

Interdisciplinary symposium on sepsis  
Amphithéâtre Laroque - Ministère de la Santé  
8 septembre 2022

# Systemic inflammatory response: lessons from a model organism

Jean-Luc IMLER

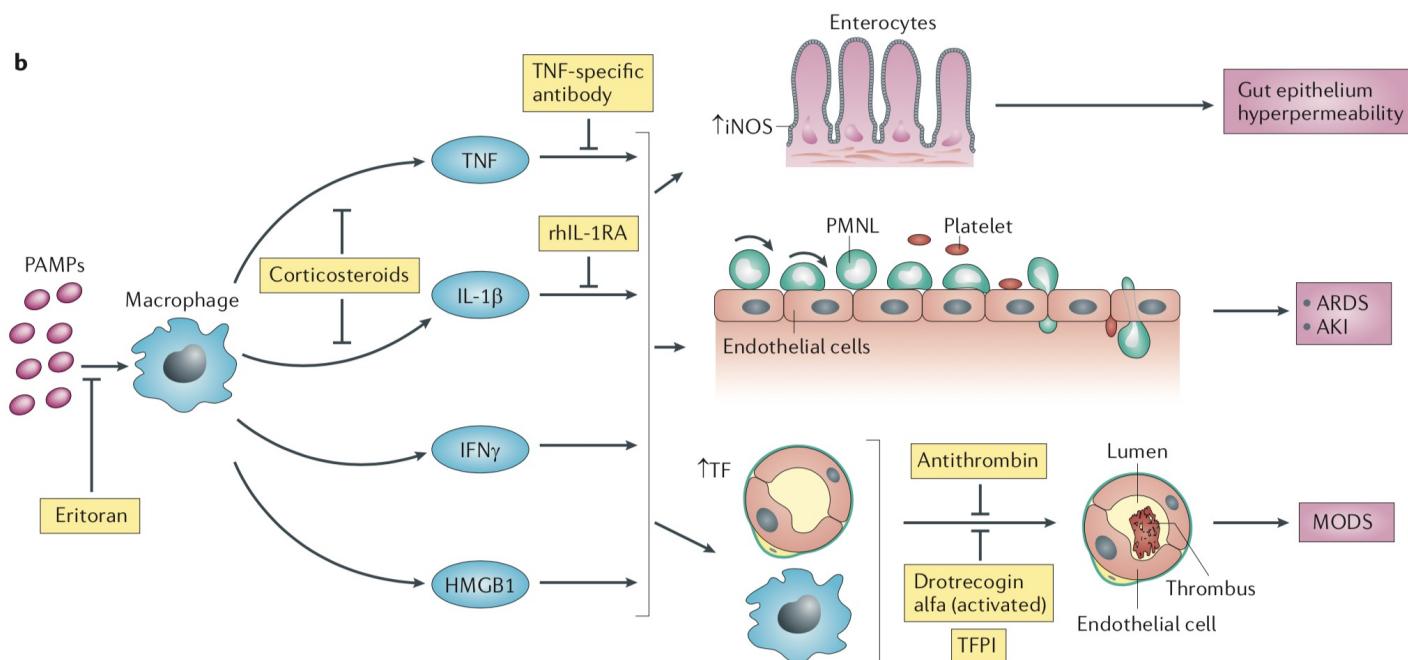
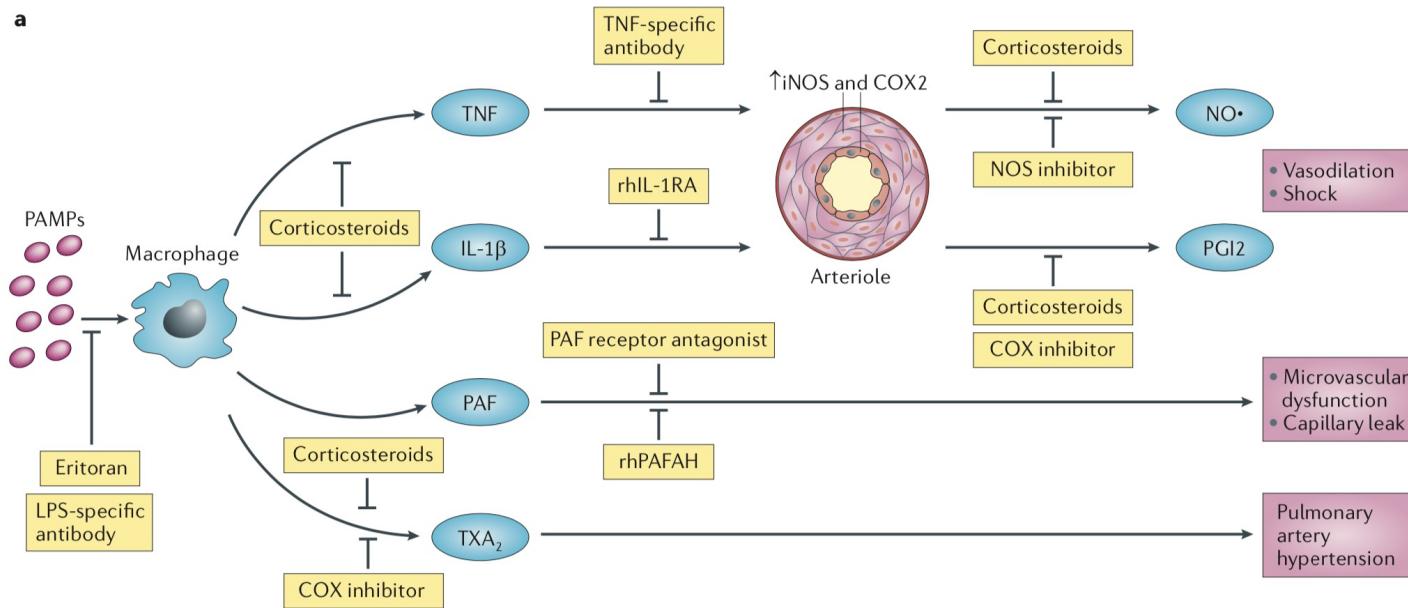


广州霍夫曼免疫研究所  
*Sino-French Hoffmann Institute*



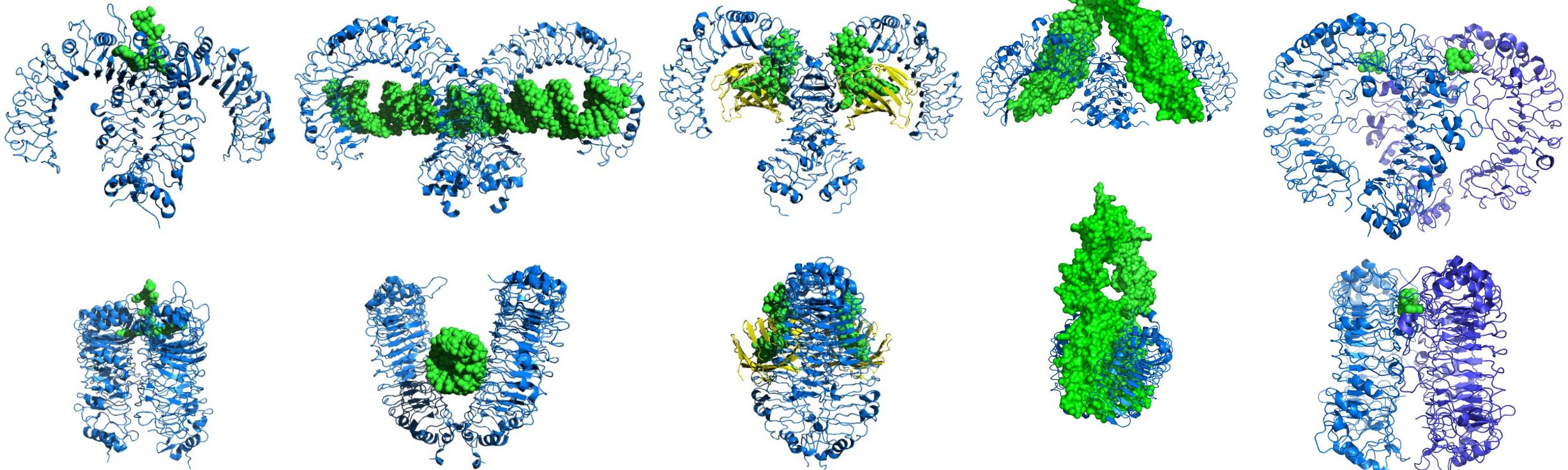
Université de Strasbourg

# Simplified model for the pathogenesis of severe sepsis and septic shock



Organ dysfunction

# Accommodation of a broad range of ligands by the ectodomain of Toll-like receptors (TLRs)



**TLR1+TLR2 + lipopeptide**  
2:1 complex  
(2Z7X)  
Jin et al. 2007

**TLR3+dsRNA**  
2:1 complex  
(3CIY)  
Liu et al. 2008

**TLR4+MD-2+LPS**  
2:2:2 complex  
(3FXI)  
Park et al. 2009

**TLR5+flagellin**  
2:2 complex  
(3V47)  
Yoon et al. 2012

**TLR8+ssRNA**  
2:2 complex  
(3W3G)  
Tanji et al. 2013

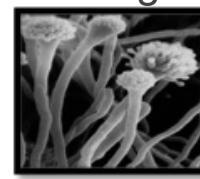
Courtesy of Dr. M. Gangloff, Cambridge U.

# Insects and infections

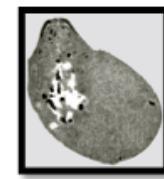
Bacteria



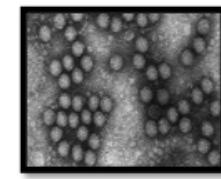
Fungi



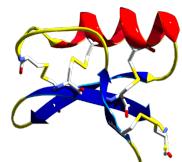
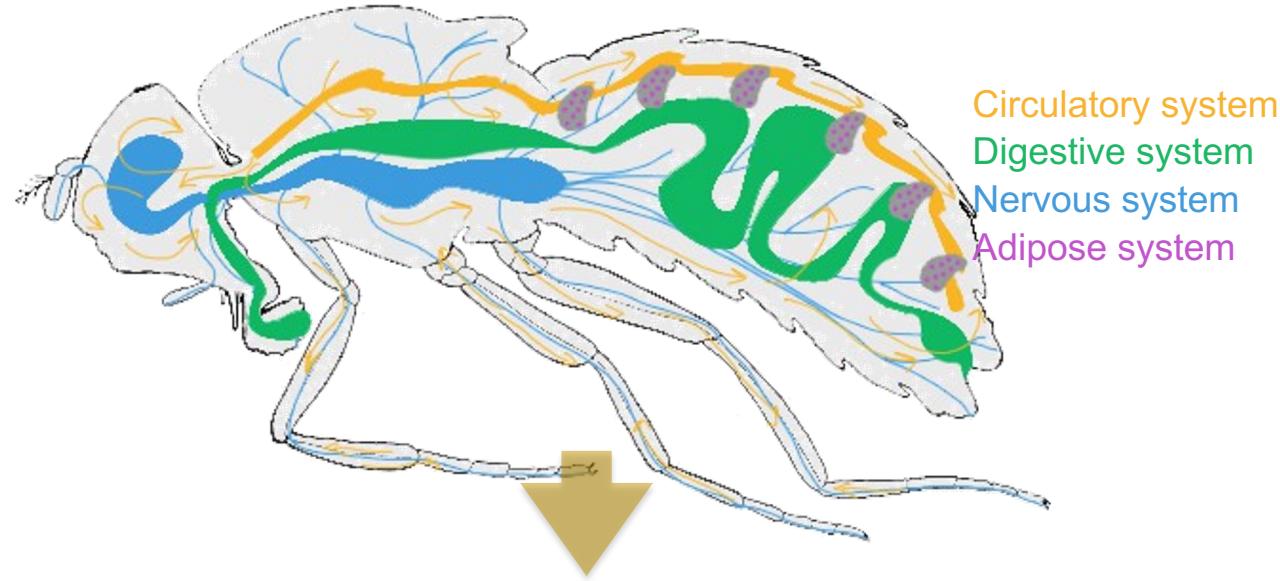
Protozoa



