowin	1	Fungi	10 μM	nd

Yuchen Huan, 2020

Bruno Lemaitre, 2007



Jules Alphonse Hoffmann
French immunologist

Born: August 2, 1941 (age 81) Luxembourg
Awards And Honors: Nobel Prize (2011)
Subjects Of Study: Drosophila immune system nonspecific immunity

Insect defensins: inducible antibacterial peptides*

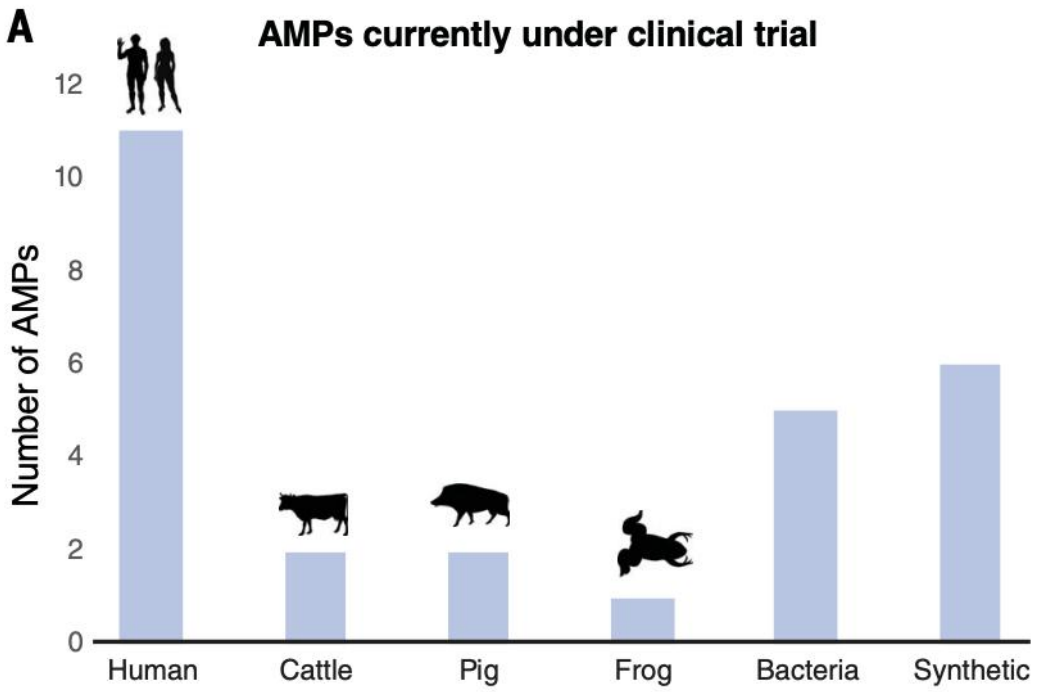
Jules A. Hoffmann and Charles Hetru

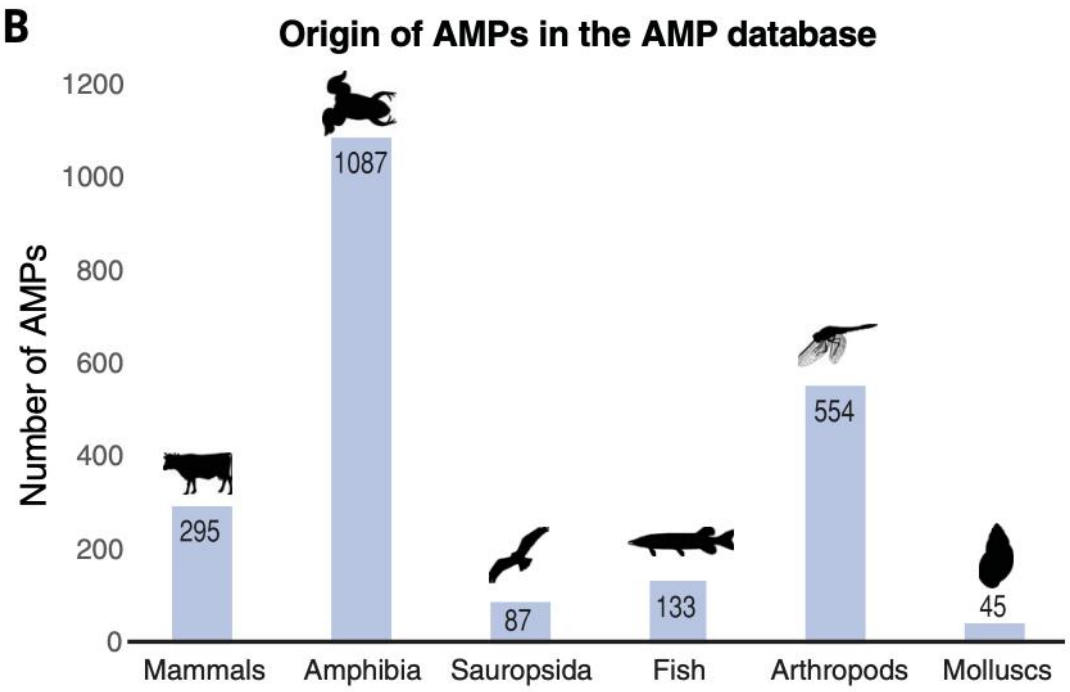
In response to bacterial challenge or trauma, insects produce a battery of bactericidal or bacteriostatic molecules with a broad spectrum of activity against Gram-positive and/or Gram-negative bacteria; most are small-sized cationic peptides. This review focuses on insect defensins, a large group of inducible antibacterial peptides that are present both in ancient and recent insect orders. This immune response of insects shares many of the characteristics of the mammalian acute phase response.

