THE GUT-BRAIN AXIS, METABOLISM & LONGEVITY

or, what a tiny nematode can tell us about biology and medicine

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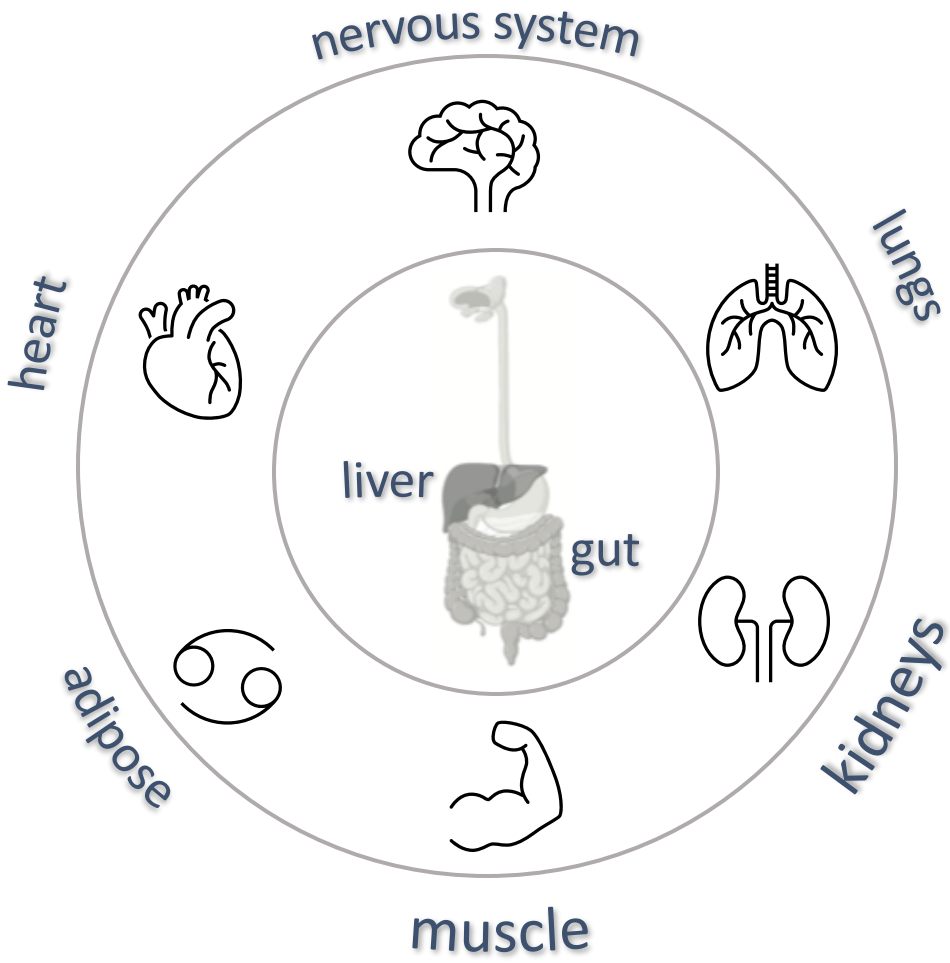
Organs & cells within the body communicate with one another



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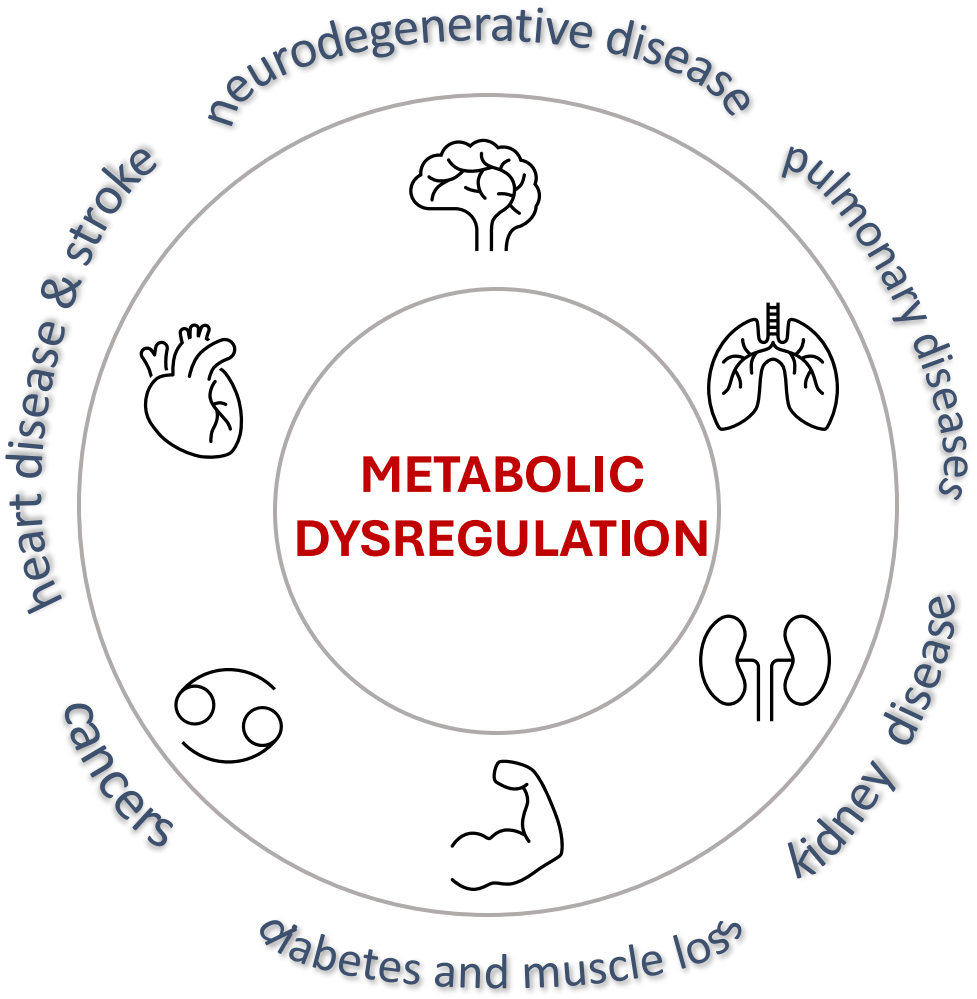
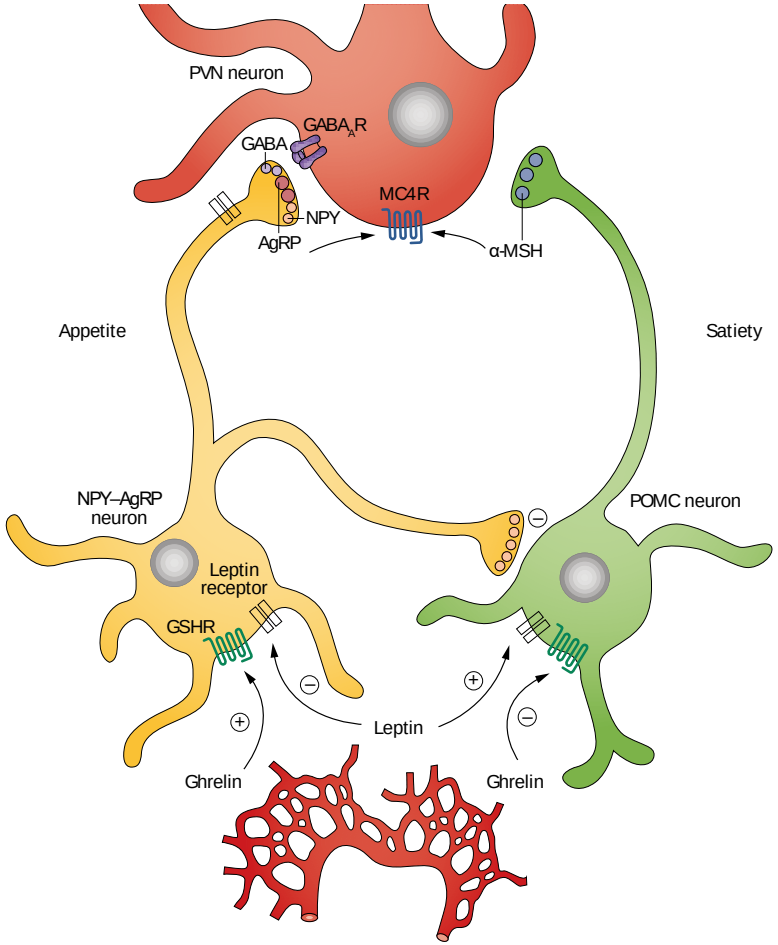
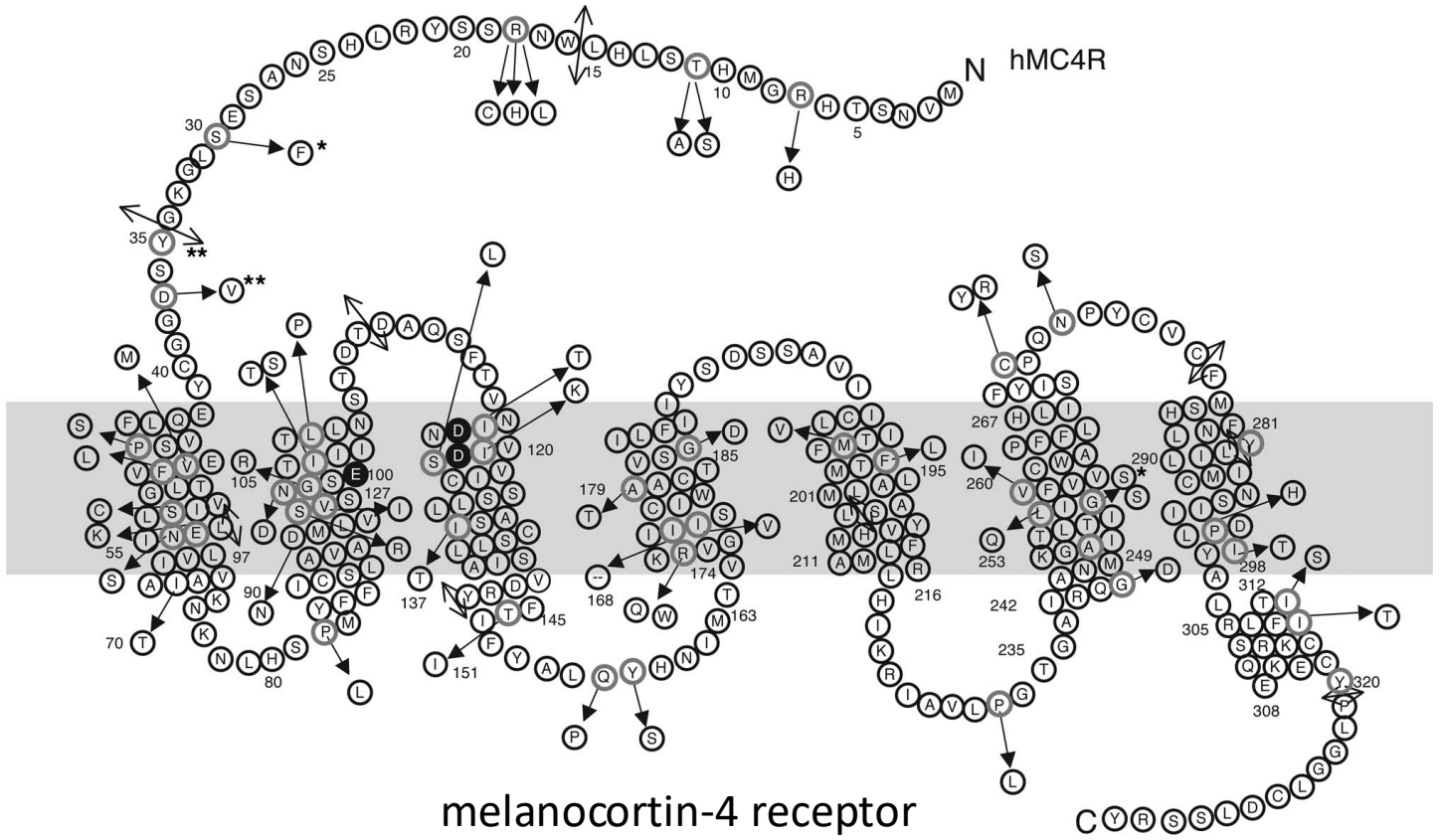