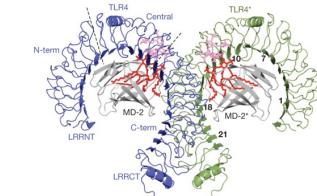
Virus



J. Hoffmann



Production of  
antimicrobial  
molecules

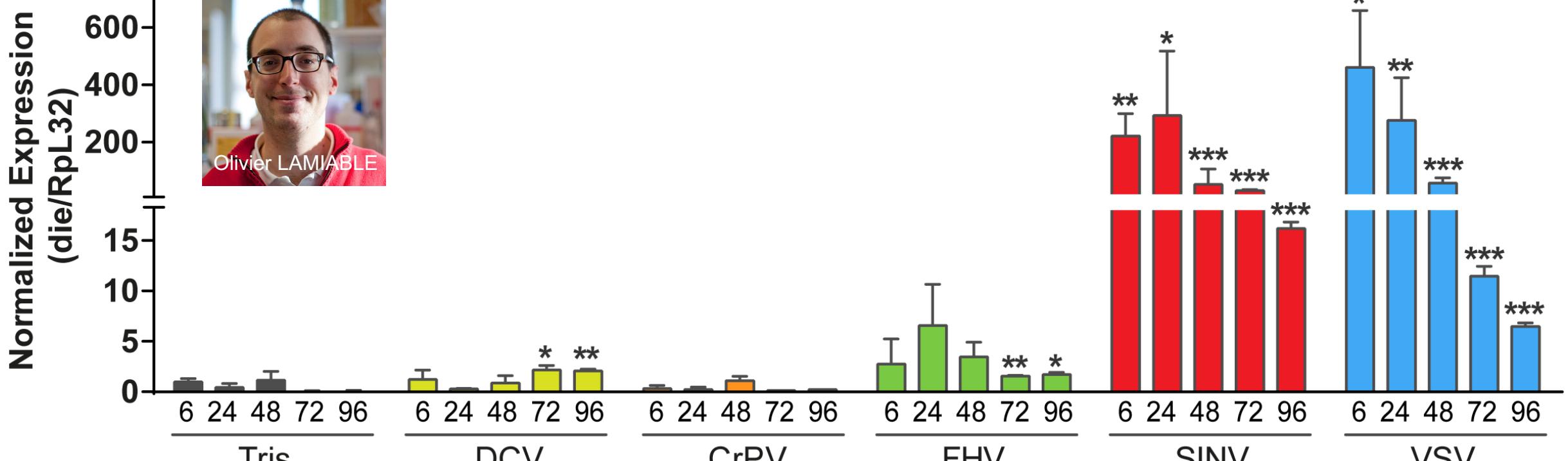


Evolutionarily conserved  
mechanisms  
(e.g. Toll like receptors)

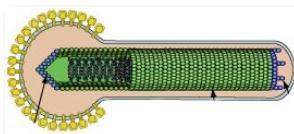


Vector borne disease  
(e.g. plasmodium,  
dengue)

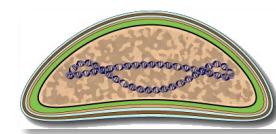
# The gene *diedel* (*die*) is strongly induced by several viruses



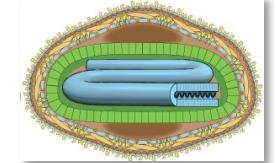
& hijacked by:



PsunG  
XcGV  
HaGV



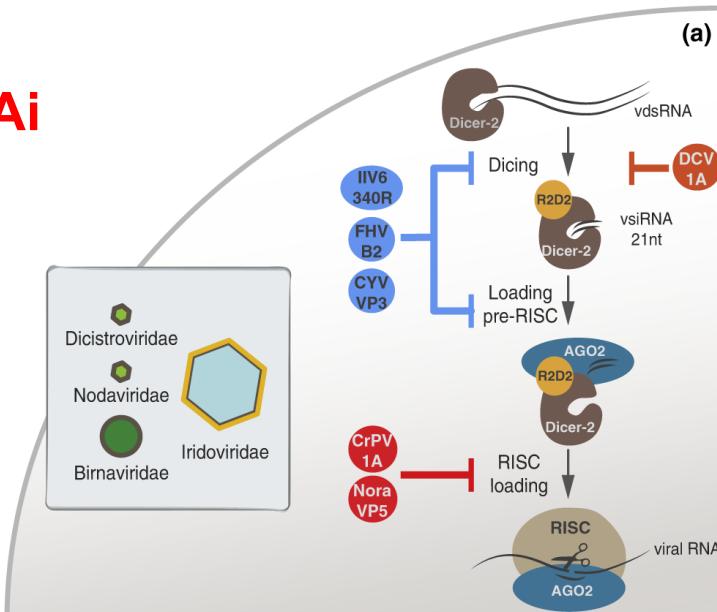
HVAV3V  
SfAV-1A



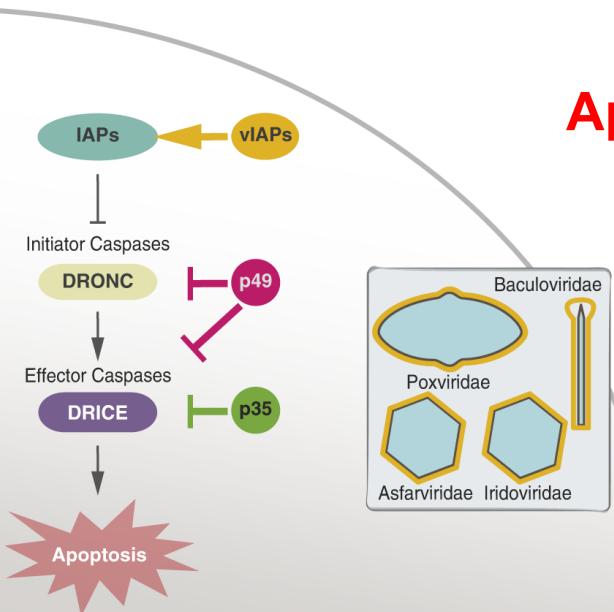
MySEV

# Immunology taught by viruses

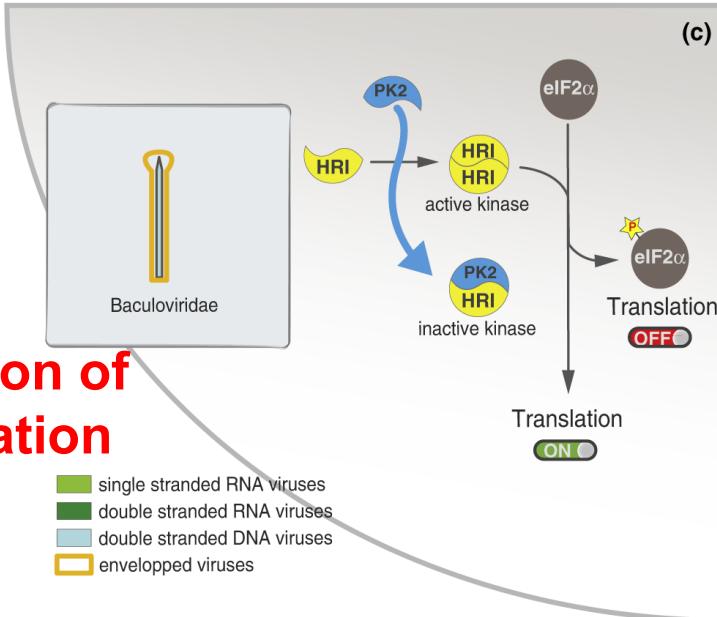
## RNAi



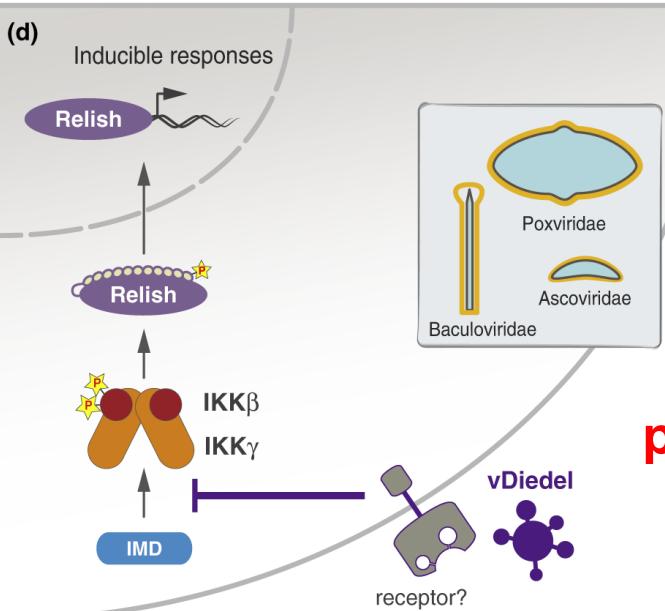
## Apoptosis



## Inhibition of translation



## IMD pathway



# What link between the IMD pathway and antiviral immunity?

Implication of IKK $\beta$  and NF- $\kappa$ B in an antiviral response

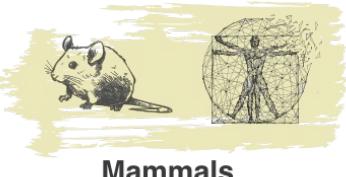
Identification of 10 genes induced by viruses and IKK $\beta$ -dependent

Identification of 2 genes necessary and sufficient to control DCV replication



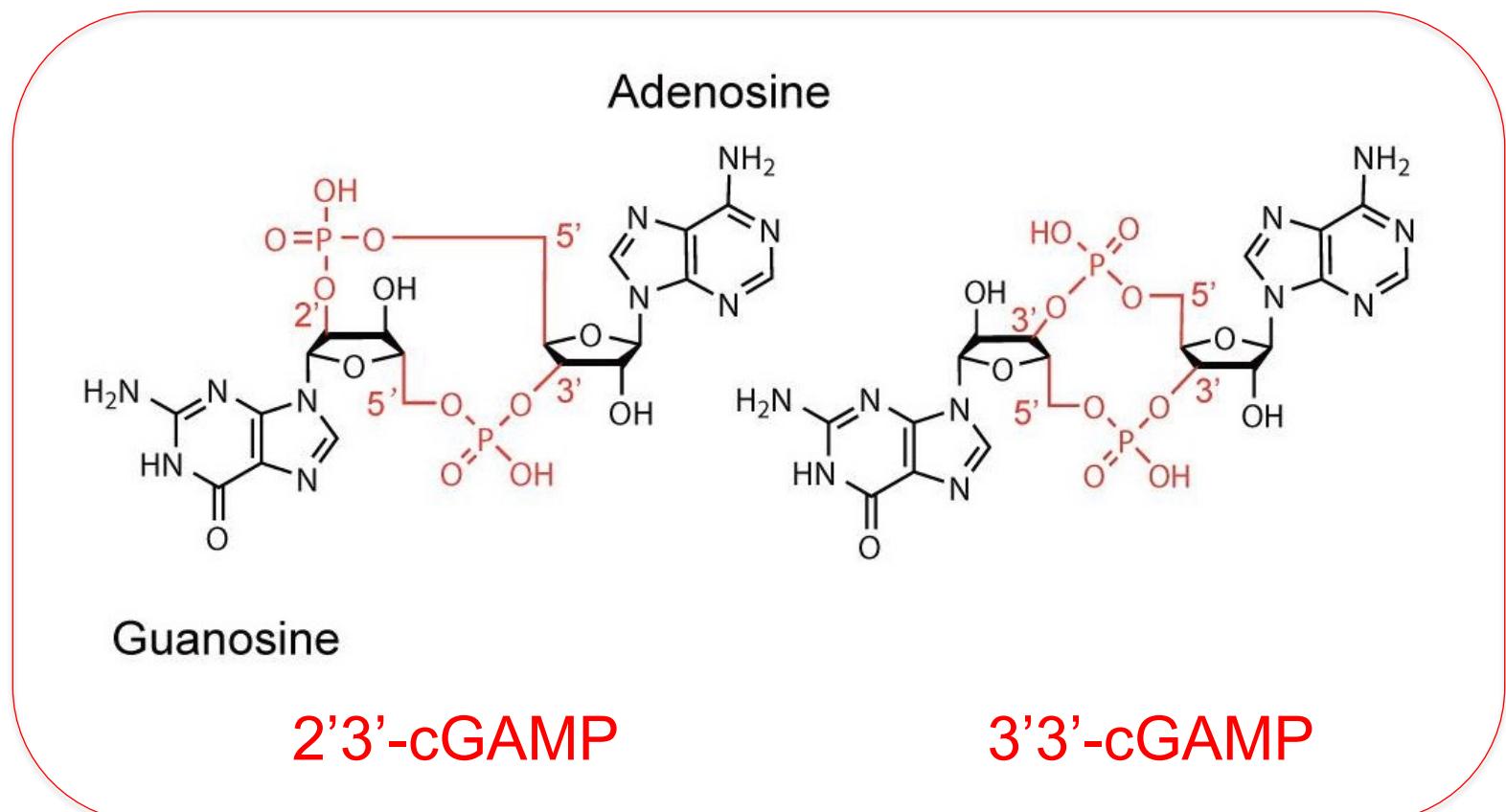
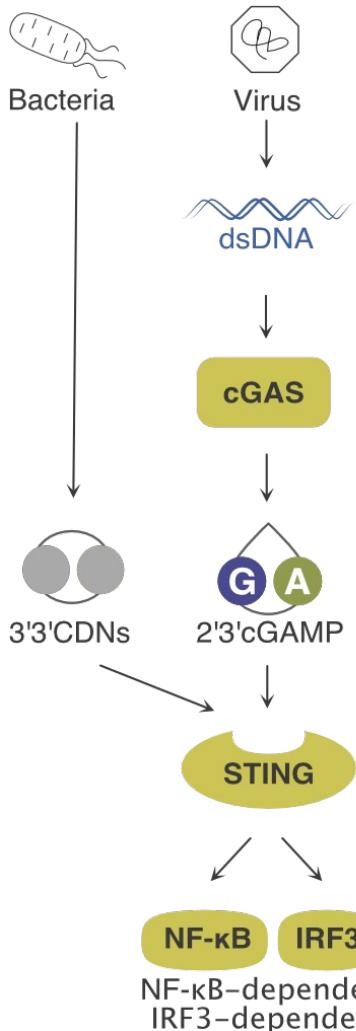
**dSTING, Nazo**