Immune system  Sleep

?

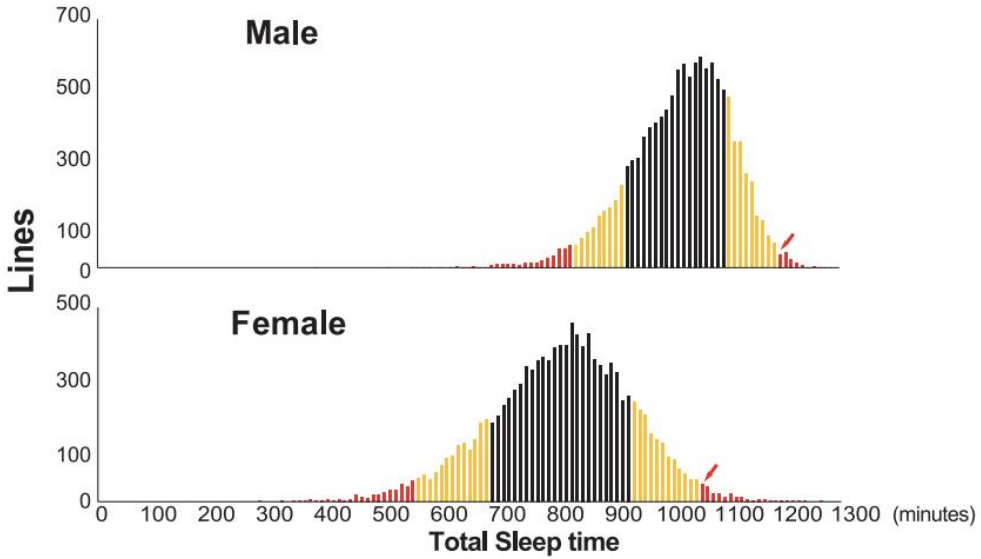
Evolution of AMPs and origin of AMPs as drugs