Scientific Origins and Interests

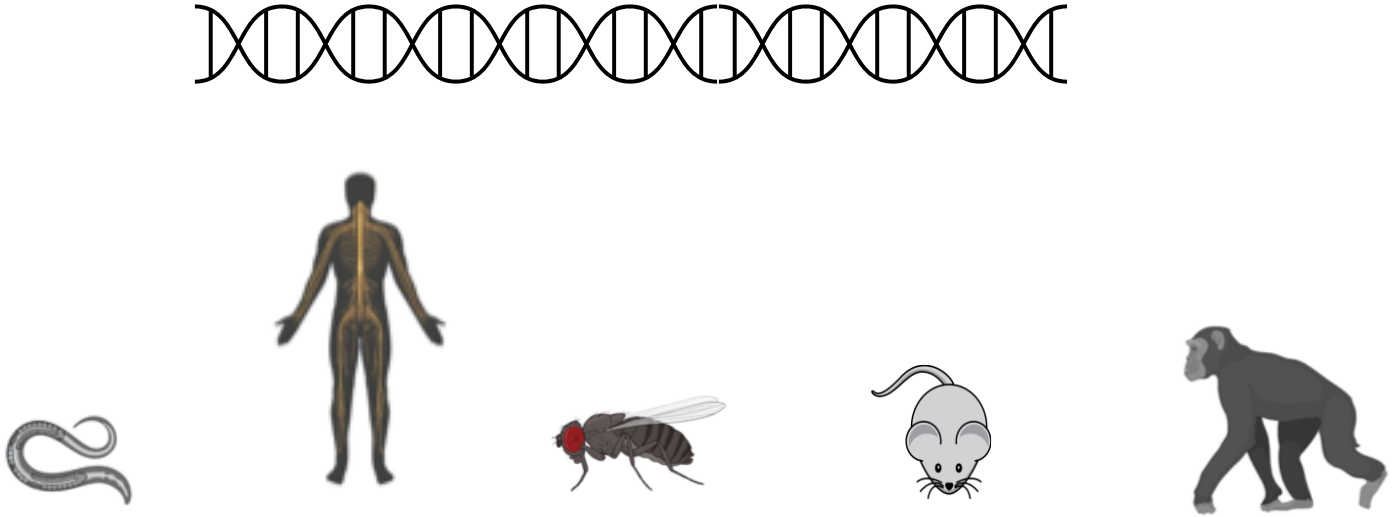


Nasrallah & Horvath, 2014



Srinivasan et al., 2004

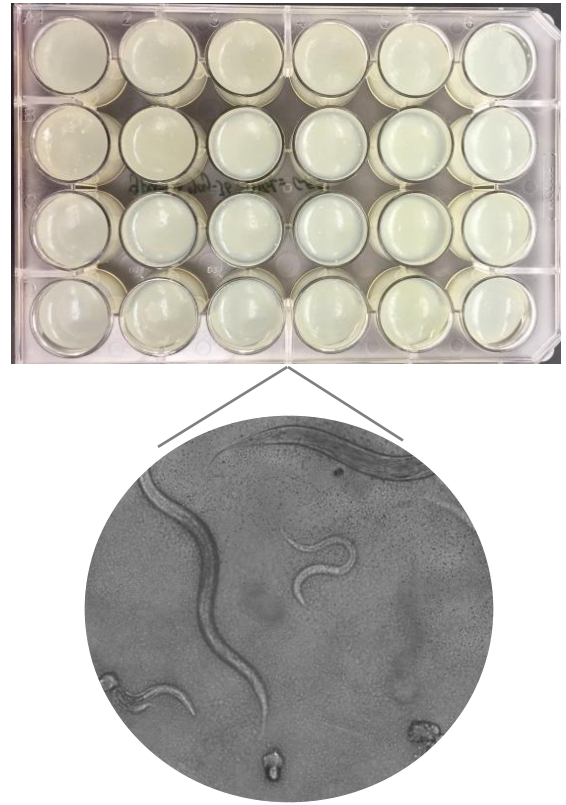
Genomic Revolution 2000s - date



Shared genes and genetic ancestry between species!

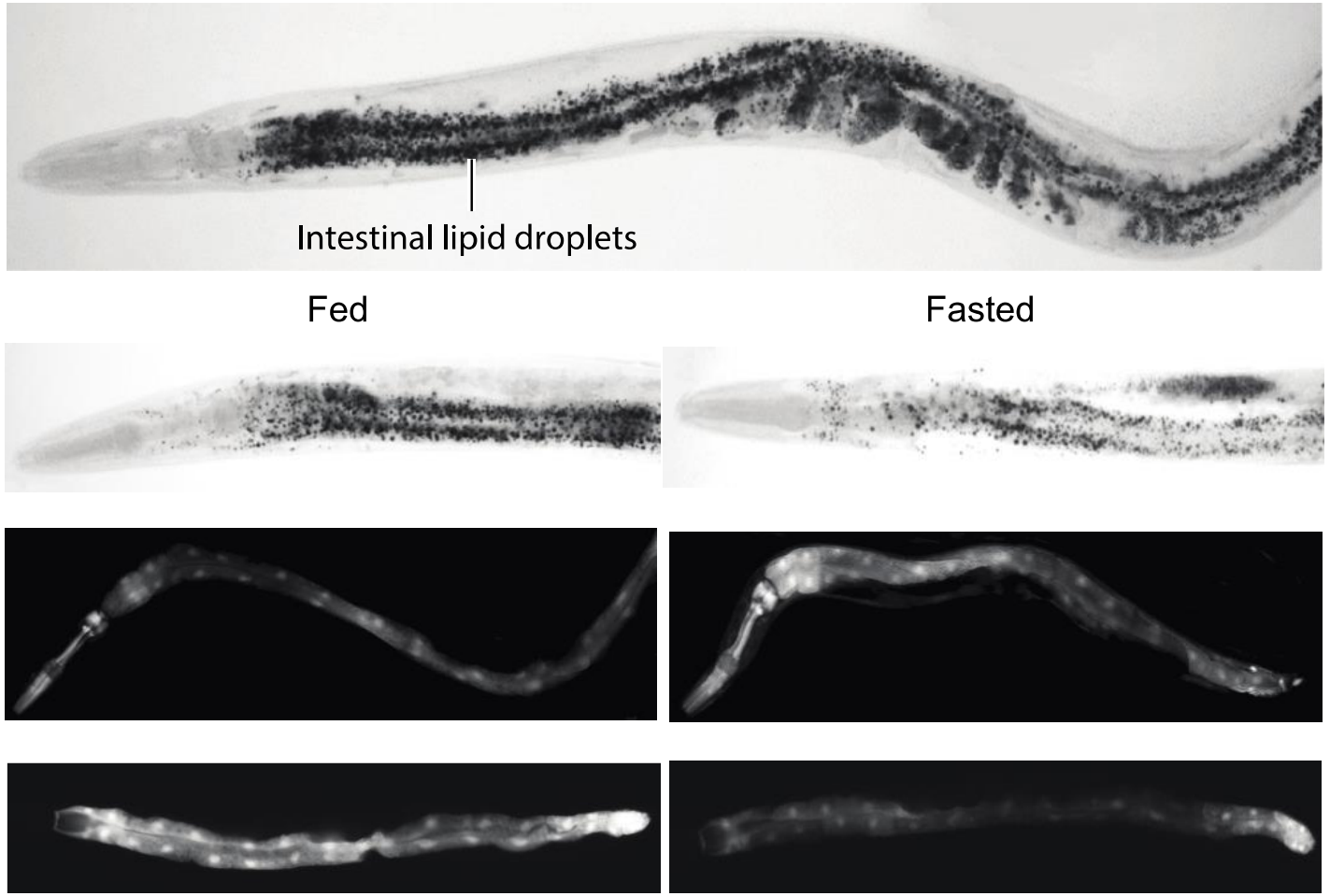
Uncovering new aspects of the gut-brain axis, at scale

Caenorhabditis elegans

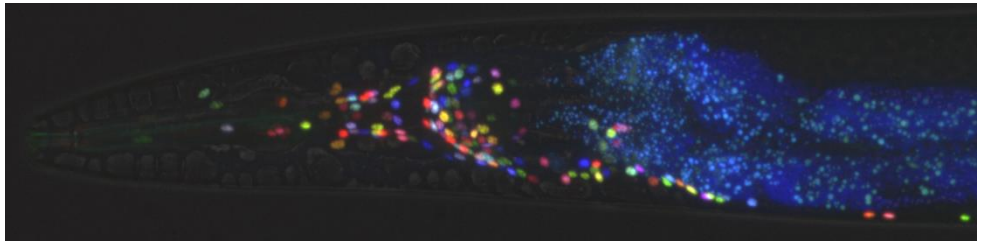


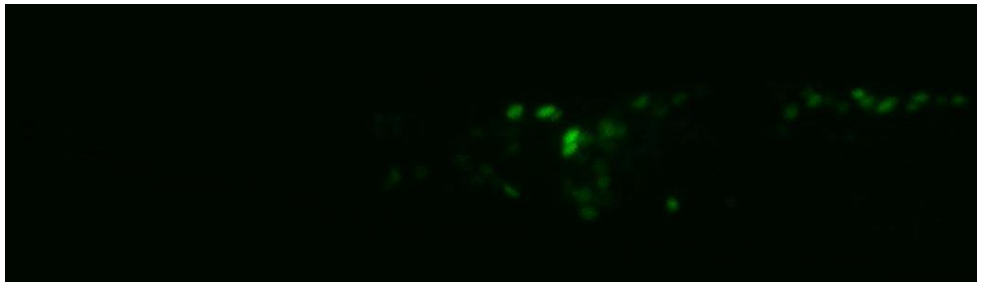
- ❖ Similar genomes, powerful genetic and molecular tools
- ❖ Speed – life cycle, lifespan, size
- ❖ Scale – genes x drugs x phenotype in living animals

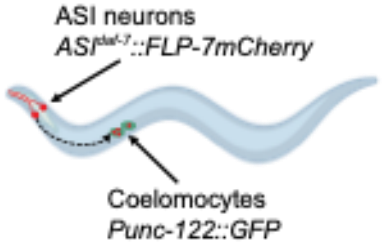
Uncovering new aspects of the gut-brain axis, at scale

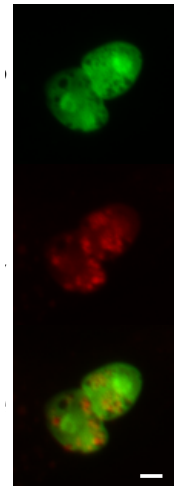


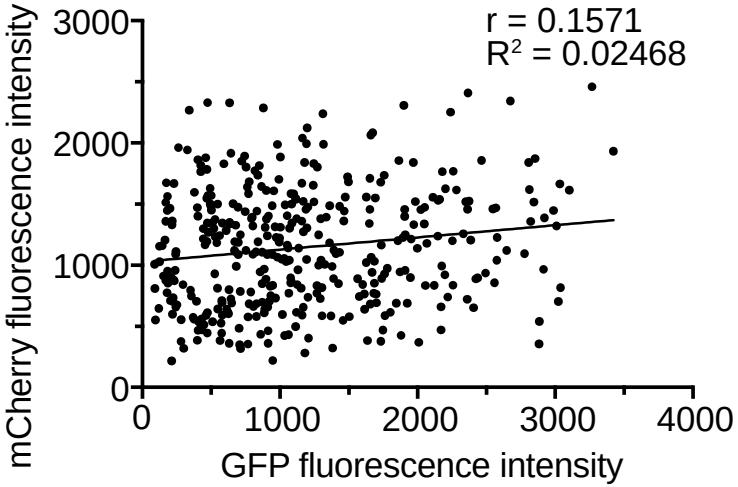
Uncovering new aspects of the gut-brain axis, at scale









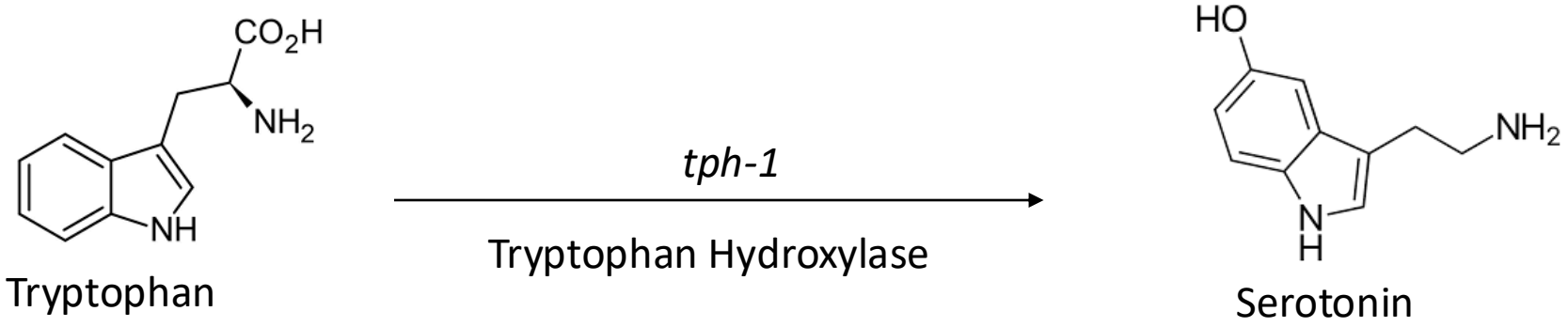


THE GUT-BRAIN AXIS, METABOLISM & LONGEVITY

or, what a tiny nematode can tell us about biology and medicine

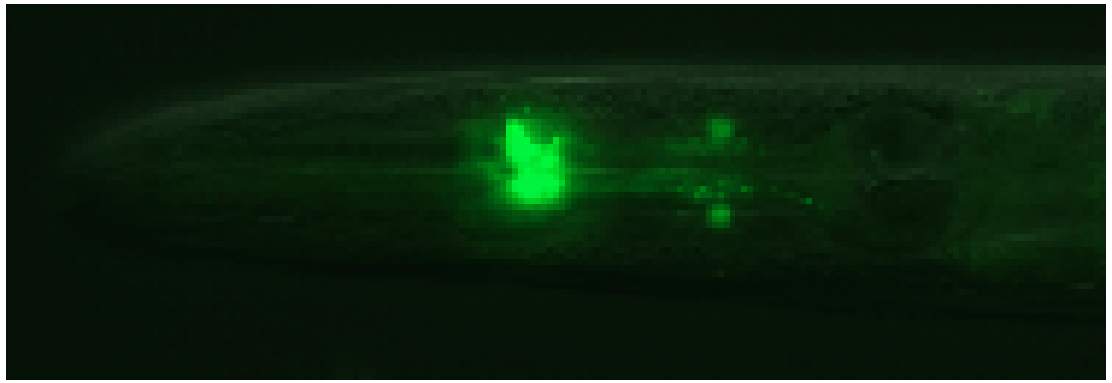
- The neurotransmitter serotonin is a principal driver of fat loss
- Discovery of a brain-to-gut messenger: a Tachykinin peptide
- Discovery of a gut signal induced by fasting : a novel Insulin
- Translating – from basic to clinic