# cGAS-STING: an evolutionarily conserved pathway



Mammals

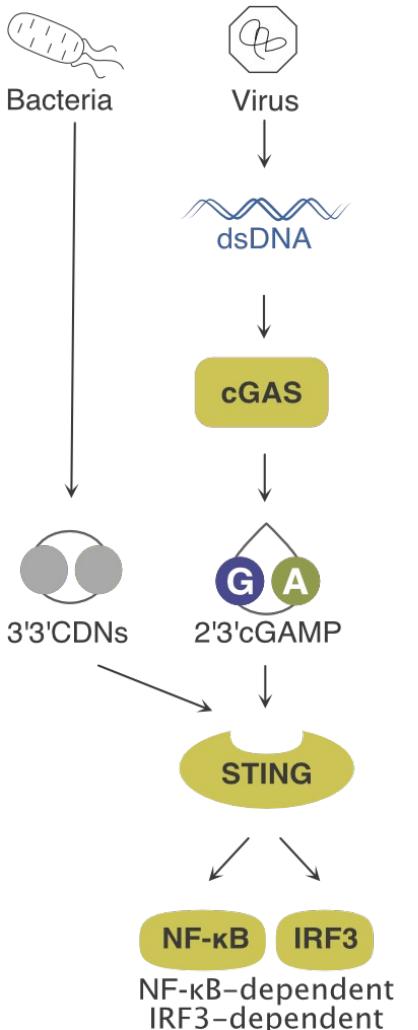
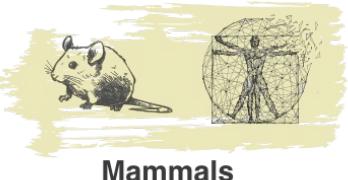
Mammals



# TMEM173 Drives Lethal Coagulation in Sepsis

Hui Zhang,<sup>1,12</sup> Ling Zeng,<sup>2,12</sup> Min Xie,<sup>1</sup> Jiao Liu,<sup>3</sup> Borong Zhou,<sup>3</sup> Runliu Wu,<sup>4</sup> Lizhi Cao,<sup>1</sup> Guido Kroemer,<sup>5,6,7,8,9</sup> Haichao Wang,<sup>10</sup> Timothy R. Billiar,<sup>11</sup> Herbert J. Zeh,<sup>4</sup> Rui Kang,<sup>4</sup> Jianxin Jiang,<sup>2,\*</sup> Yan Yu,<sup>1,\*</sup> and Daolin Tang<sup>3,4,13,\*</sup>

# cGAS-STING: an evolutionarily conserved pathway



## Immunity

### Article

## Interferon-Independent Activities of Mammalian STING Mediate Antiviral Response and Tumor Immune Evasion

Jianjun Wu,<sup>1</sup> Nicole Dobbs,<sup>1</sup> Kun Yang,<sup>1</sup> and Nan Yan<sup>1,2,3,\*</sup>

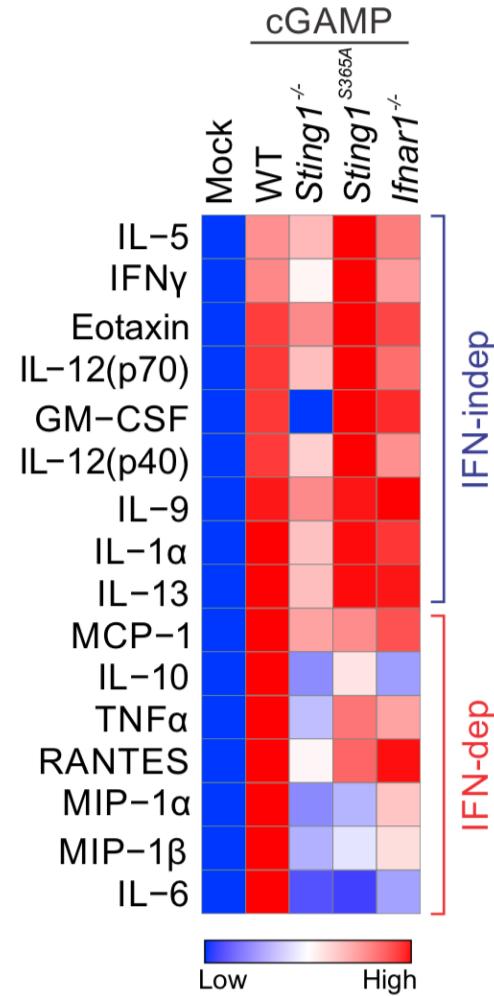
<sup>1</sup>Department of Immunology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

<sup>2</sup>Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

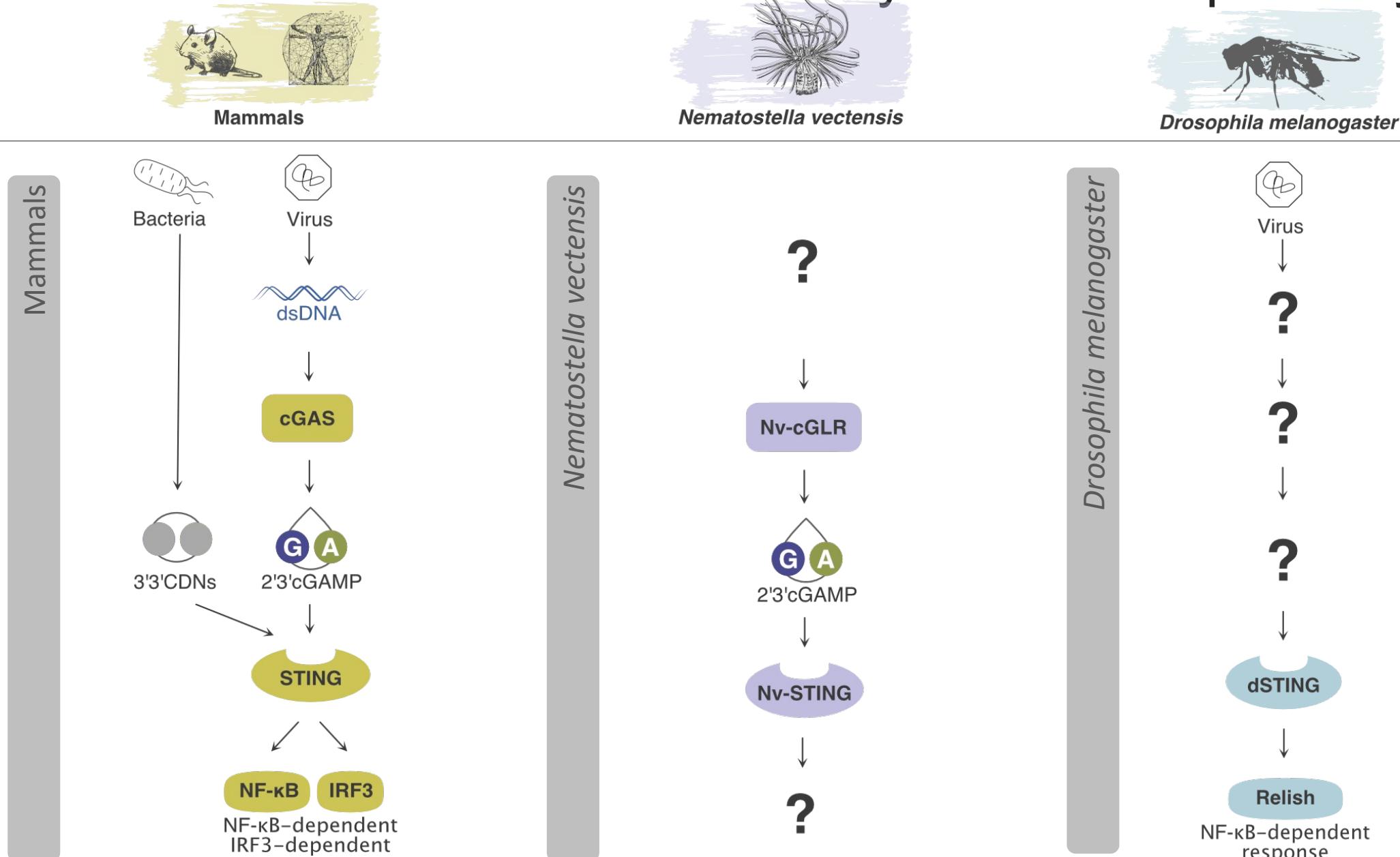
<sup>3</sup>Lead Contact

\*Correspondence: [nan.yan@utsouthwestern.edu](mailto:nan.yan@utsouthwestern.edu)