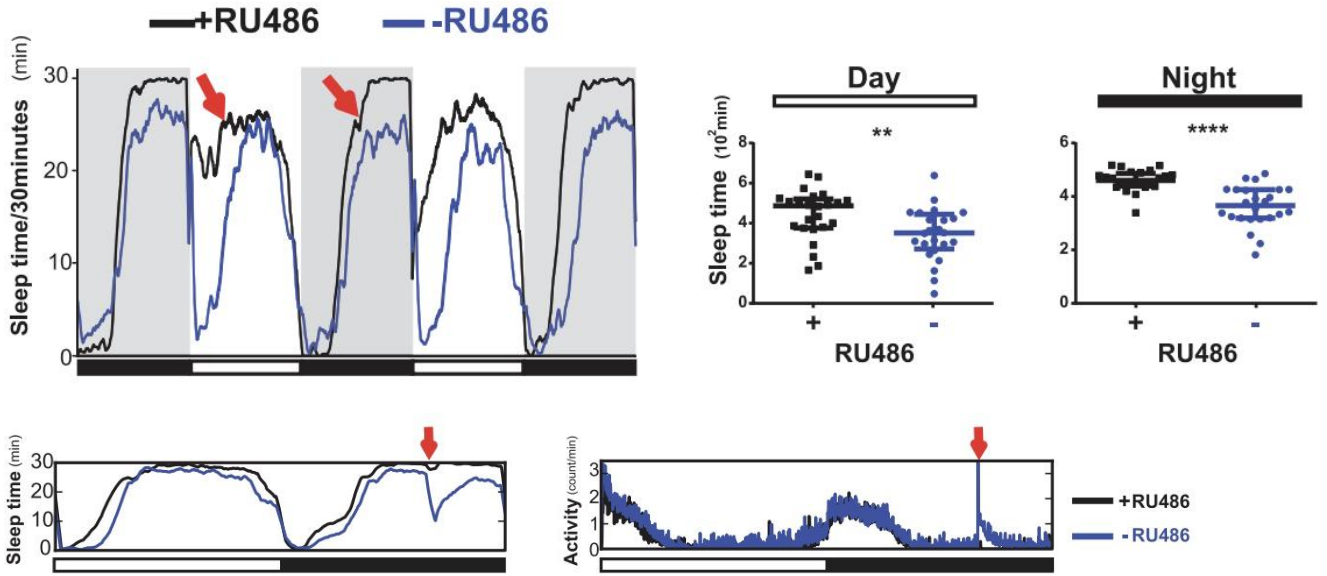


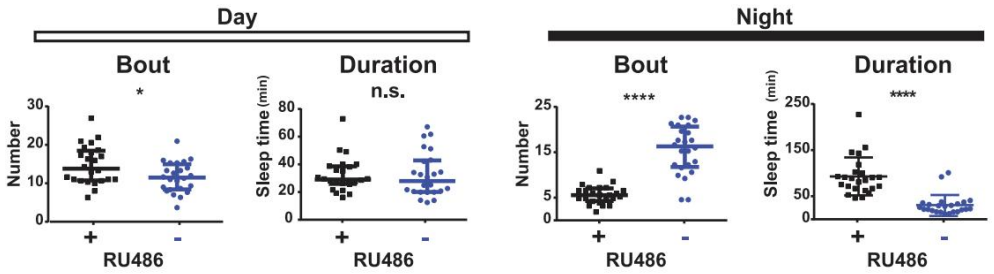


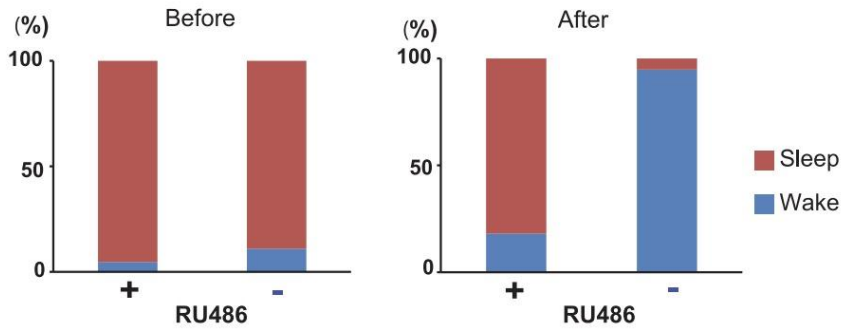
Brian P. Lazzaro, 2020