Serotonin is a principal driver of fat loss

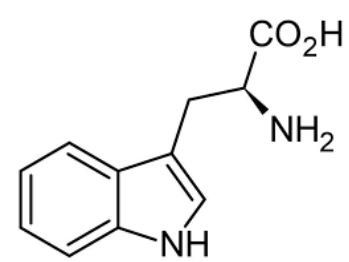


Tryptophan

Serotonin



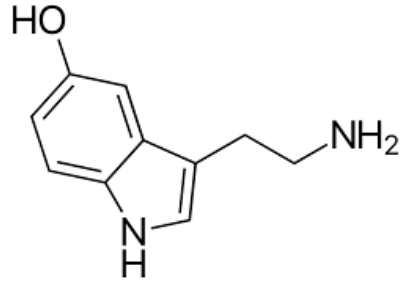
Serotonin is made in neurons



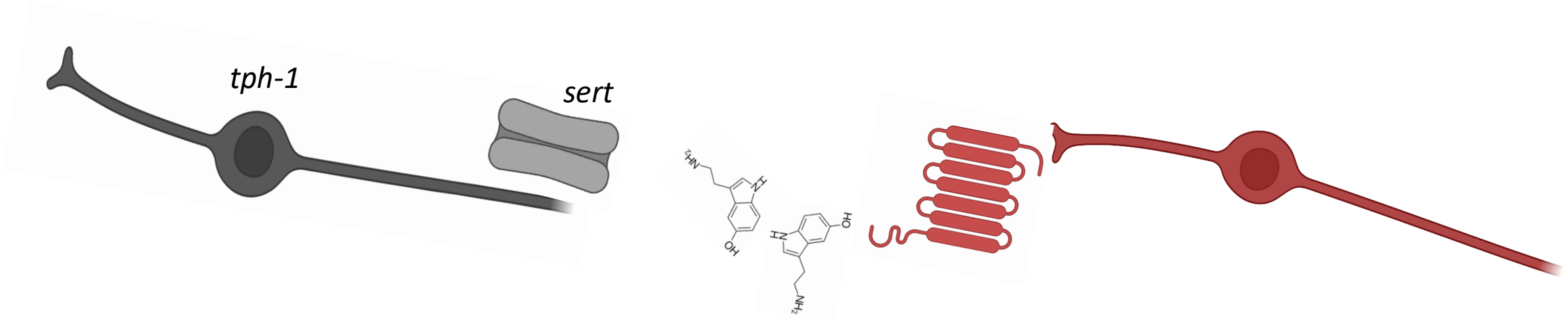
Tryptophan

tph-1

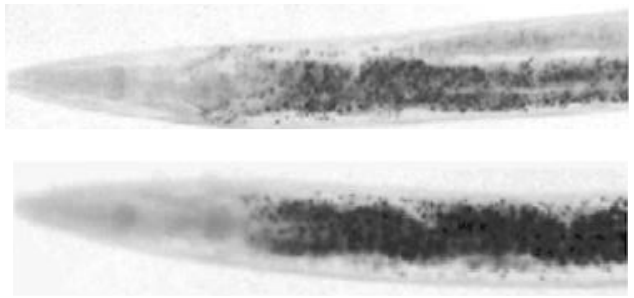
Tryptophan Hydroxylase



Serotonin

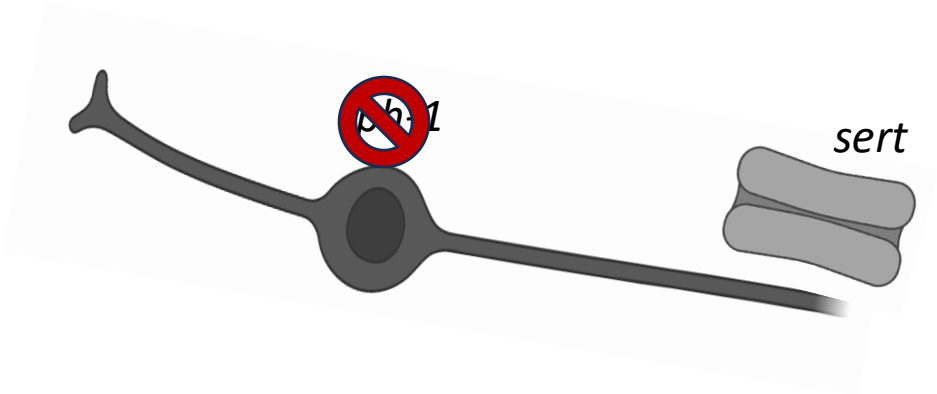


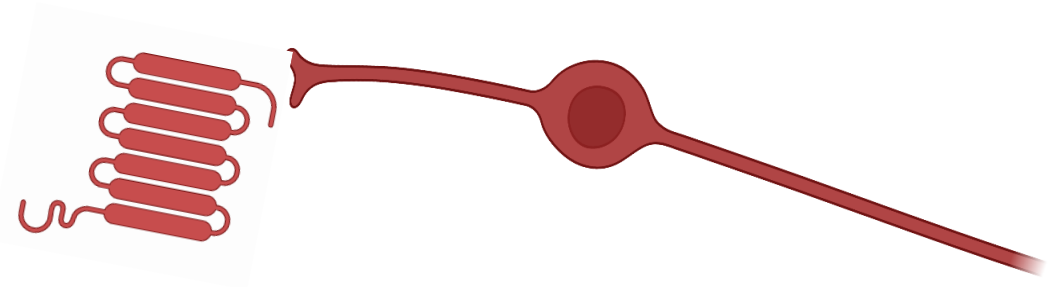
Serotonin is made in neurons and controls fat in the intestine



control

tph-1 -/-



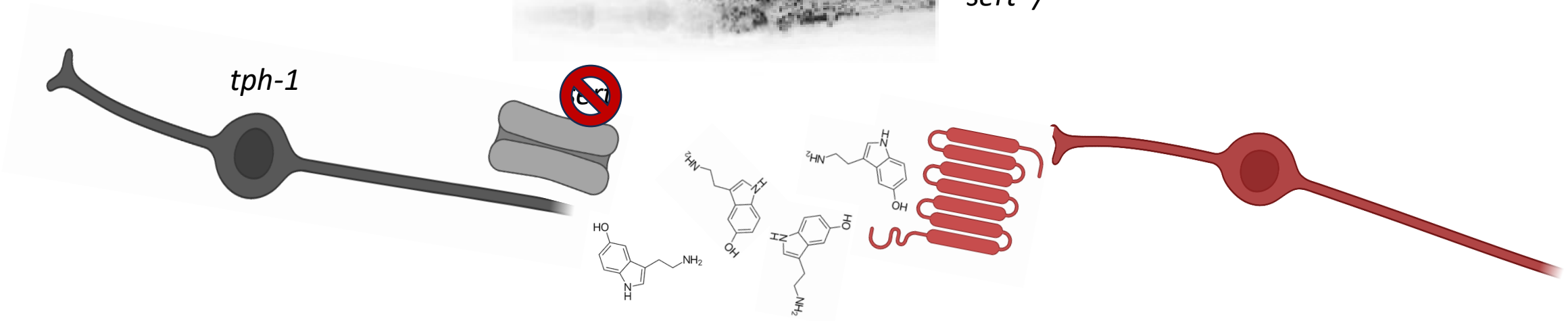


Serotonin is made in neurons and controls fat in the intestine

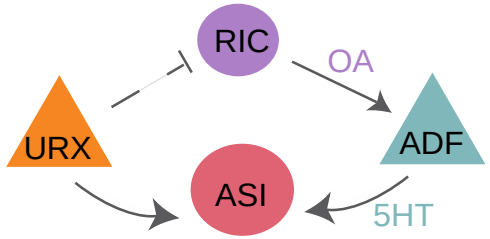
control

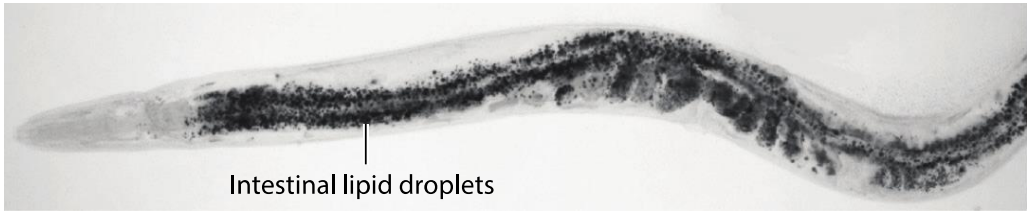
tph-1 -/-

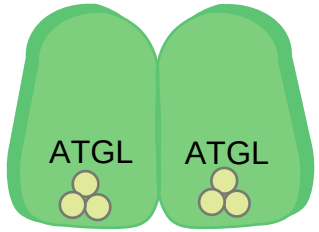
sert -/-

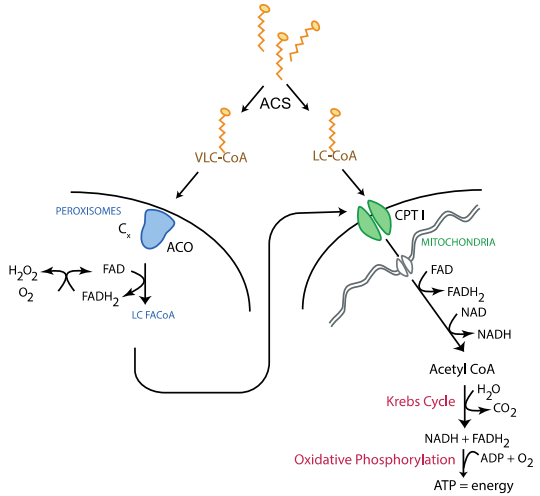


Serotonin drives fat loss by increasing energy expenditure*



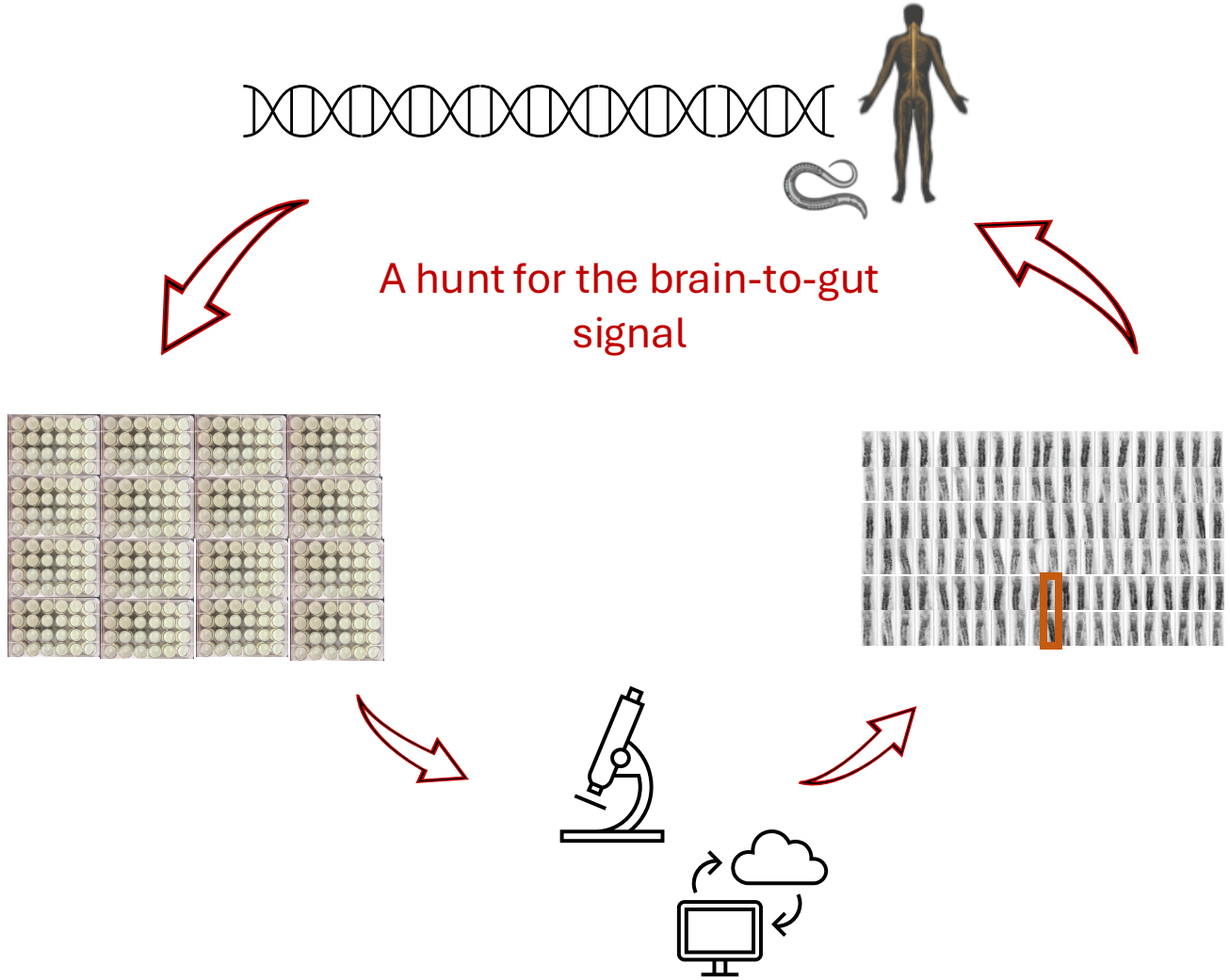




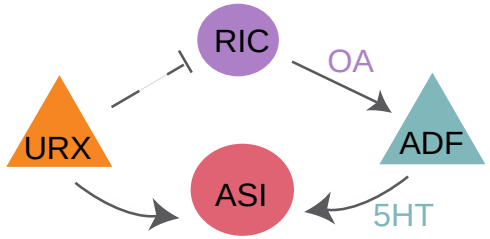


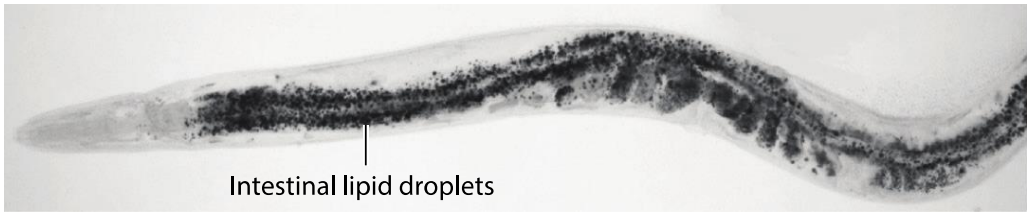
Srinivasan et al, 2008 PMID 18522834
Noble et al 2013 PMID 24120942