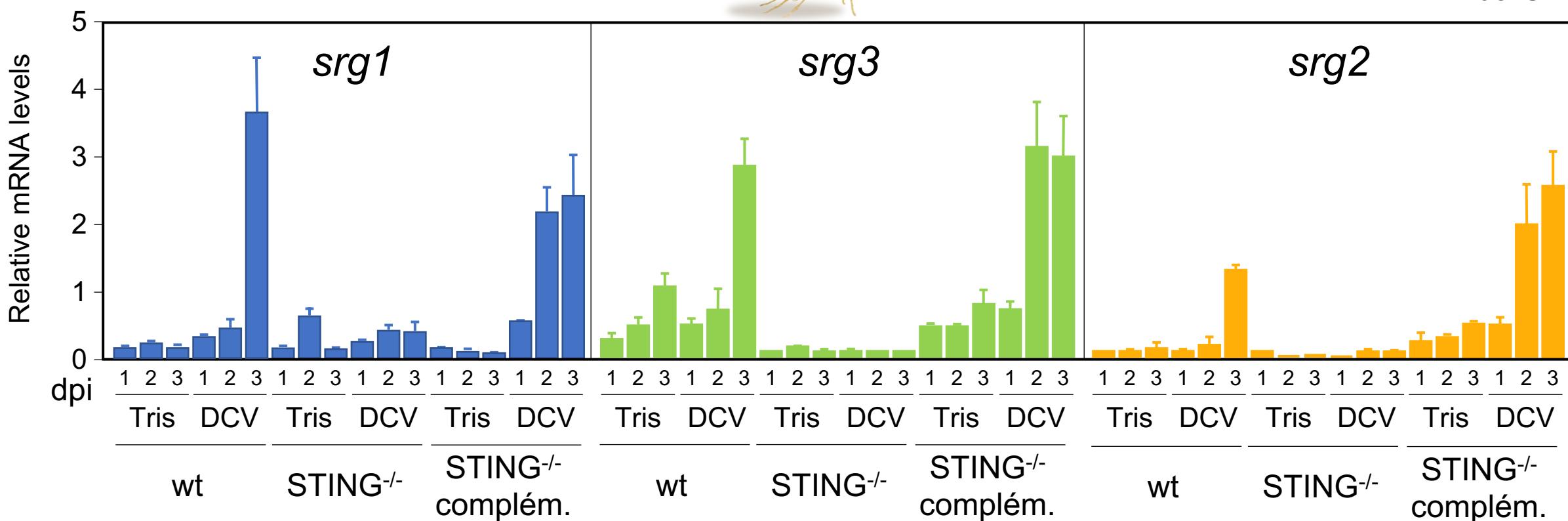
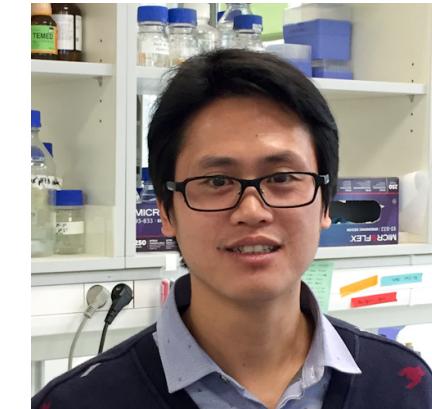
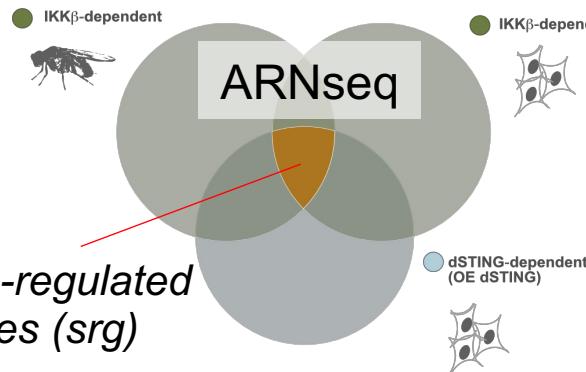
<https://doi.org/10.1016/j.jimmuni.2020.06.009>



# cGAS-STING: an evolutionarily conserved pathway



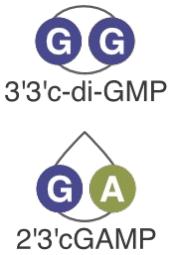
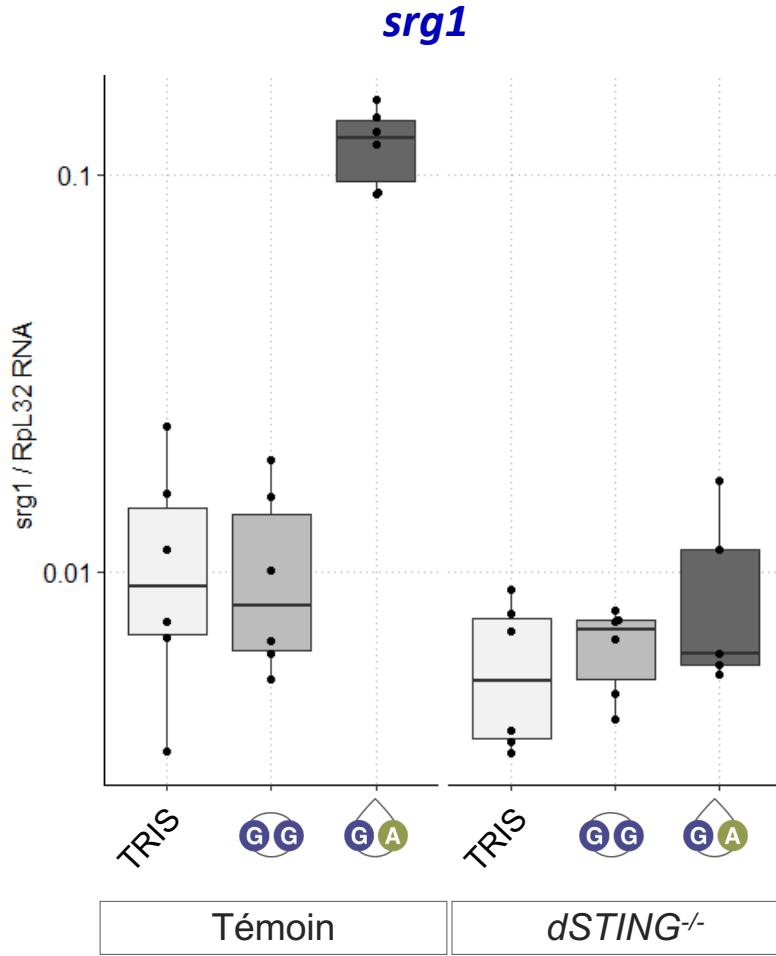
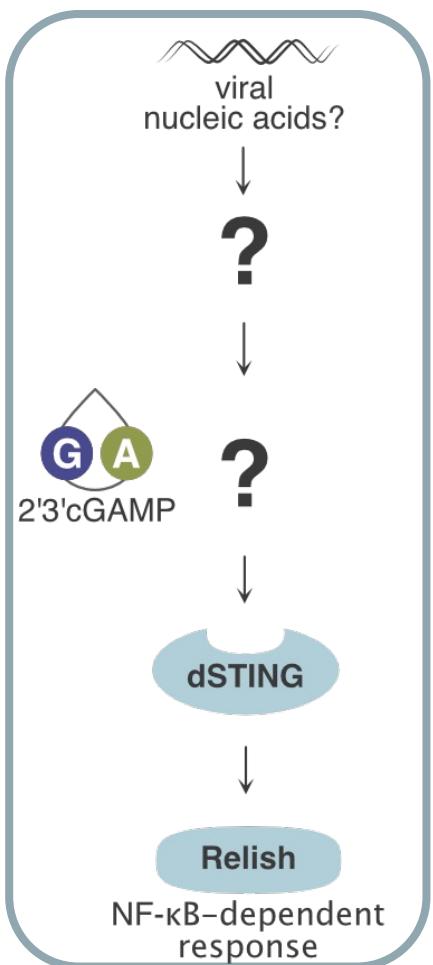
# Identification & validation of STING-regulated genes (*srg*)



# 2'3'-cGAMP induces a STING-NF- $\kappa$ B-dependent transcriptional response



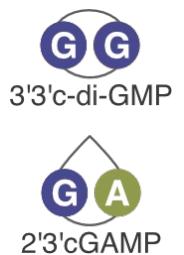
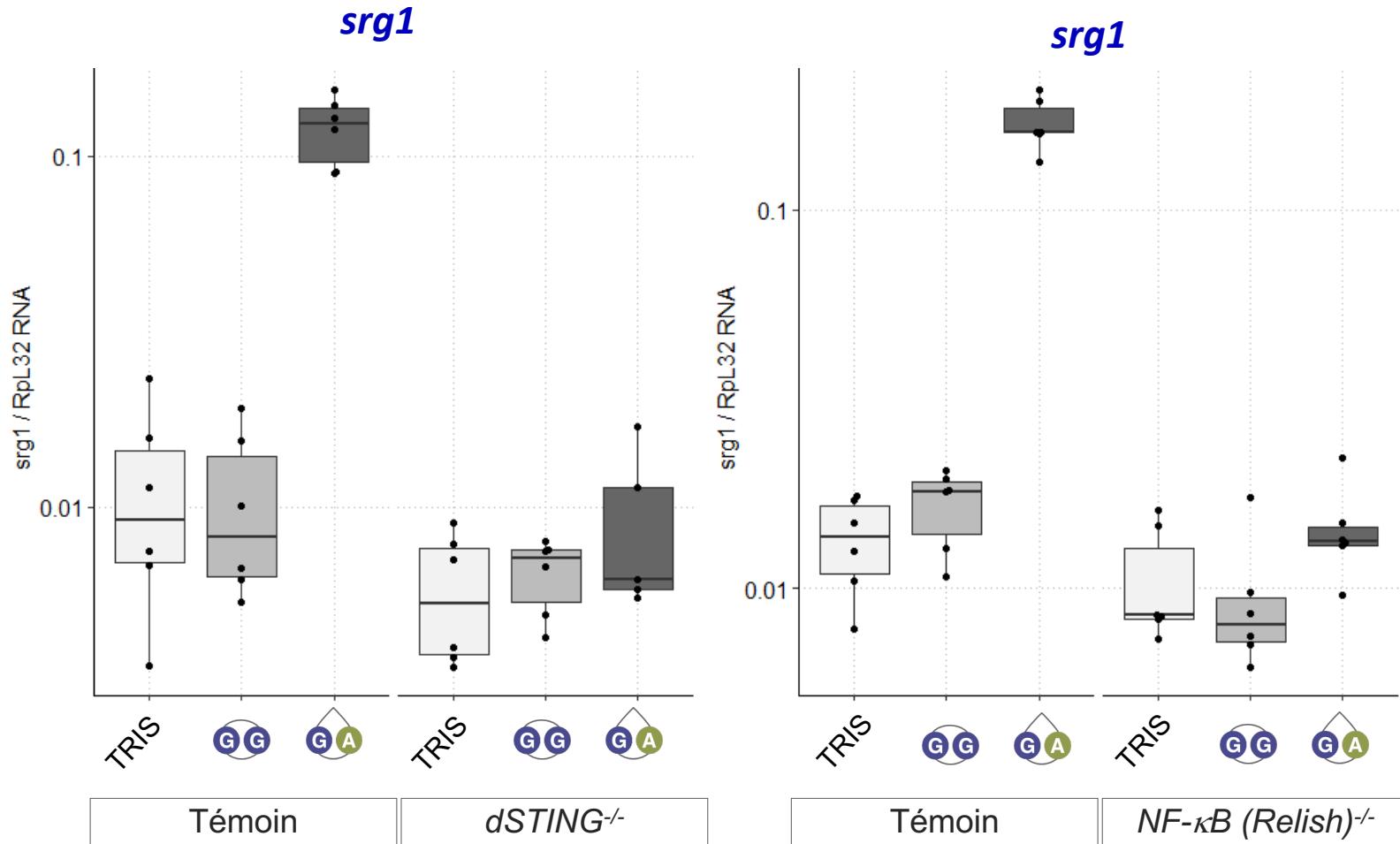
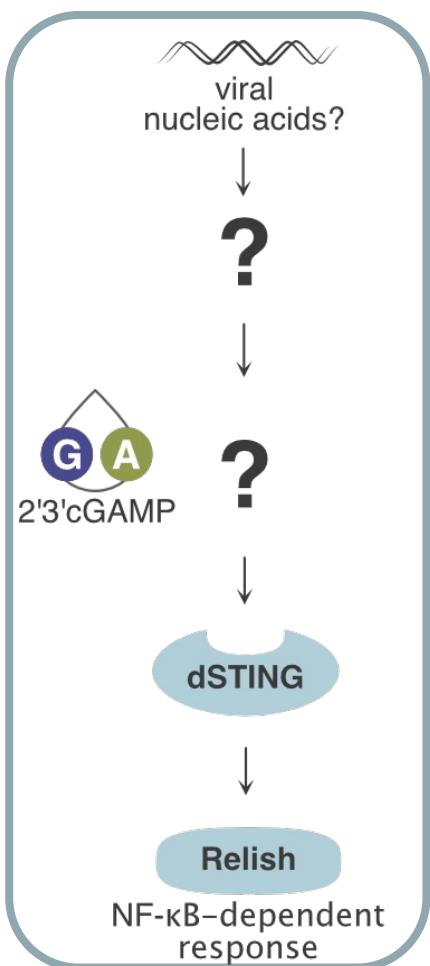
*Drosophila melanogaster*



# 2'3'-cGAMP induces a STING-NF- $\kappa$ B-dependent transcriptional response



Drosophila melanogaster



# 2'3'-cGAMP injection triggers a broad antiviral protection



*Drosophila melanogaster*

viral  
nucleic acids?