nemuri (*nur*) overexpression promotes sleep



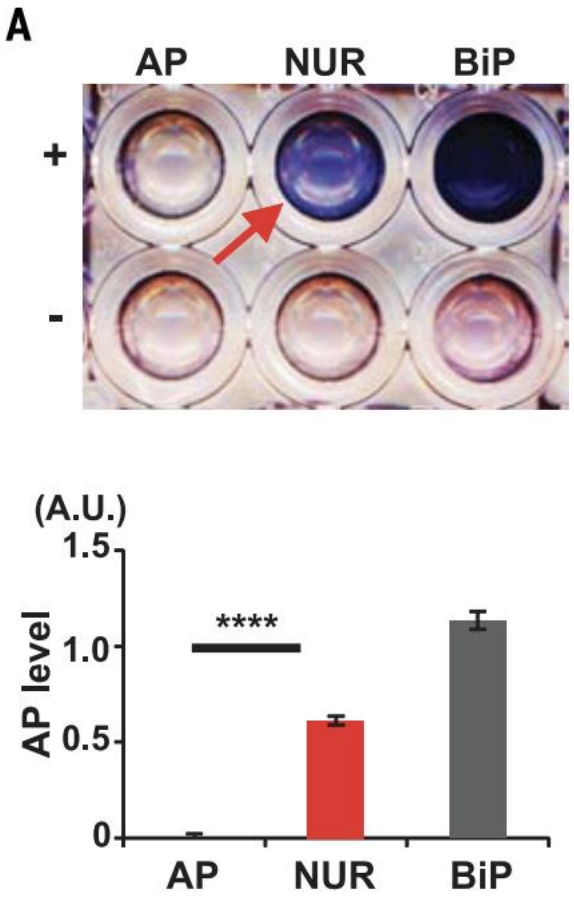


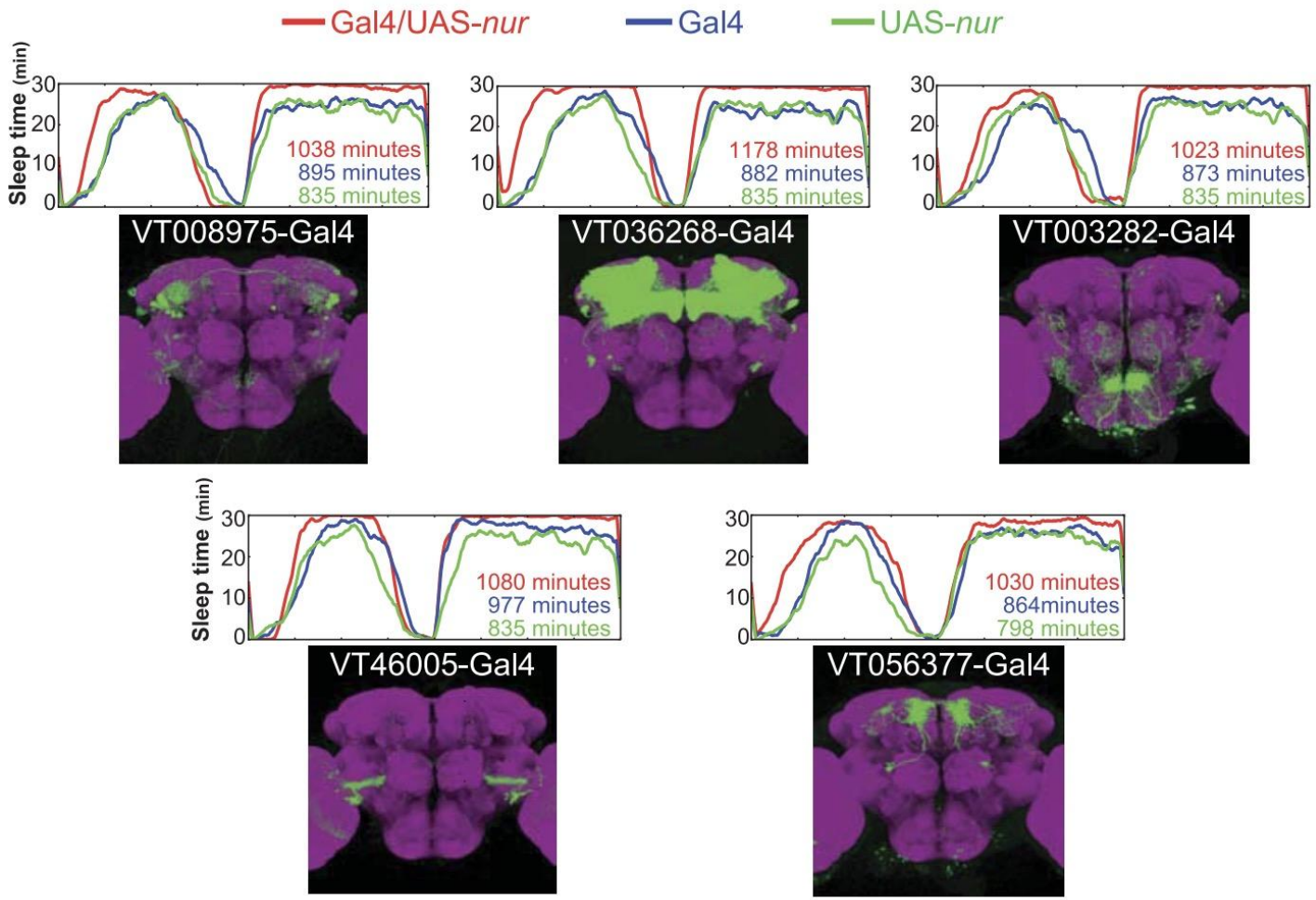