A genetic screen to discover the brain-to-gut signal …

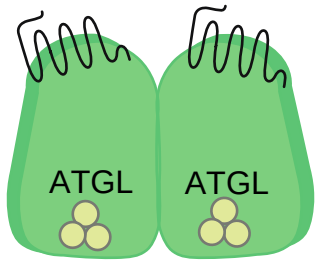


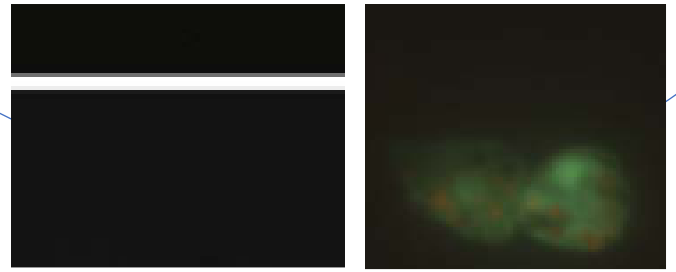
… revealed a role for a conserved Tachykinin peptide





Tachykinin Receptor NPR-22

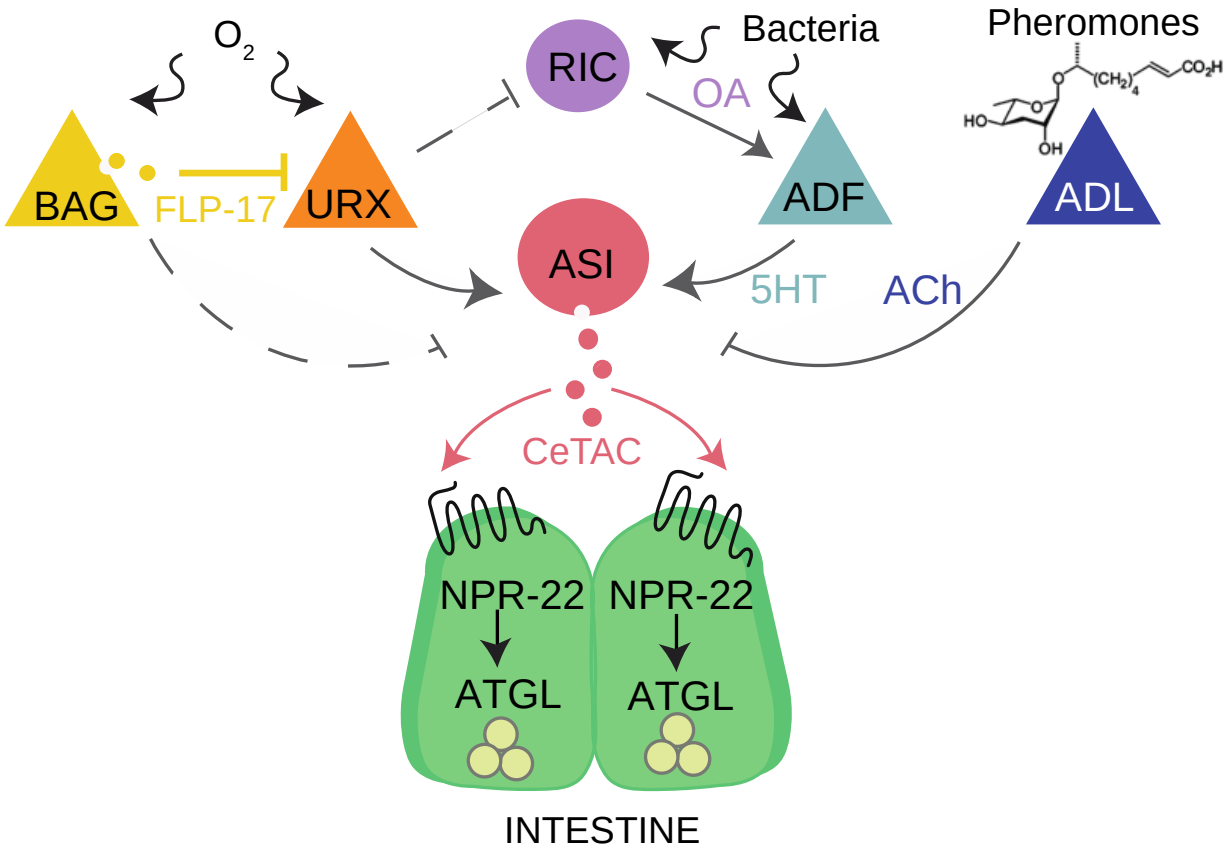




tachykinin peptide, FLP-7

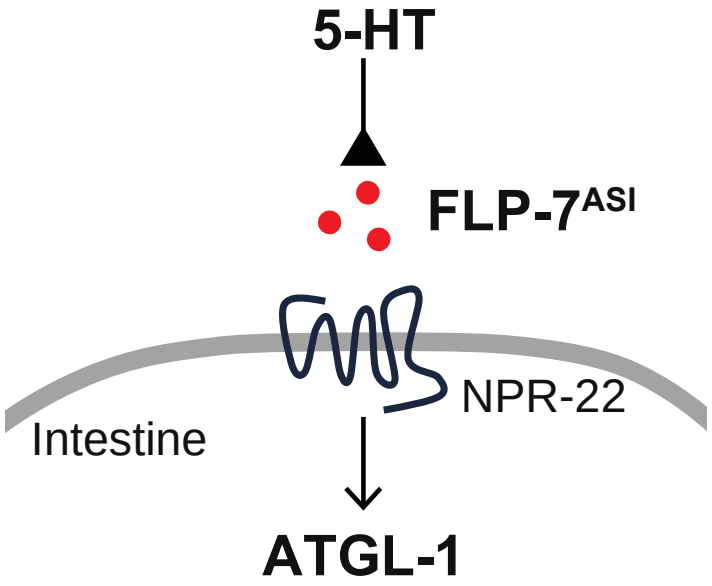
Palamiuc et al 2017 PMID 28128367

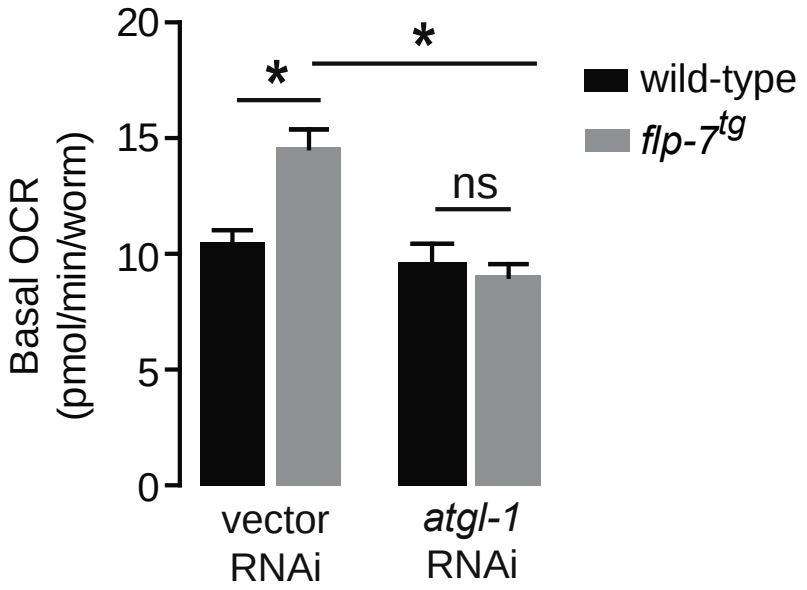
Tachykinin is the brain-to-gut signal for fat loss



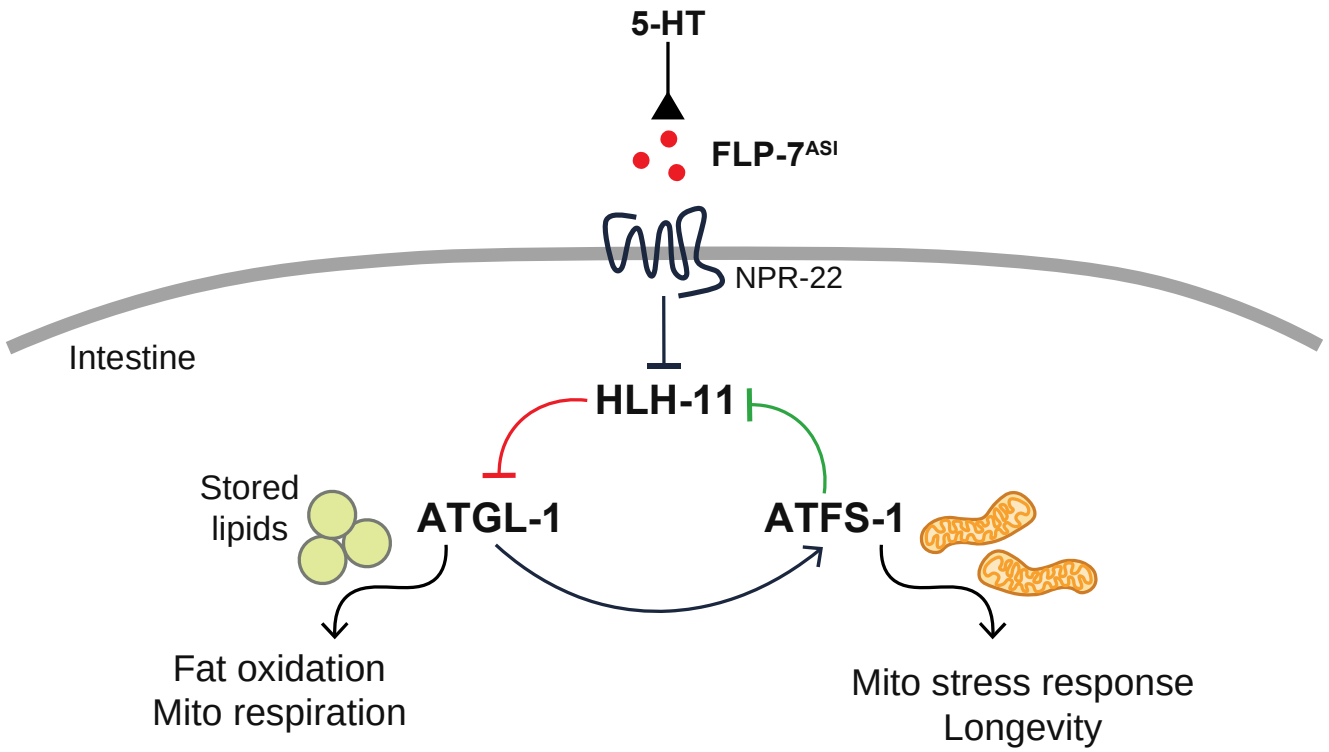
Noble et al 2013 PMID 24120942
Witham et al 2016 PMID 26876168
Hussey et al 2017 PMID 28545126
Palamiuc et al 2017 PMID 28128367
Hussey et al 2018 PMID 29579048

Tachykinin is the brain-to-gut signal for fat loss and increases energy expenditure*