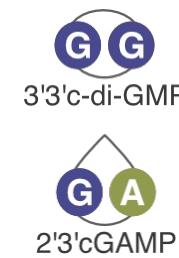
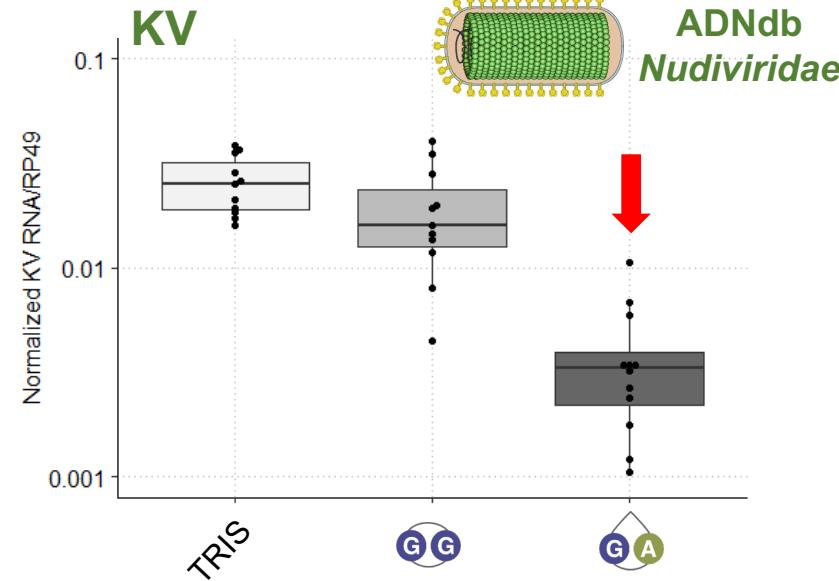
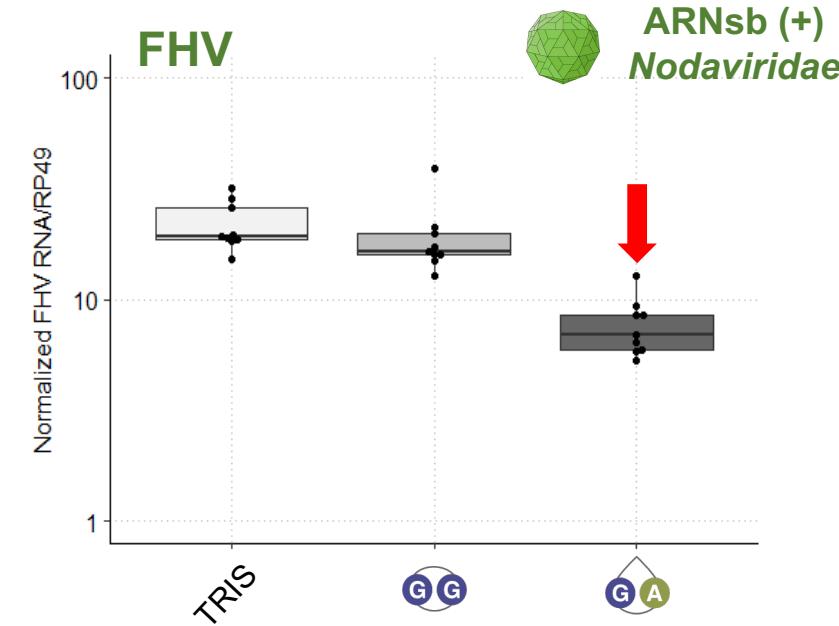
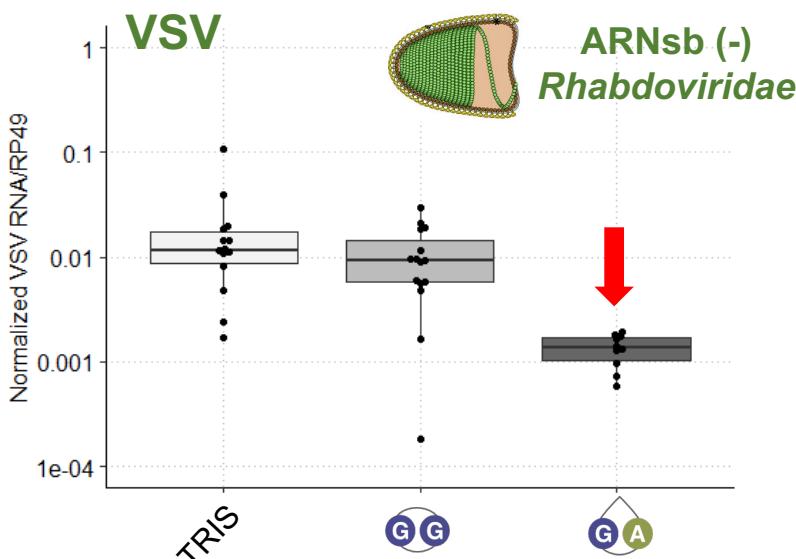
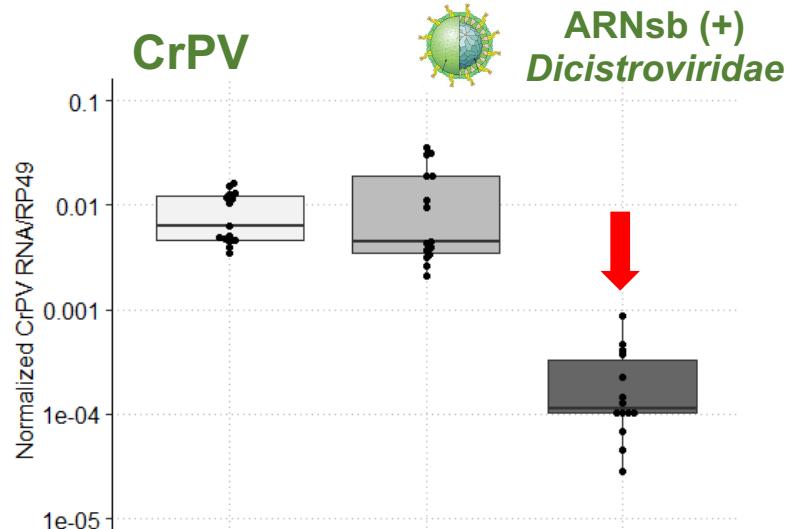
2'3'cGAMP