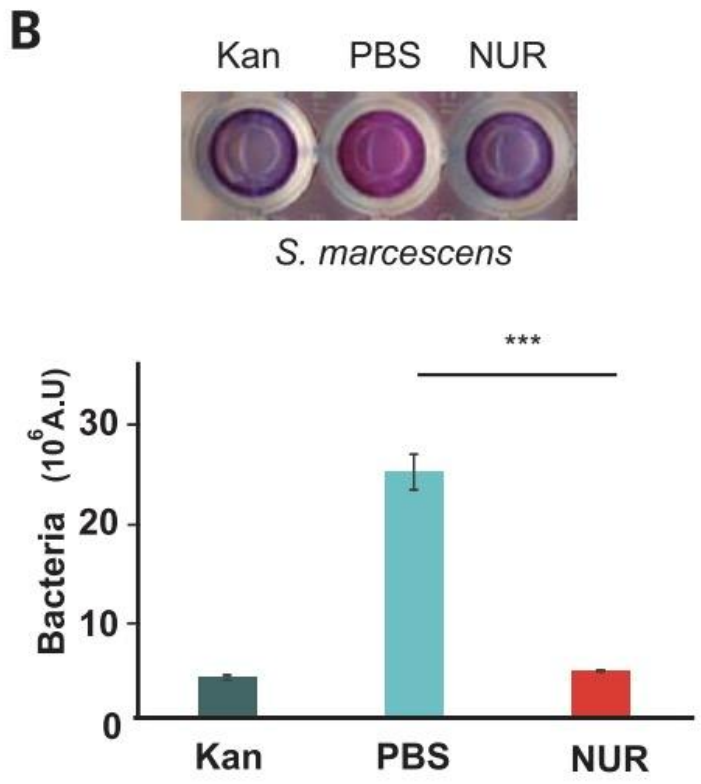
HIROFUMI TODA, 2019

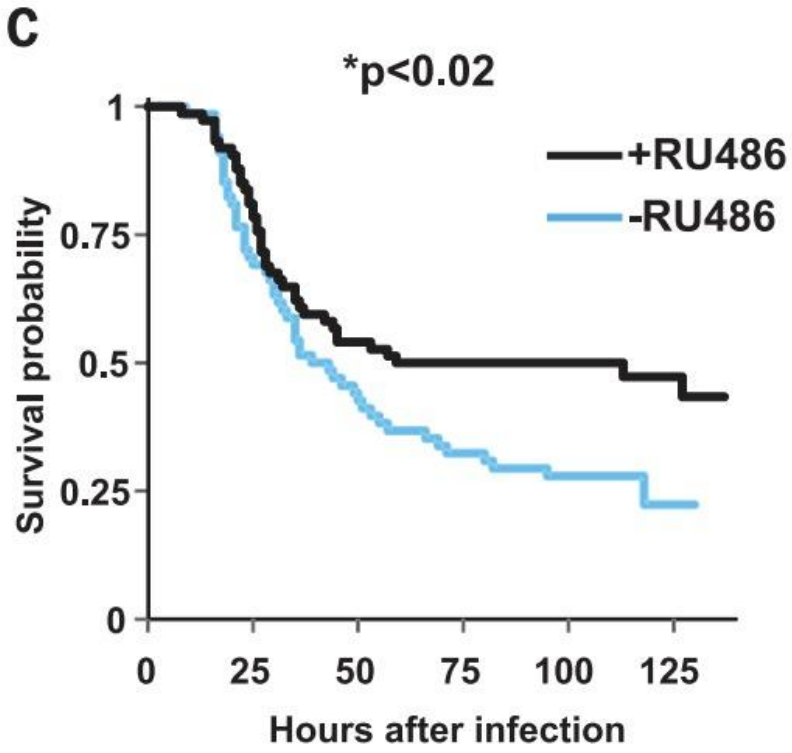
NUR is a secreted protein and its ectopic expression induces sleep