Tachykinin signaling coordinates metabolism and longevity



Littlejohn et al, 2020 PMID 33078707

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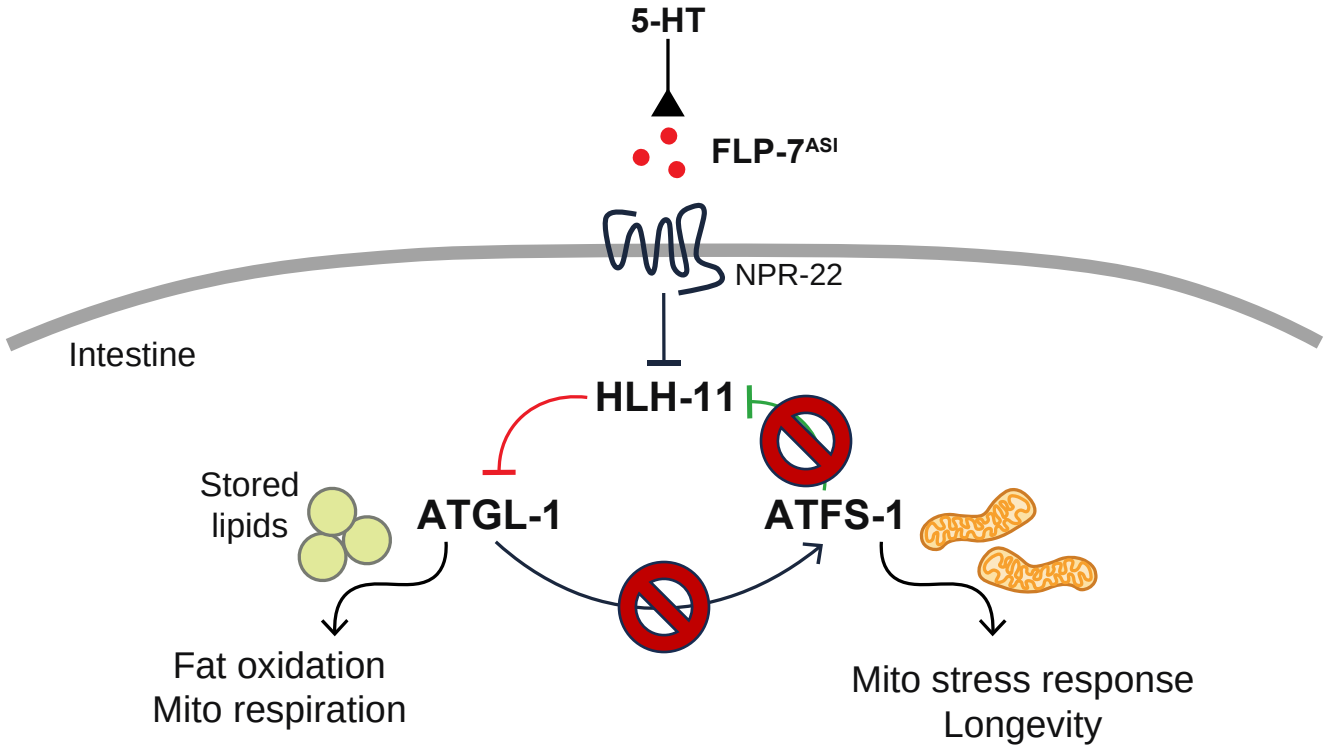

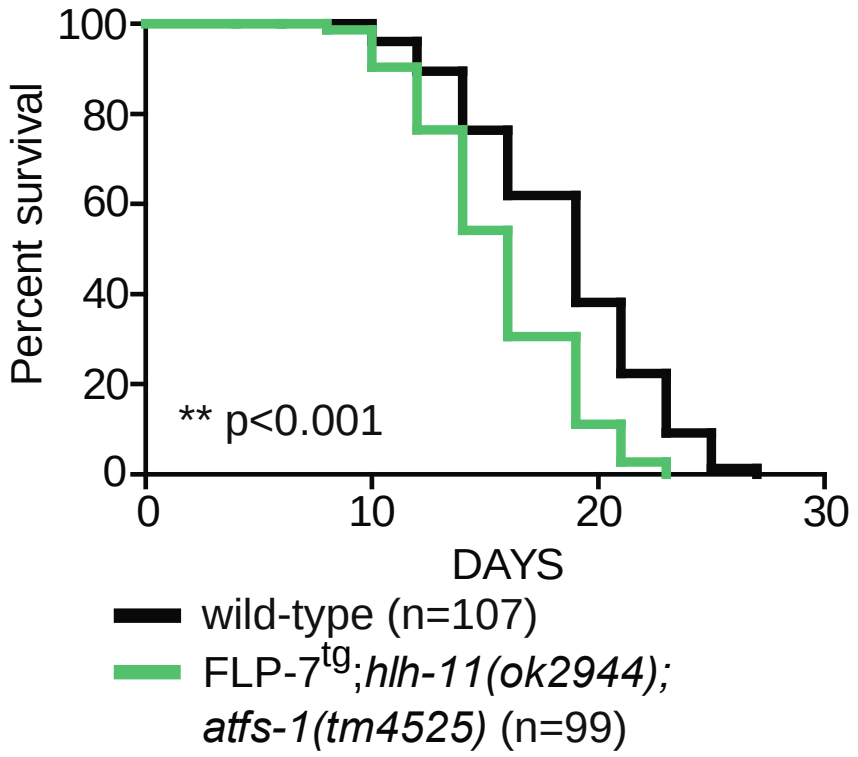

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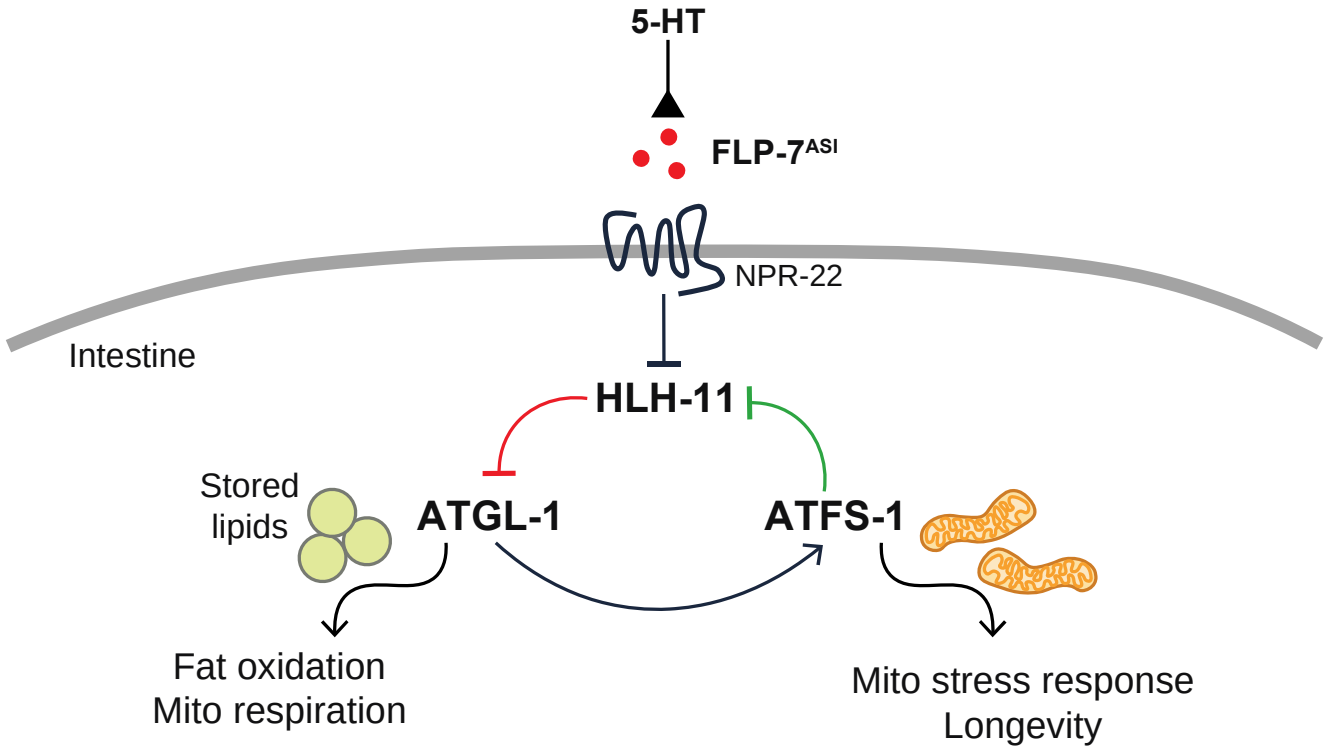

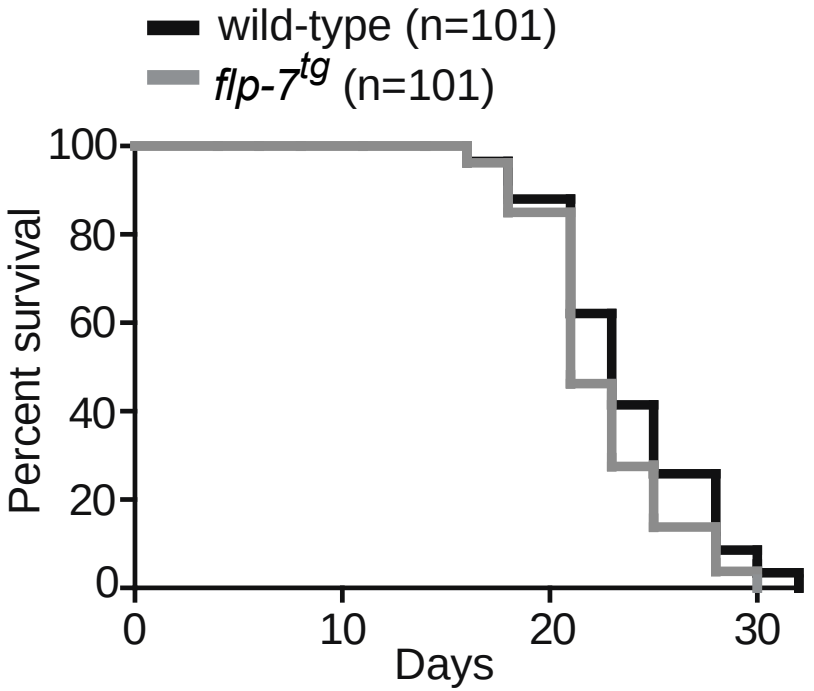

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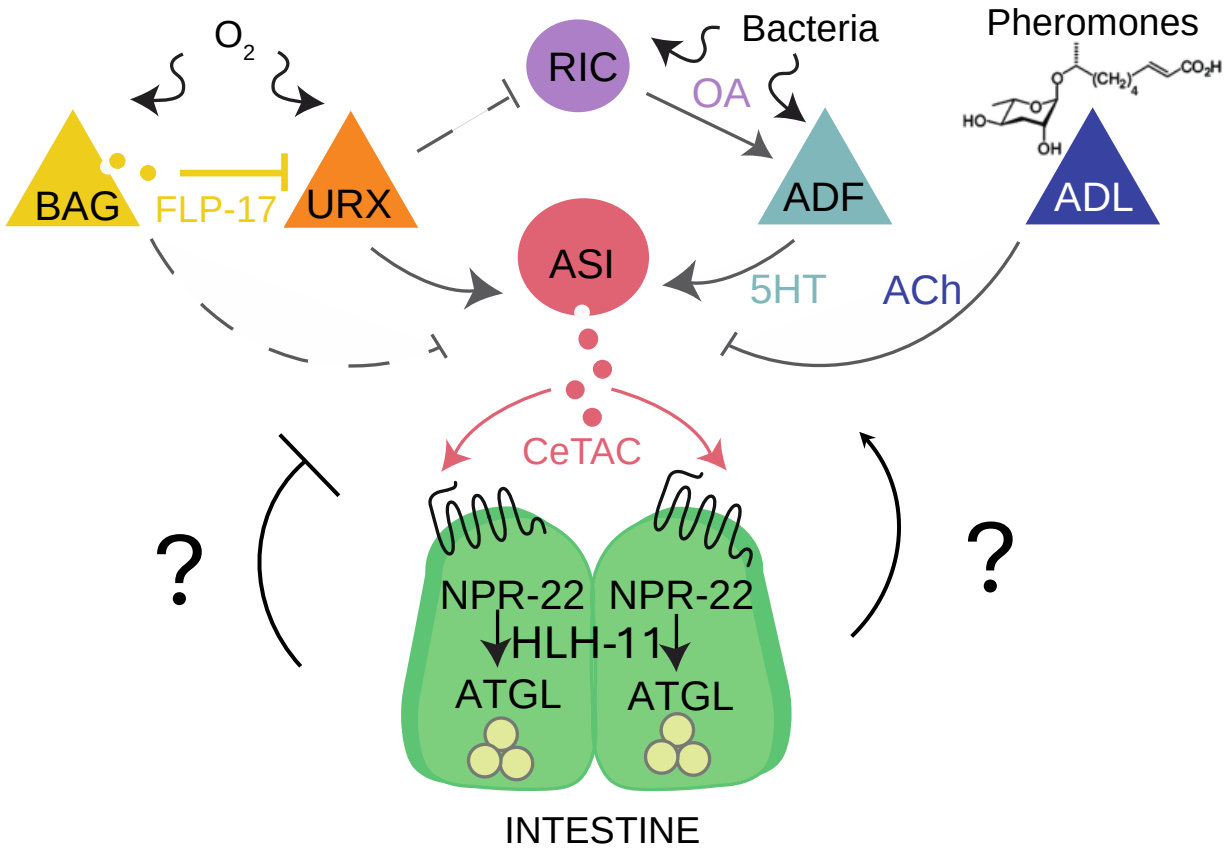
Discovery of a gut signal