dSTING



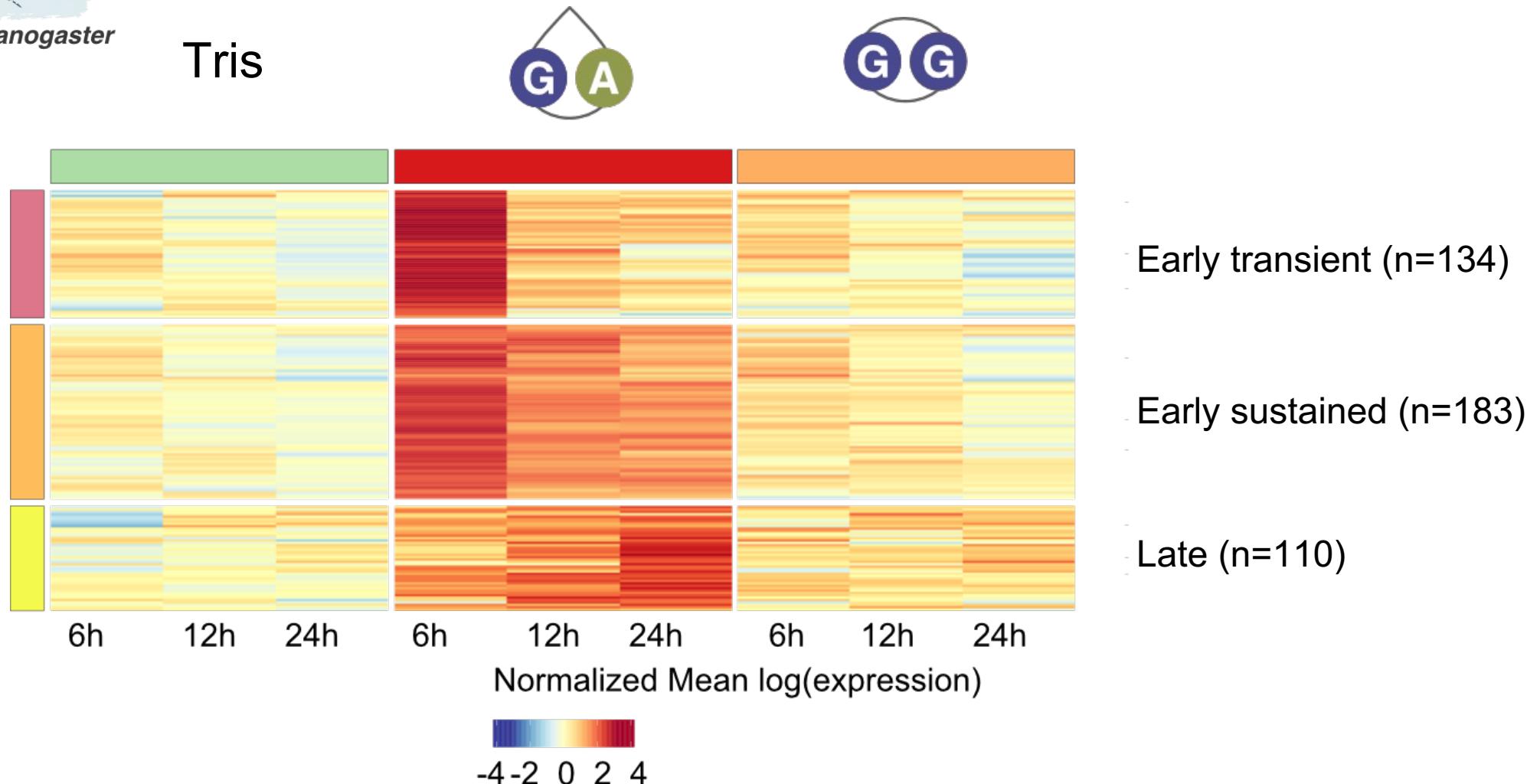
NF- $\kappa$ B-dependent  
response



# Phased transcriptional response to 2'3'-cGAMP injection



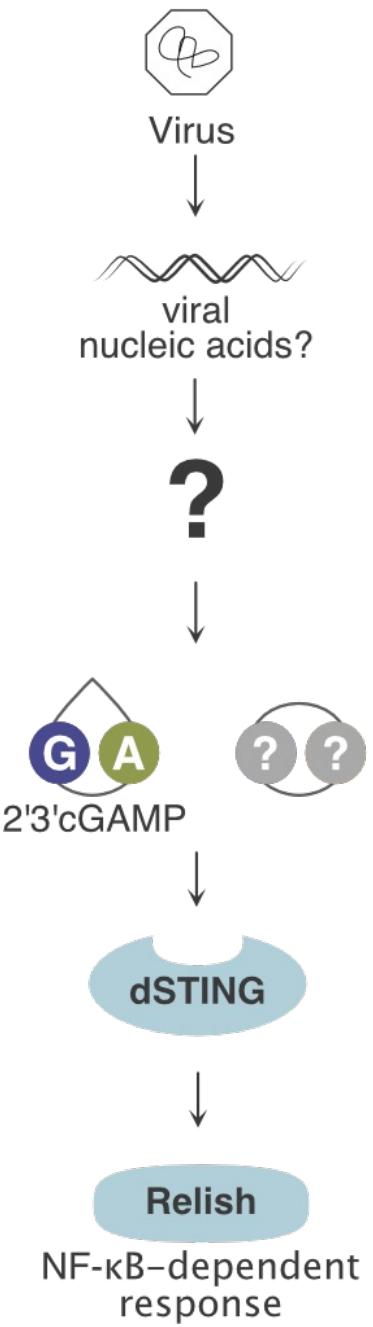
*Drosophila melanogaster*



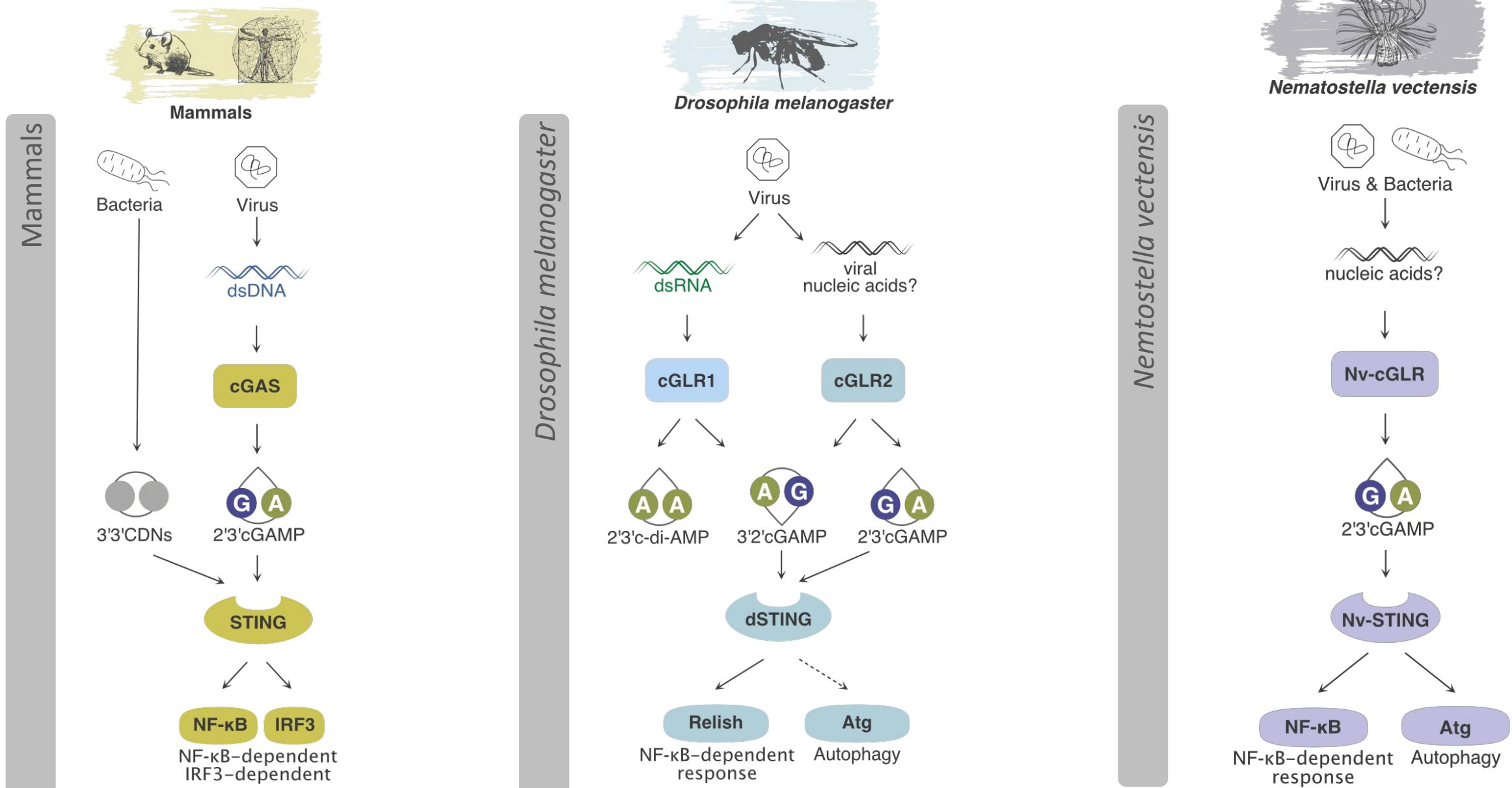


*Drosophila melanogaster*

# How is dSTING activated upon viral infection in flies?



# cGAS-like receptors trigger STING-dependent antiviral immunity in flies

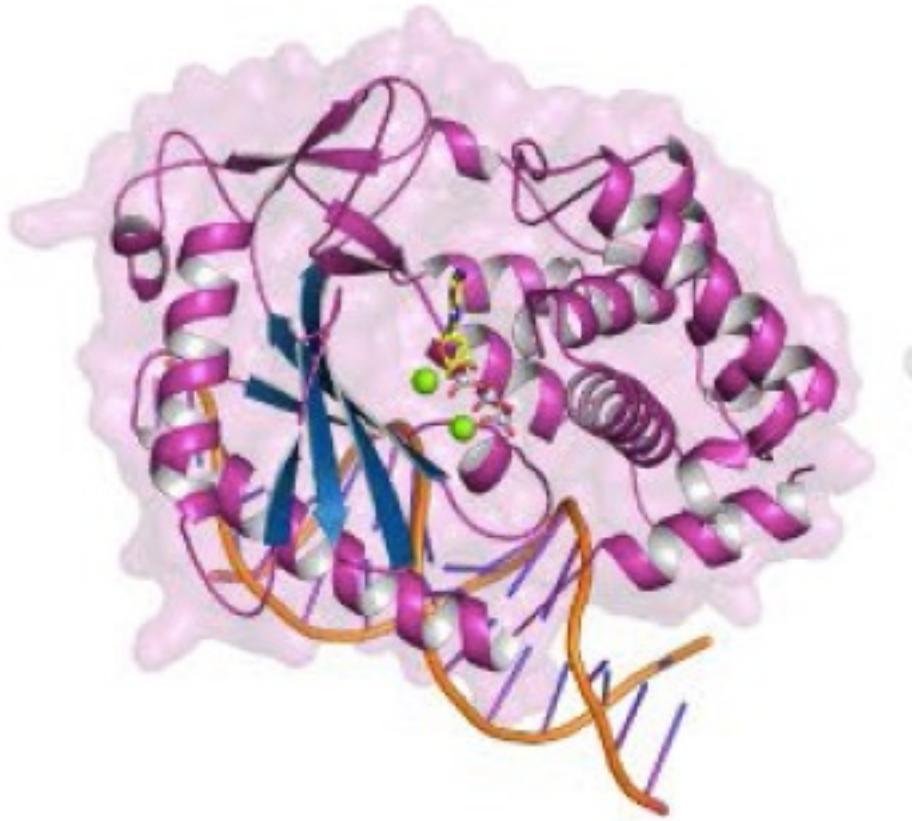


Slavik *et al* (2021), Holleufer *et al* (2021), Nature