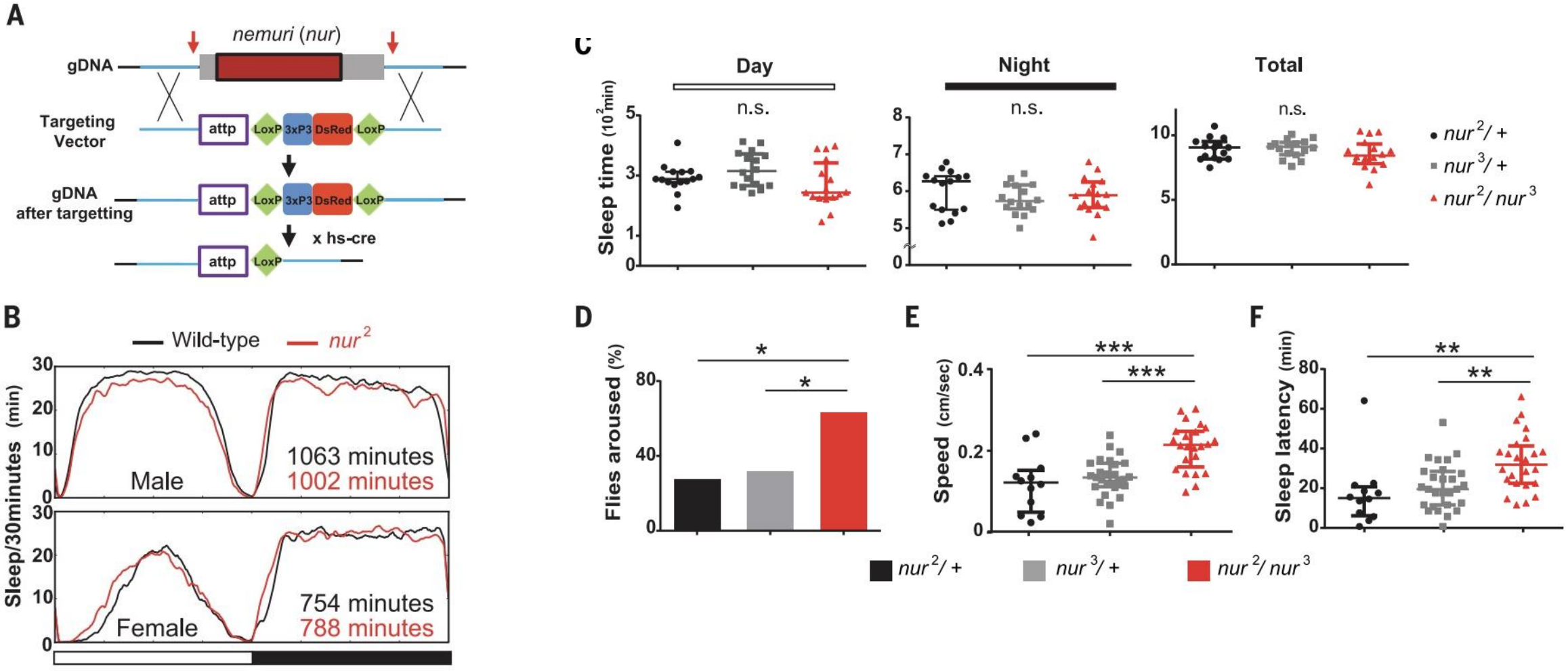


nur encodes an antimicrobial peptide that promotes survival upon expression in neurons