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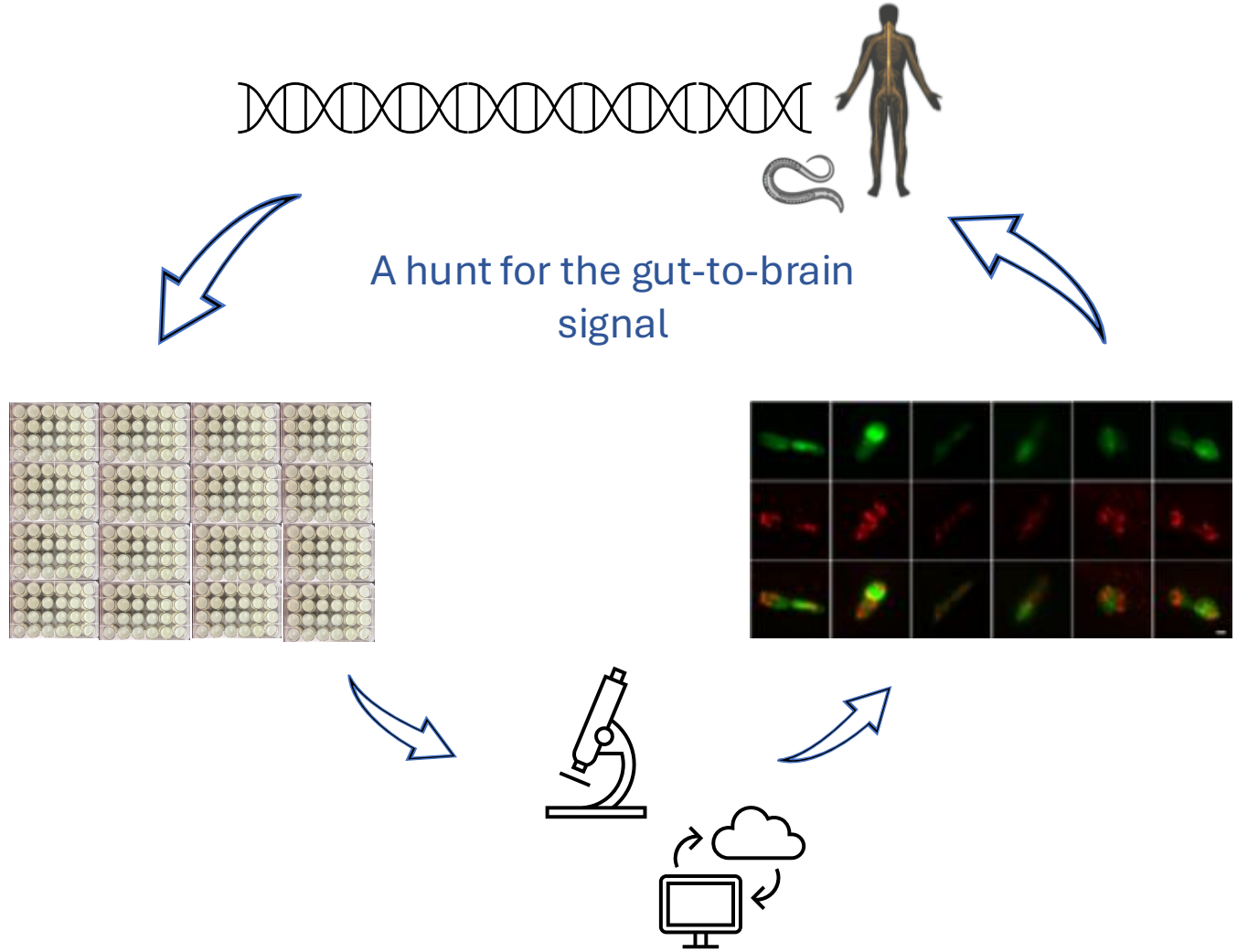
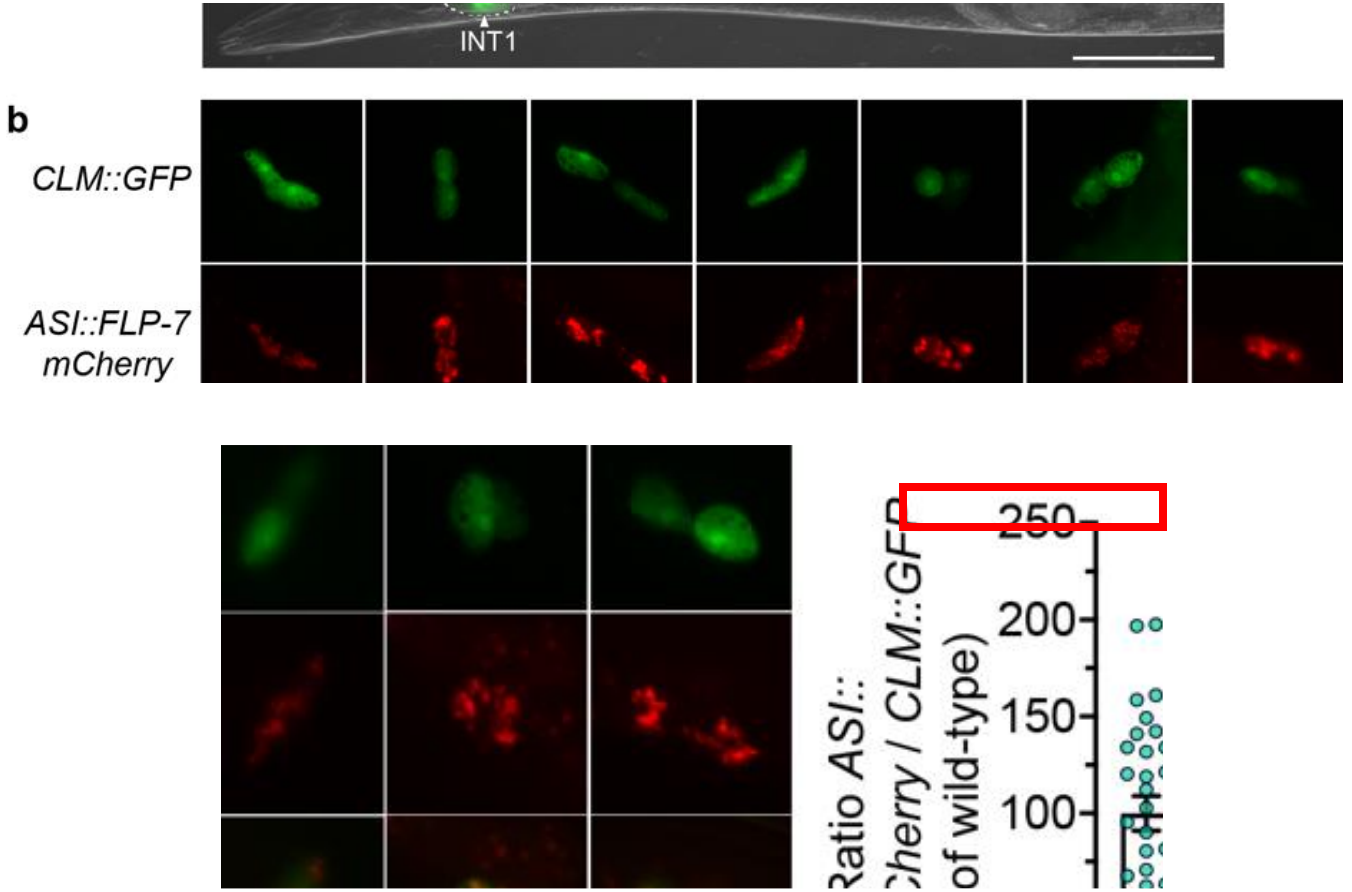


… uncovered an insulin antagonist secreted during fasting



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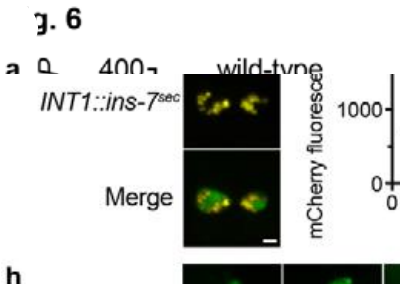