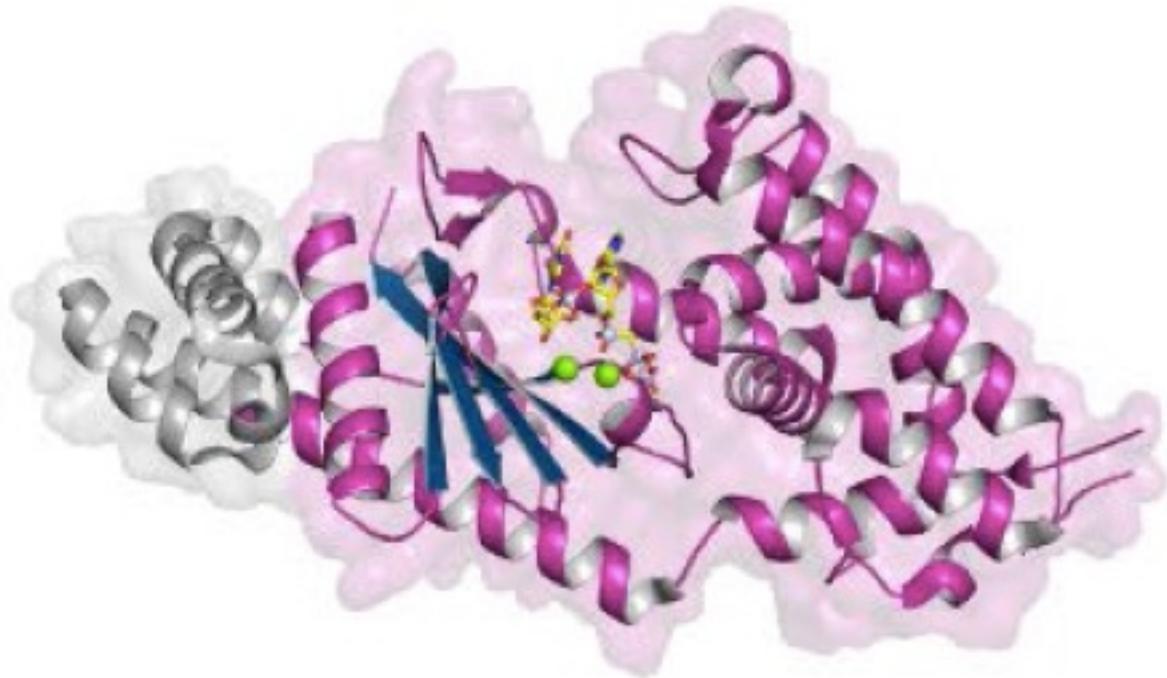
Margolis *et al* (2021), PNAS

# The cGAS/DncV-like nucleotidyl transferase (CD-Ntase) family

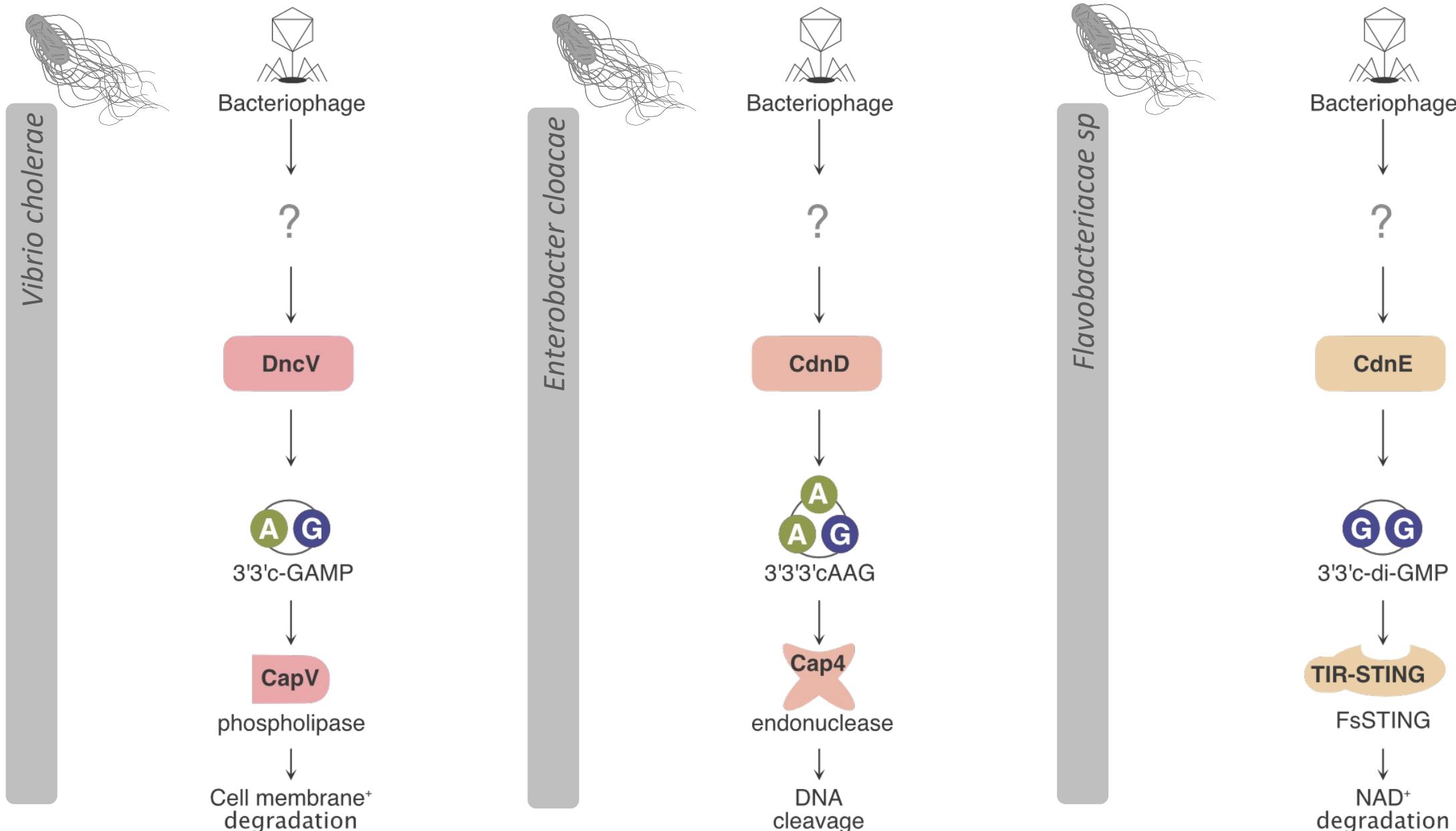
cGAS



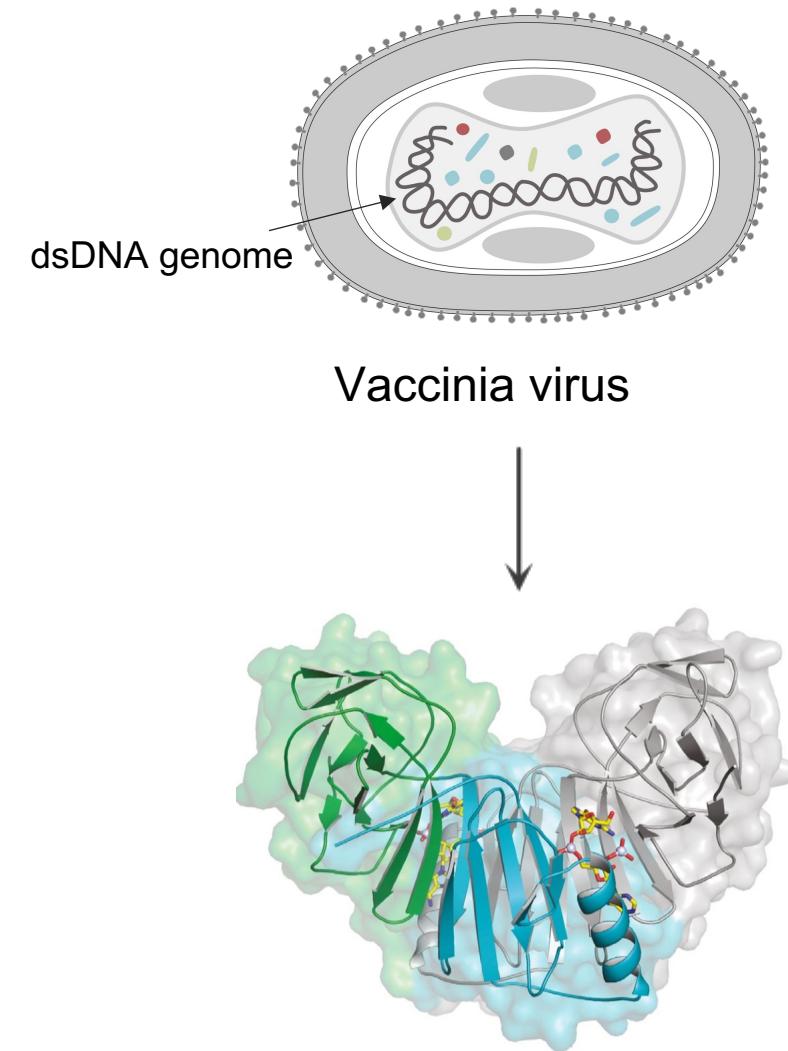
DncV  
(*V. cholerae*)



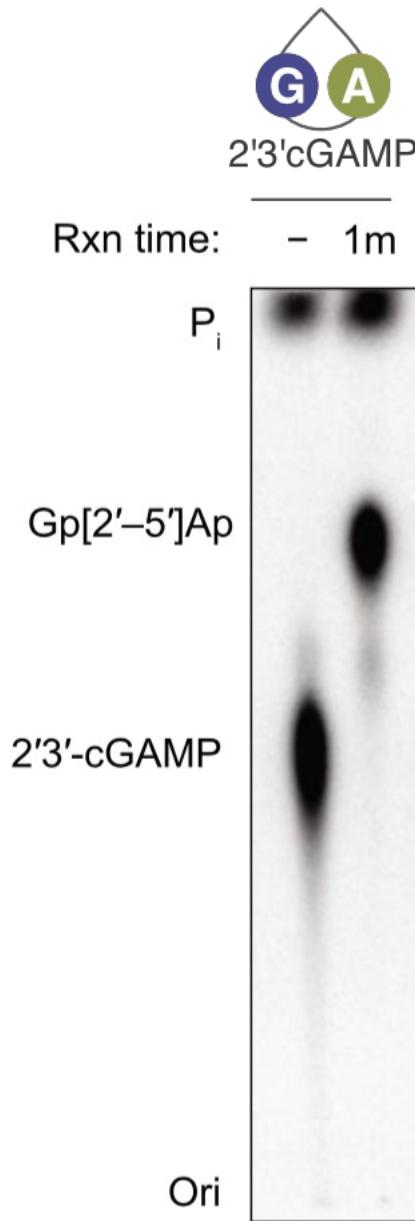
# Antiviral immunity across kingdoms: the CBASS system in bacteria



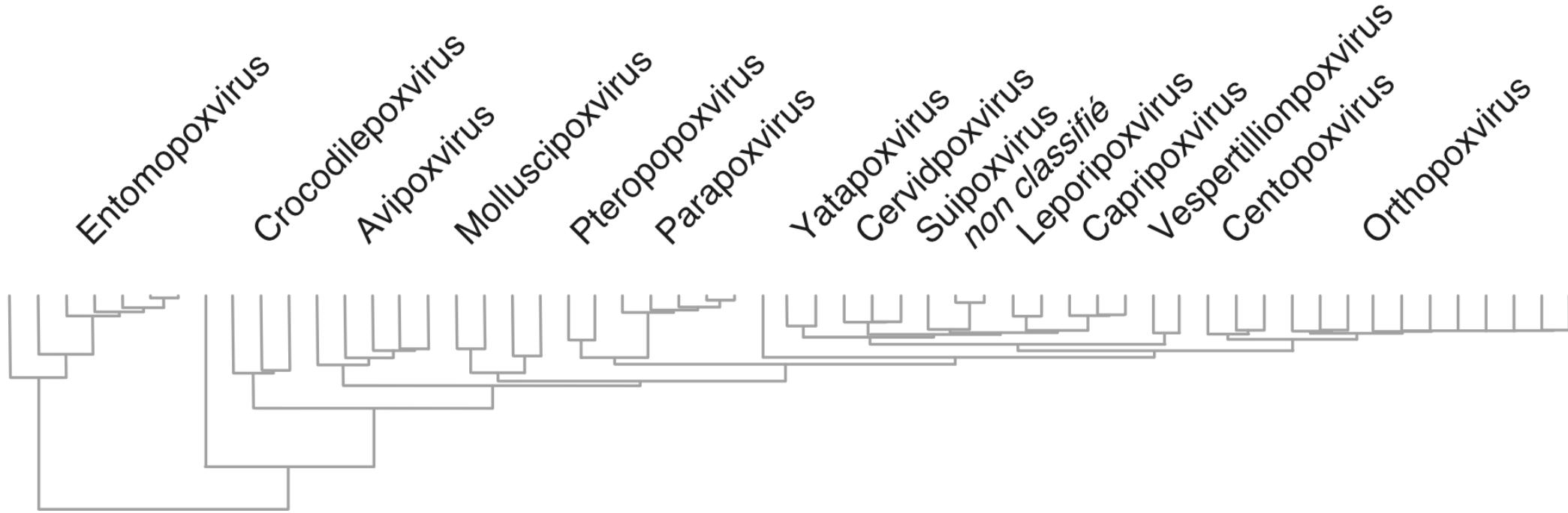
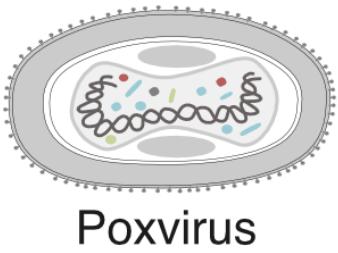
# Poxins: a family of nucleases cleaving 2'3'-cGAMP