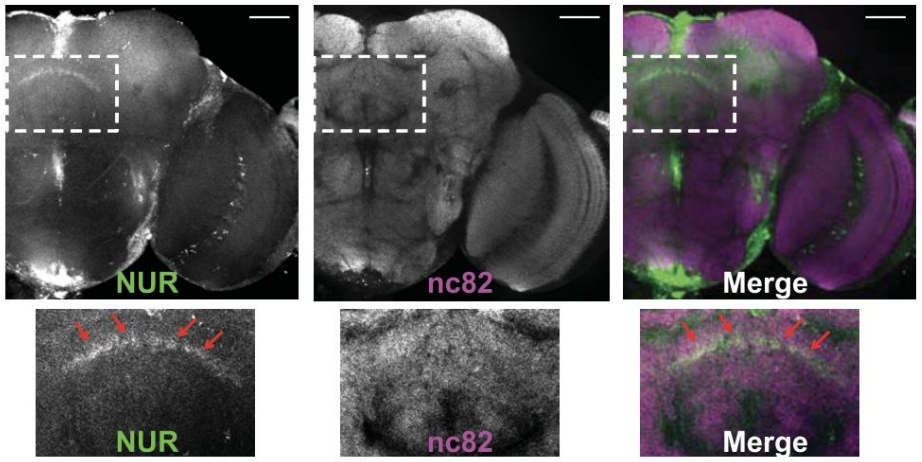


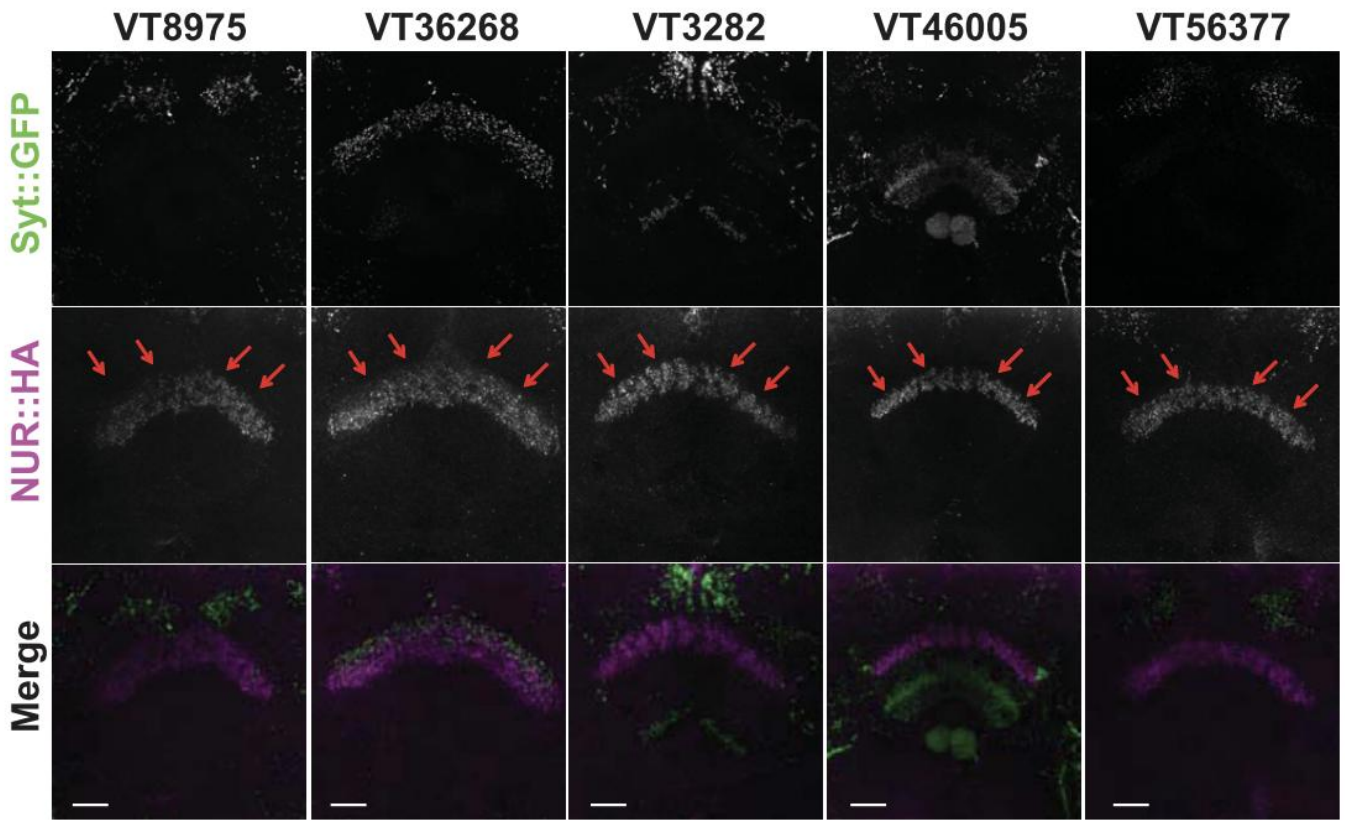


Requirement of *nur* for sleep depth and for acute sleep induction after sleep deprivation or infection



NUR is induced by sleep loss and is localized to the dFSB area of the brain





THANK YOU!