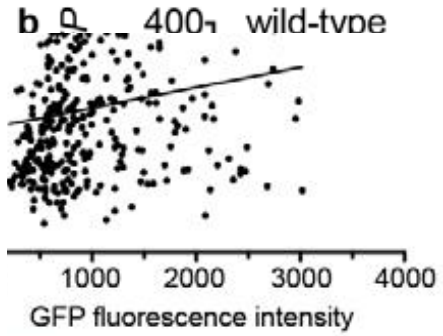

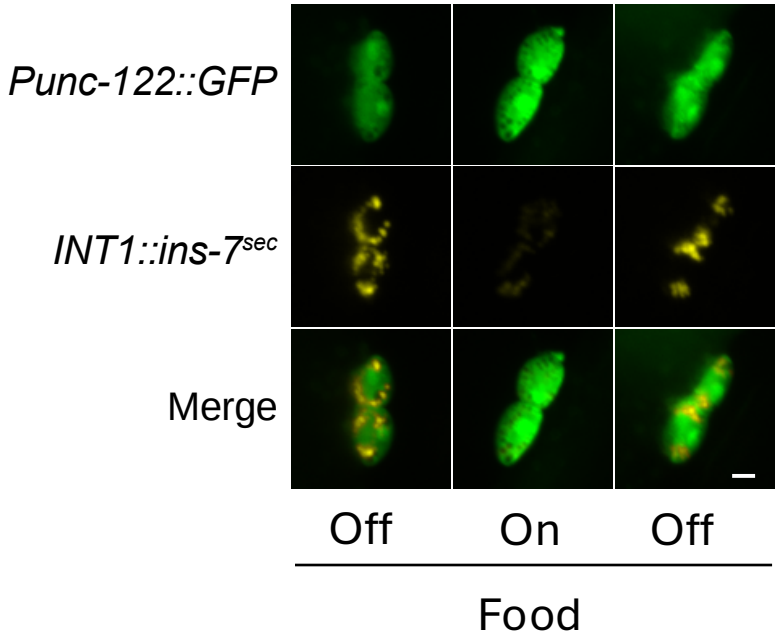

Liu at al, 2024 PMID 39127676

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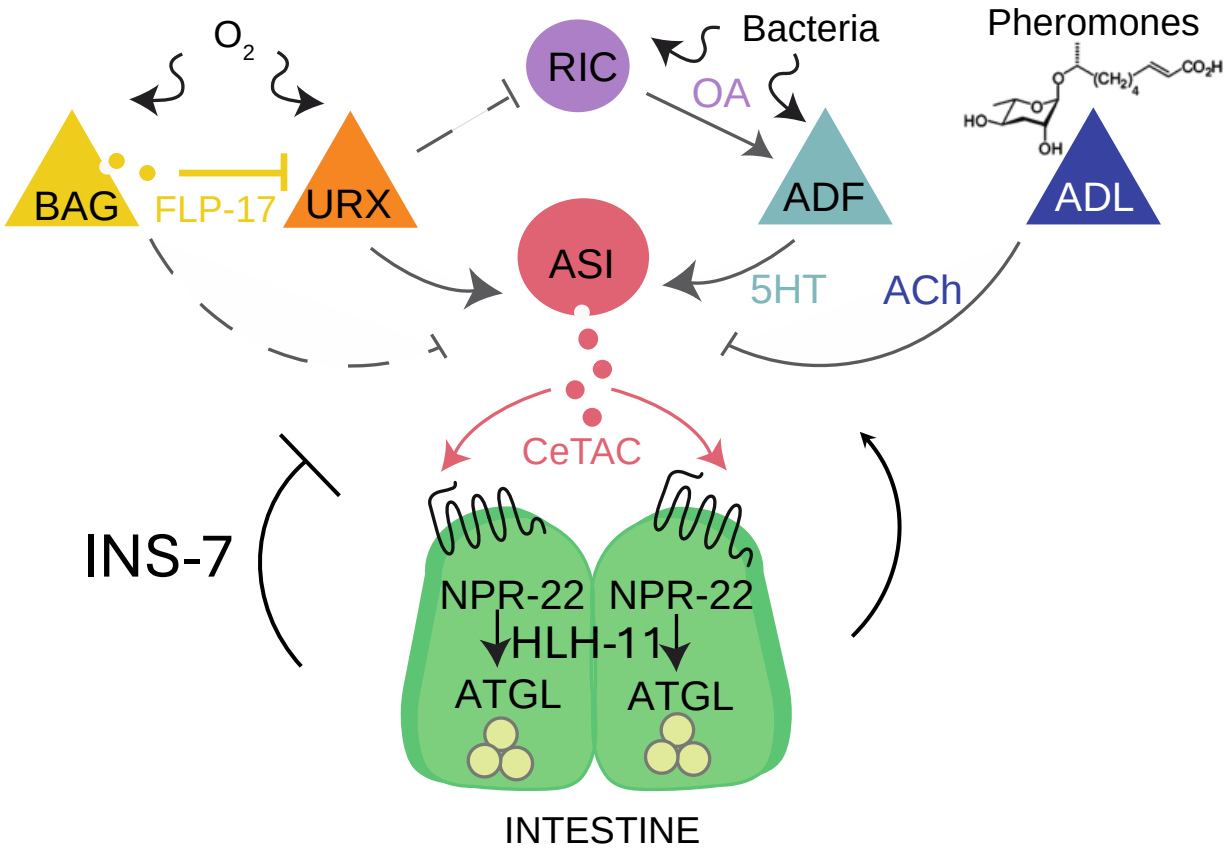
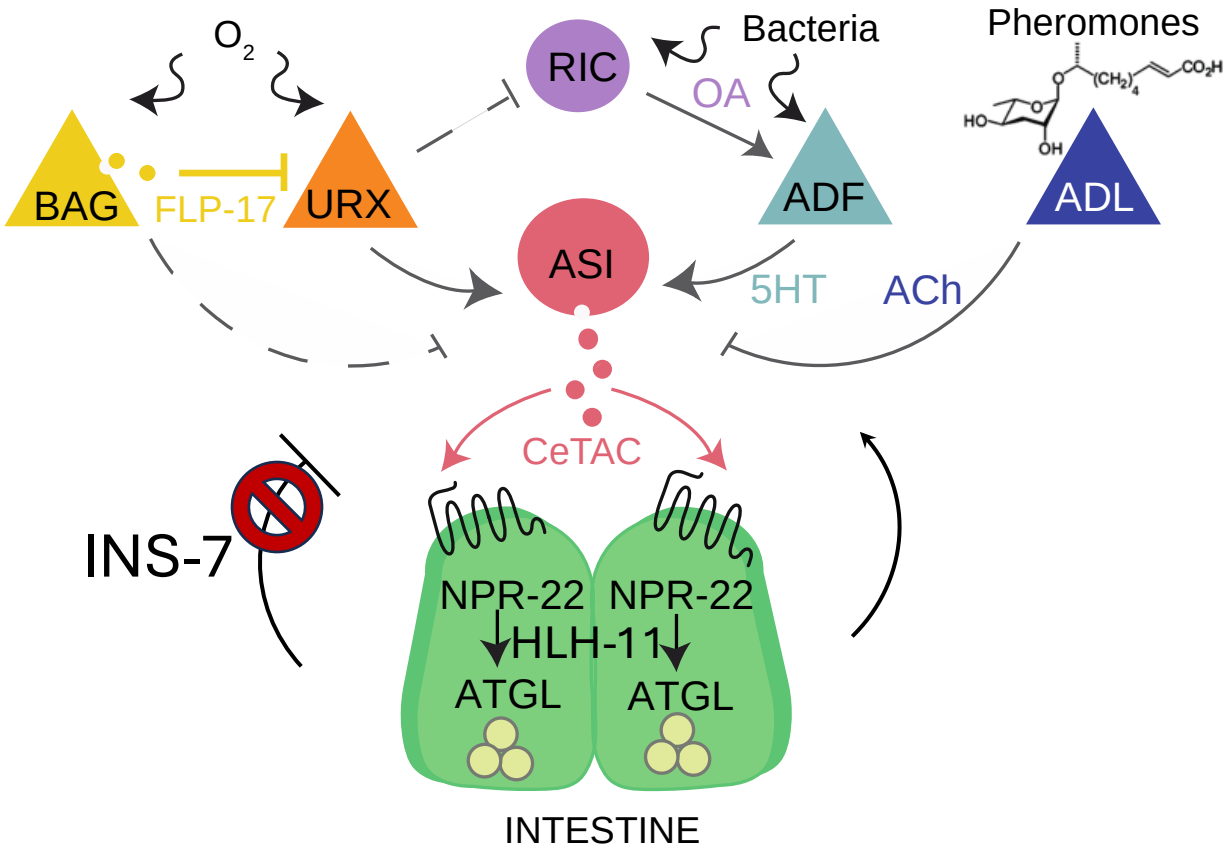
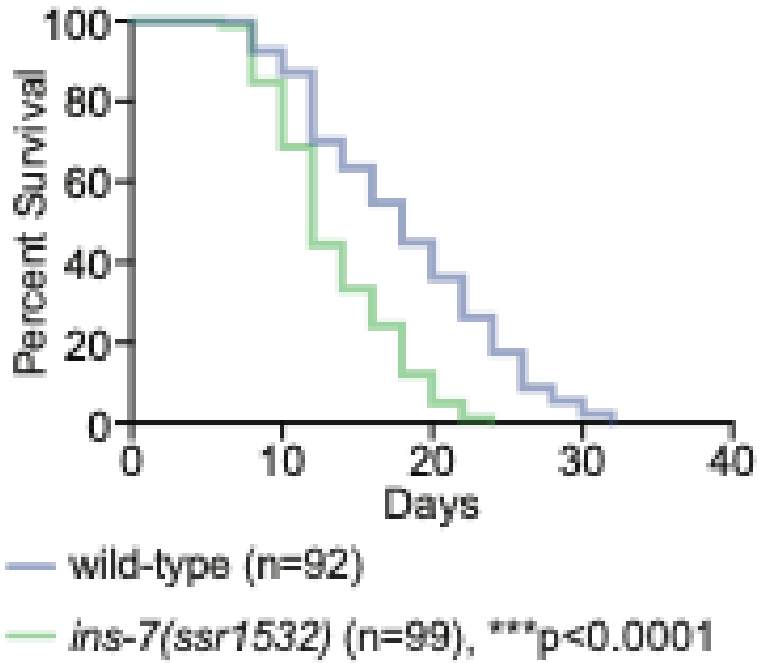


Liu at al, 2024 PMID 39127676

… uncovered an insulin antagonist secreted during fasting that also controls lifespan





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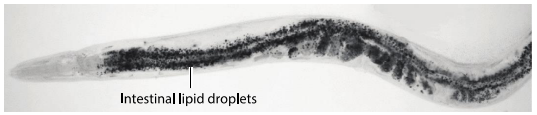
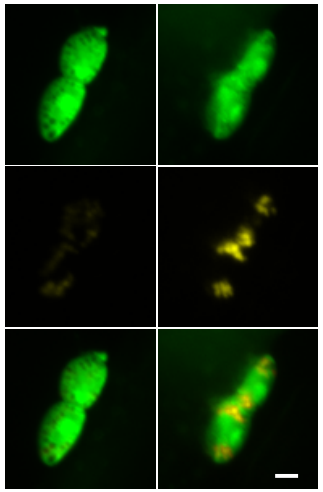
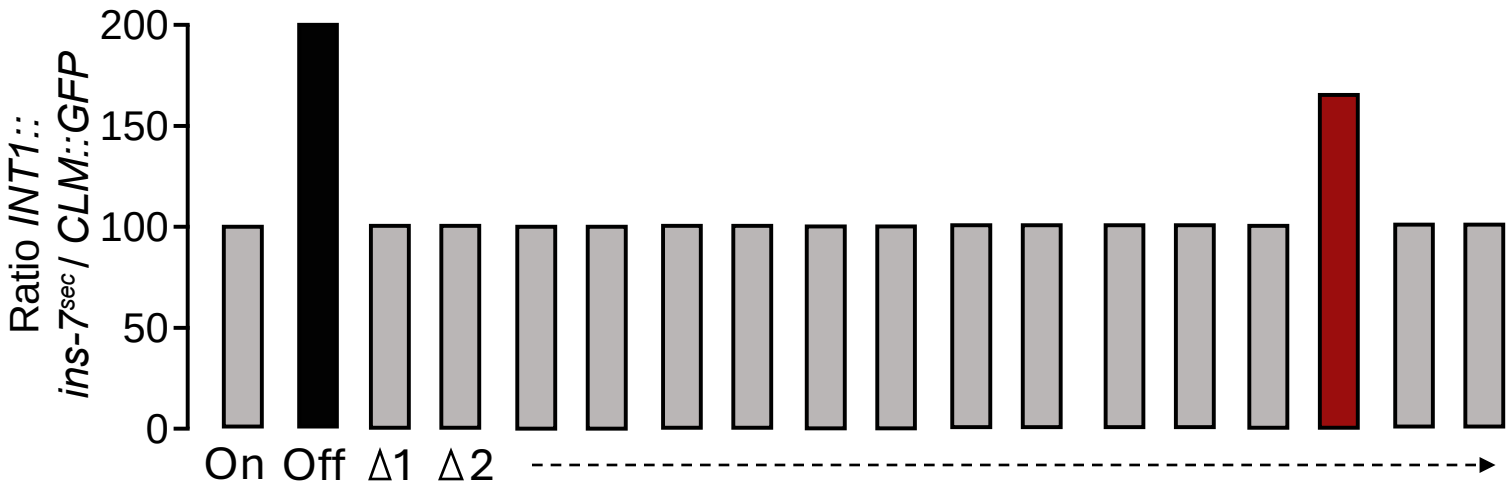
Which specific bacterial signals control gut insulin?

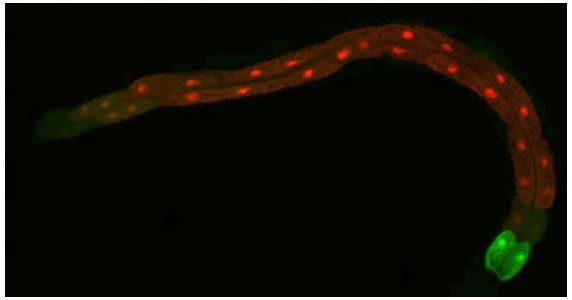


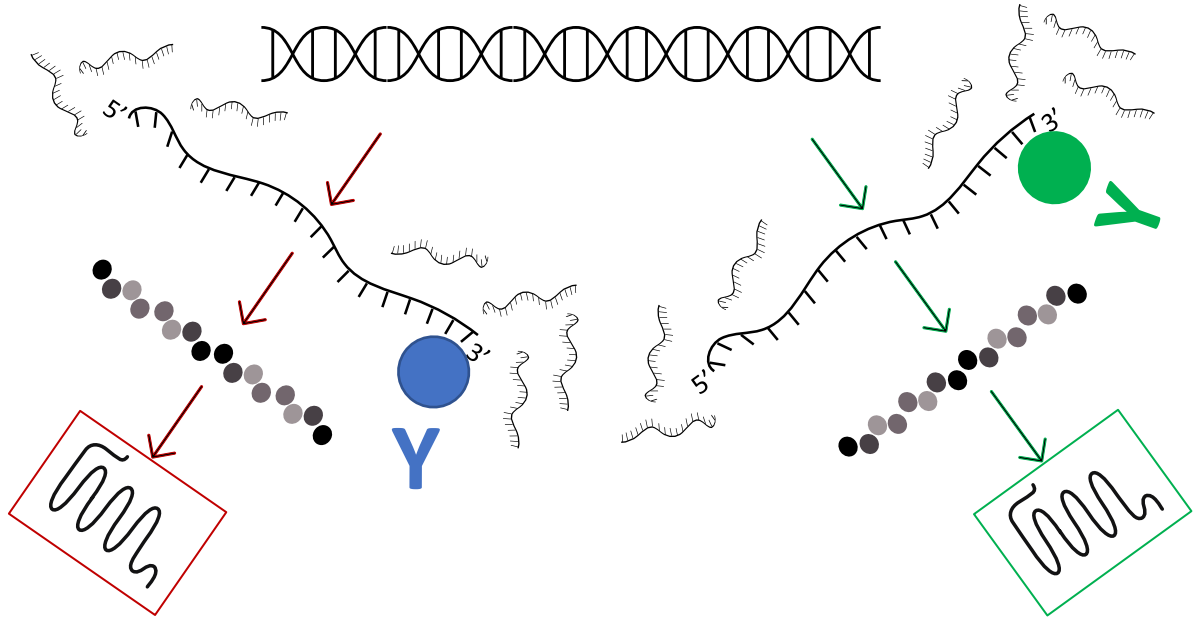




unpublished

The gut-brain axis is rich with hidden signals





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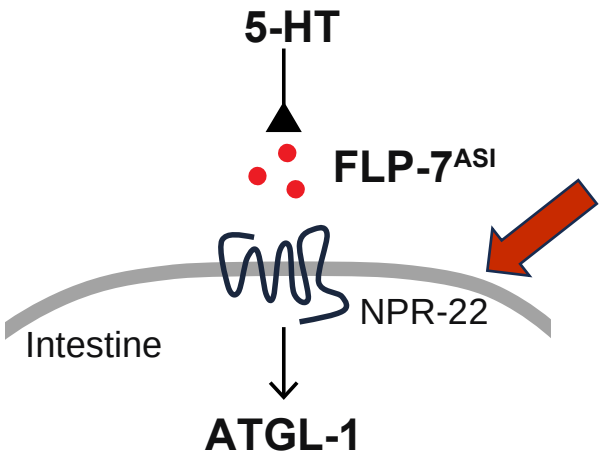
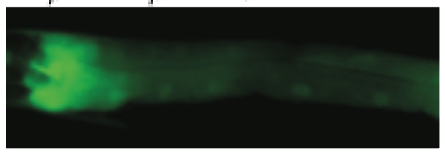
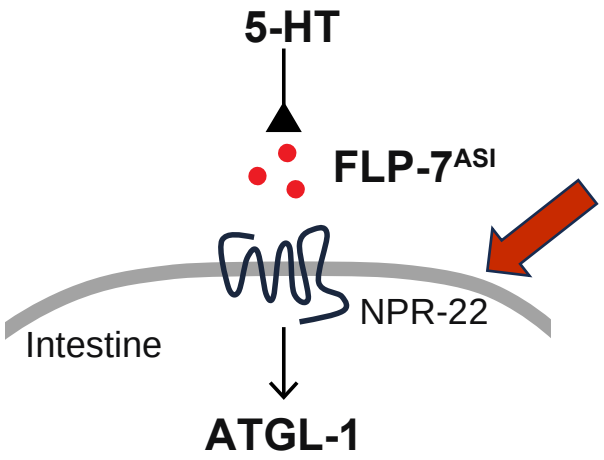
The Tachykinin Receptor NK2R in mammals