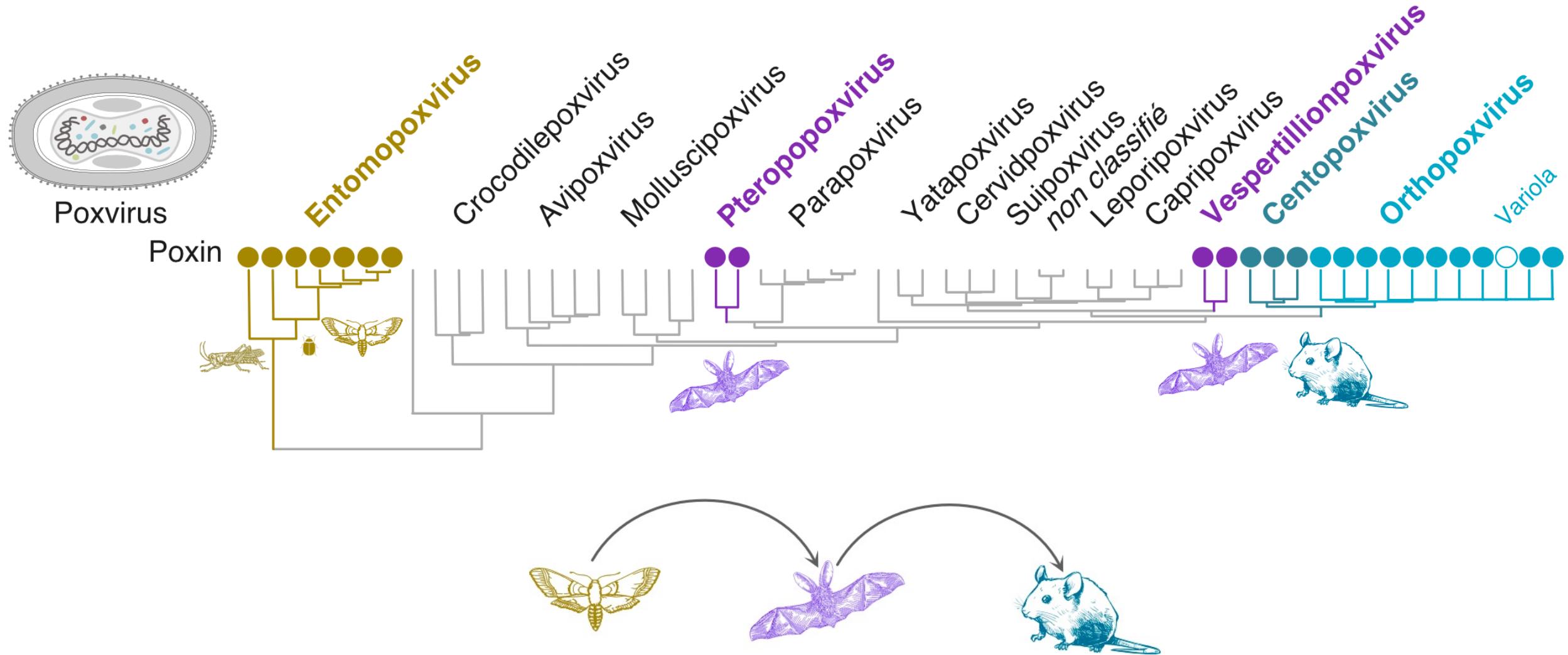
VACV Poxin



# Origin and evolution of poxins



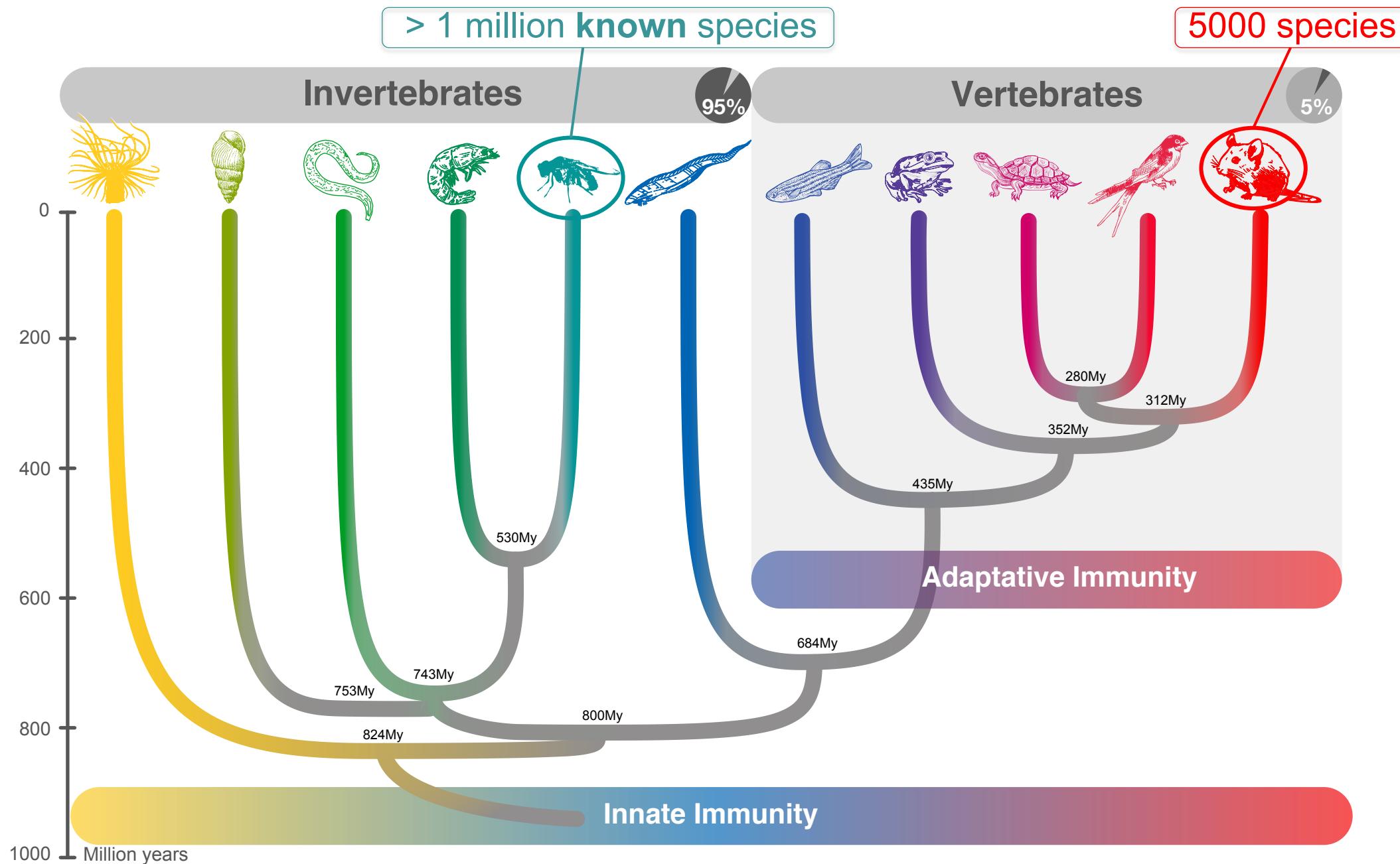
# Origin and evolution of poxins



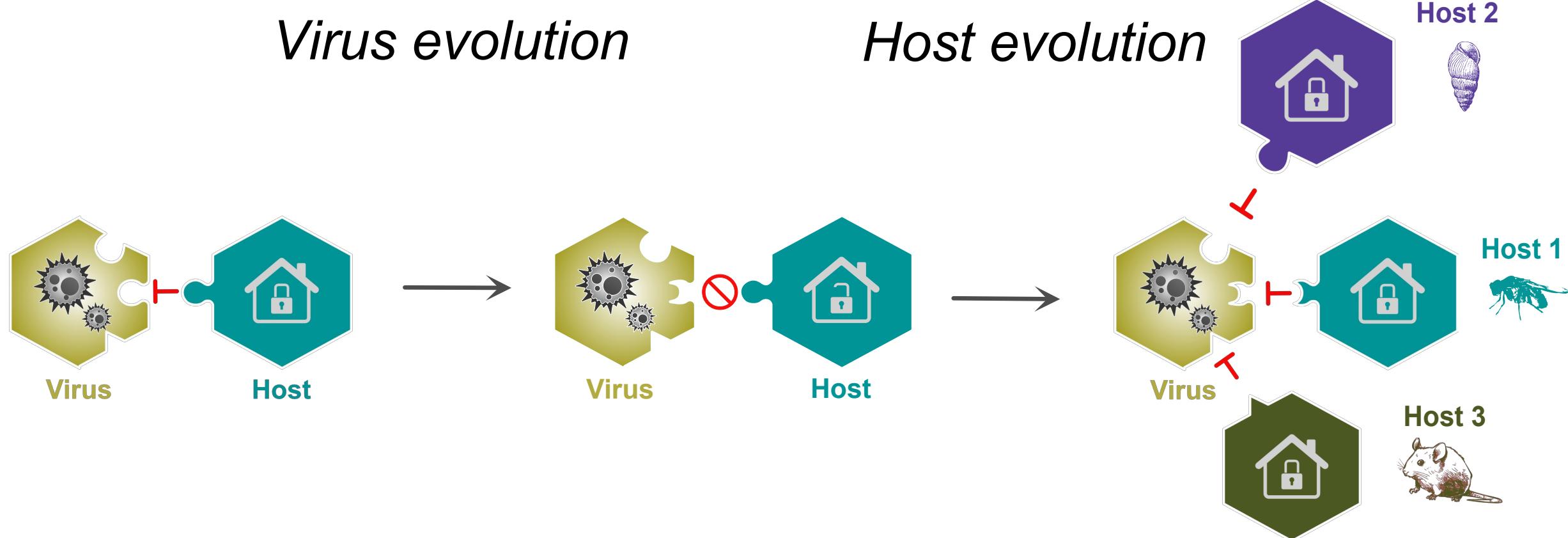


**What are the antiviral genes regulated by  
STING/IKK $\beta$  in flies?**

# The portfolio of antiviral defenses in animals

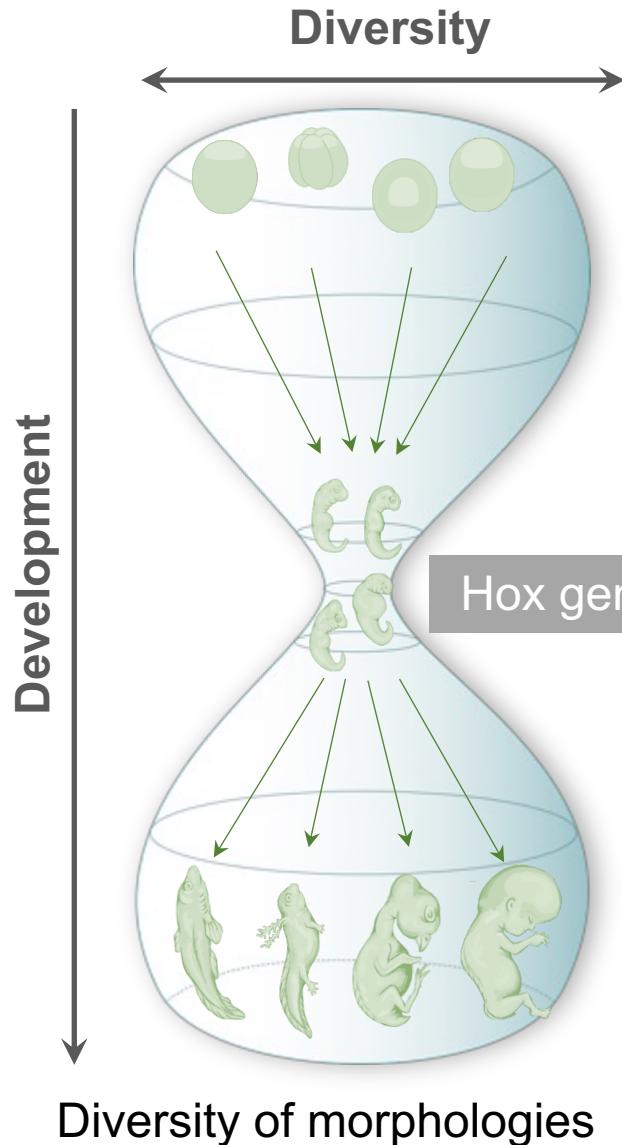


# On the interest of studying non-conserved genes

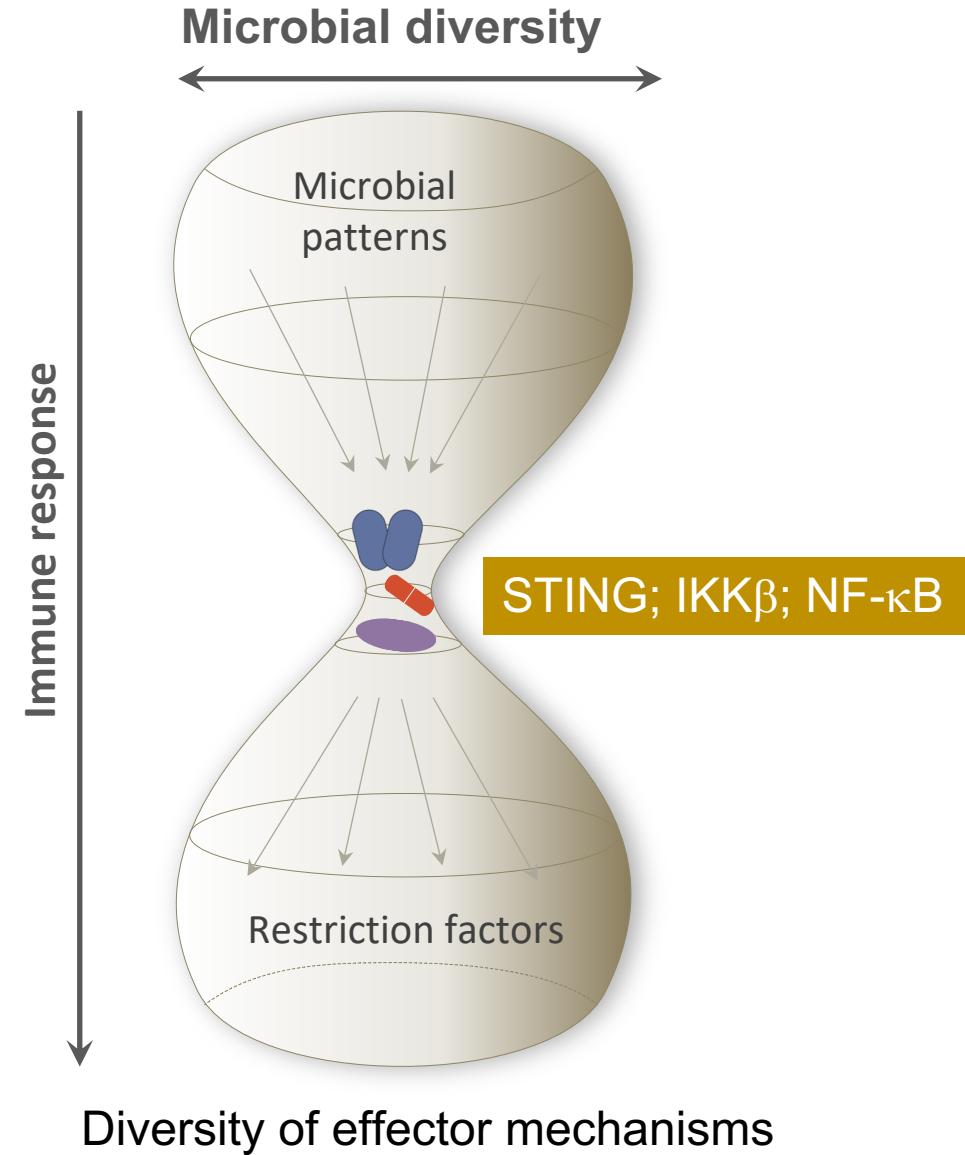


# The evo-immuno concept

## The hourglass model of development



## An hourglass model of immunity



# Acknowledgements



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广州霍夫曼免疫研究所  
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Lin Xiaoqing



Rune Hartmann  
Andreas Holleufner  
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Philip Kranzusch