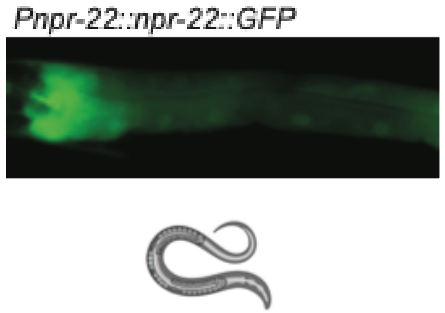


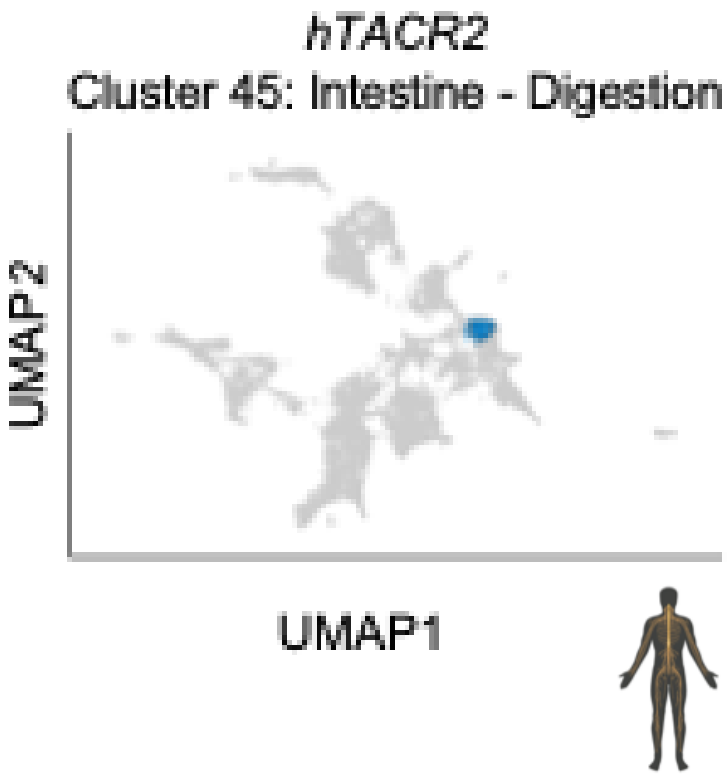
Pnpr-22::npr-22::GFP



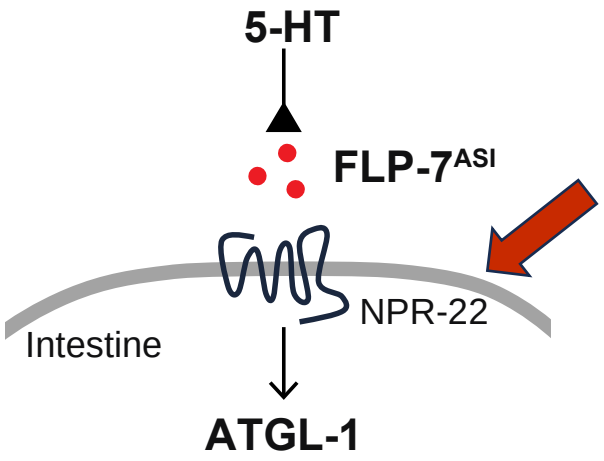
The Tachykinin Receptor NK2R in mammals







The Tachykinin Receptor NK2R in mammals



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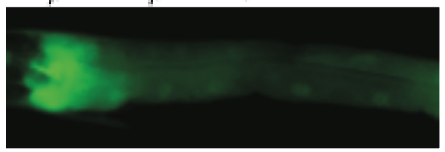
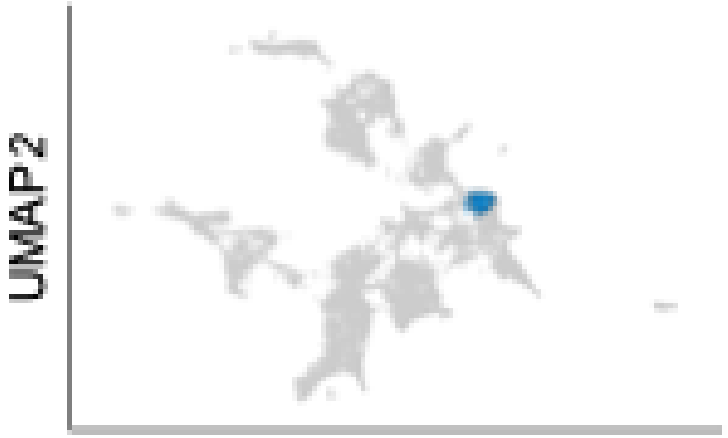
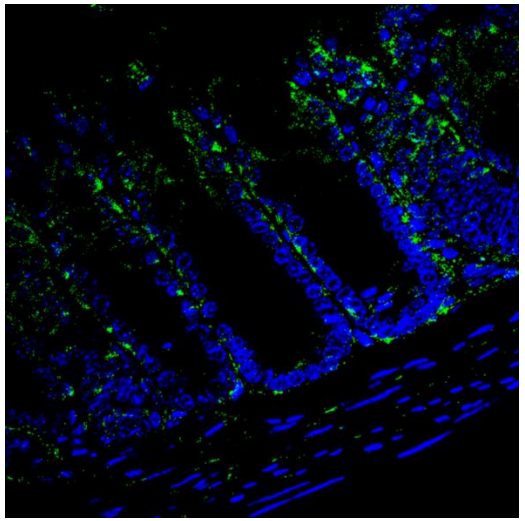


hTACR2

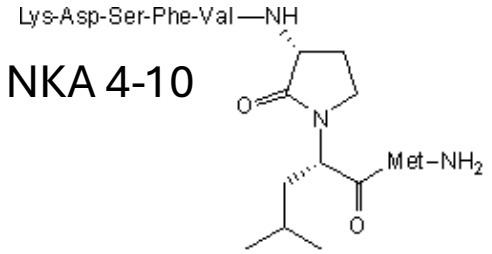
Cluster 45: Intestine - Digestion



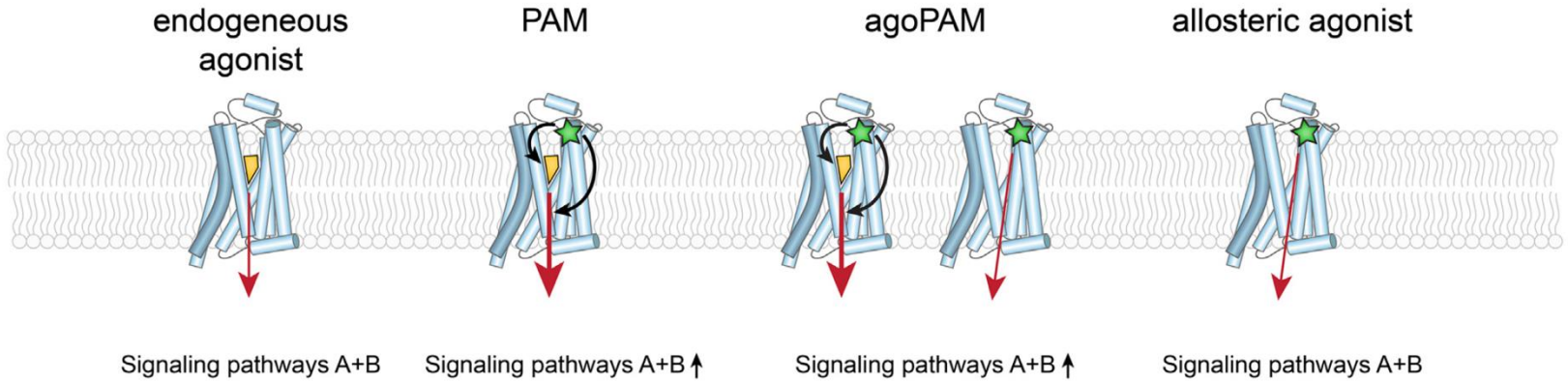


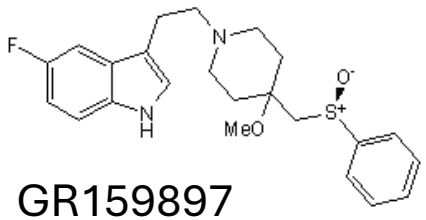
mNK2R

The Tachykinin Receptor NK2R in mammals can be modulated



NKA 4-10





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NK2R control of energy expenditure* and feeding to treat metabolic diseases

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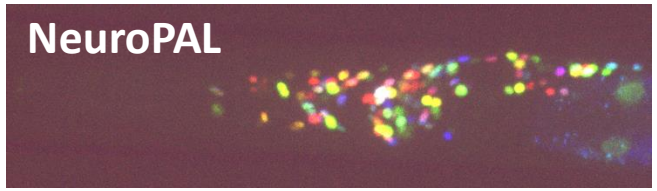
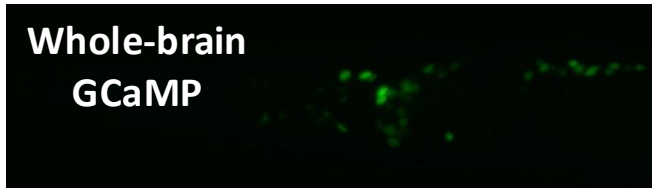
THE GUT-BRAIN AXIS, METABOLISM & LONGEVITY

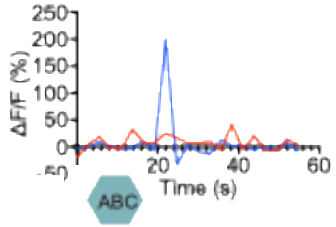
or, what a tiny nematode can tell us about biology and medicine

- The neurotransmitter serotonin is a principal driver of fat loss
- Discovery of a brain-to-gut messenger: a Tachykinin peptide
- Discovery of a gut signal induced by fasting : a novel Insulin
- Translating – from basic to clinic

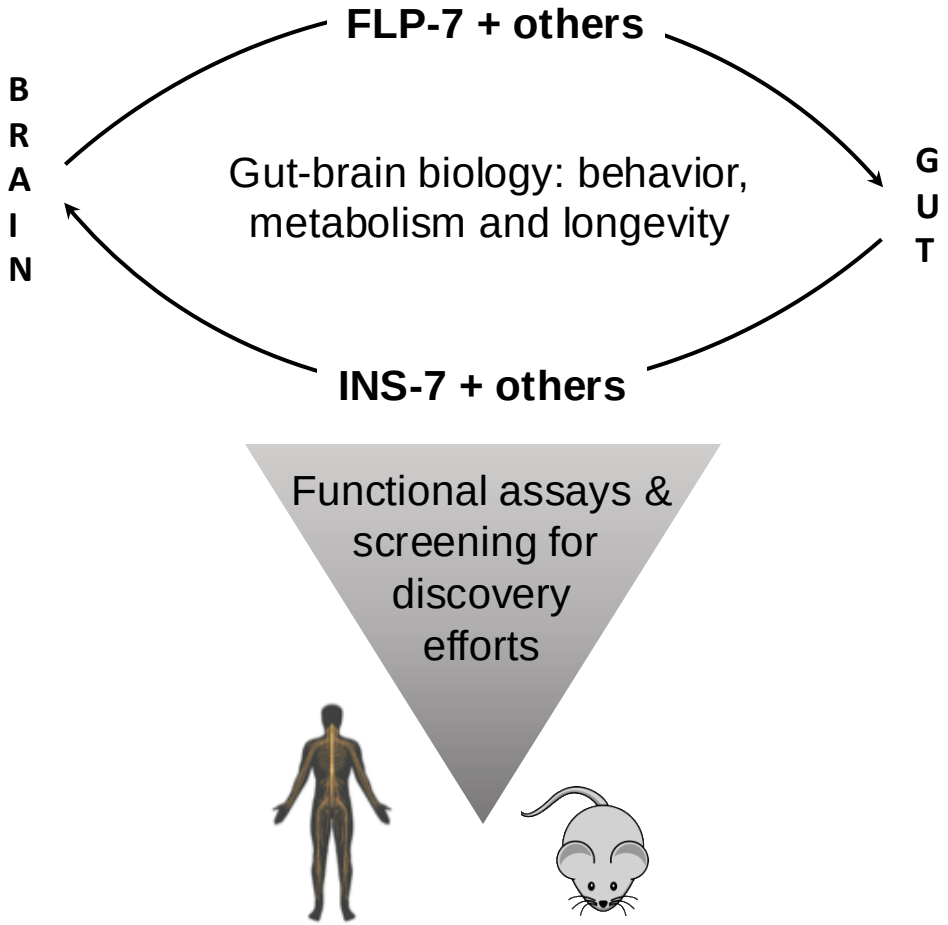
The gut-brain axis is rich with hidden signals – approaches to uncover them

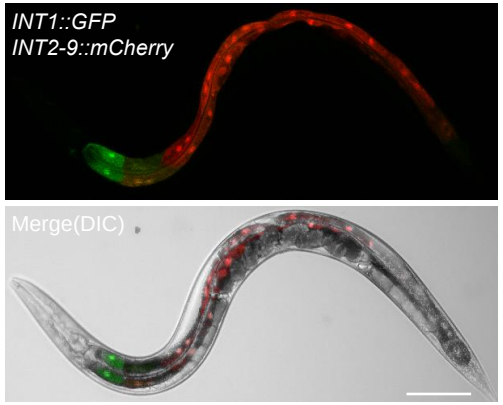


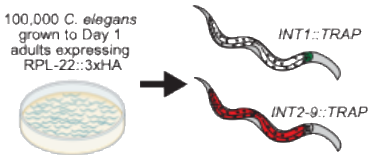




Neuropeptide genes	Expression level (TPM)
xxx-14	110634.30
xxx-21	24672.67
xxx-50	2967.18
xxx-2	2689.05
xxx-49	1949.38
xxx-14	1705.53
xxx-17	1505.49
xxx-12	1027.47
xxx-9	927.68
xxx-15	728.06
xxx-1	576.50
xxx-9	407.95







Neuropeptide genes	Expression level (TPM)
yyy-30	11847.46
yyy-5	6101.28
yyy-40	3446.24
yyy-14	2432.88
yyy-3	1803.59
yyy-55	954.48
yyy-9	861.48
yyy-79	640.74
yyy-13	614.84
yyy-61	512.73

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