

Lots of Biology

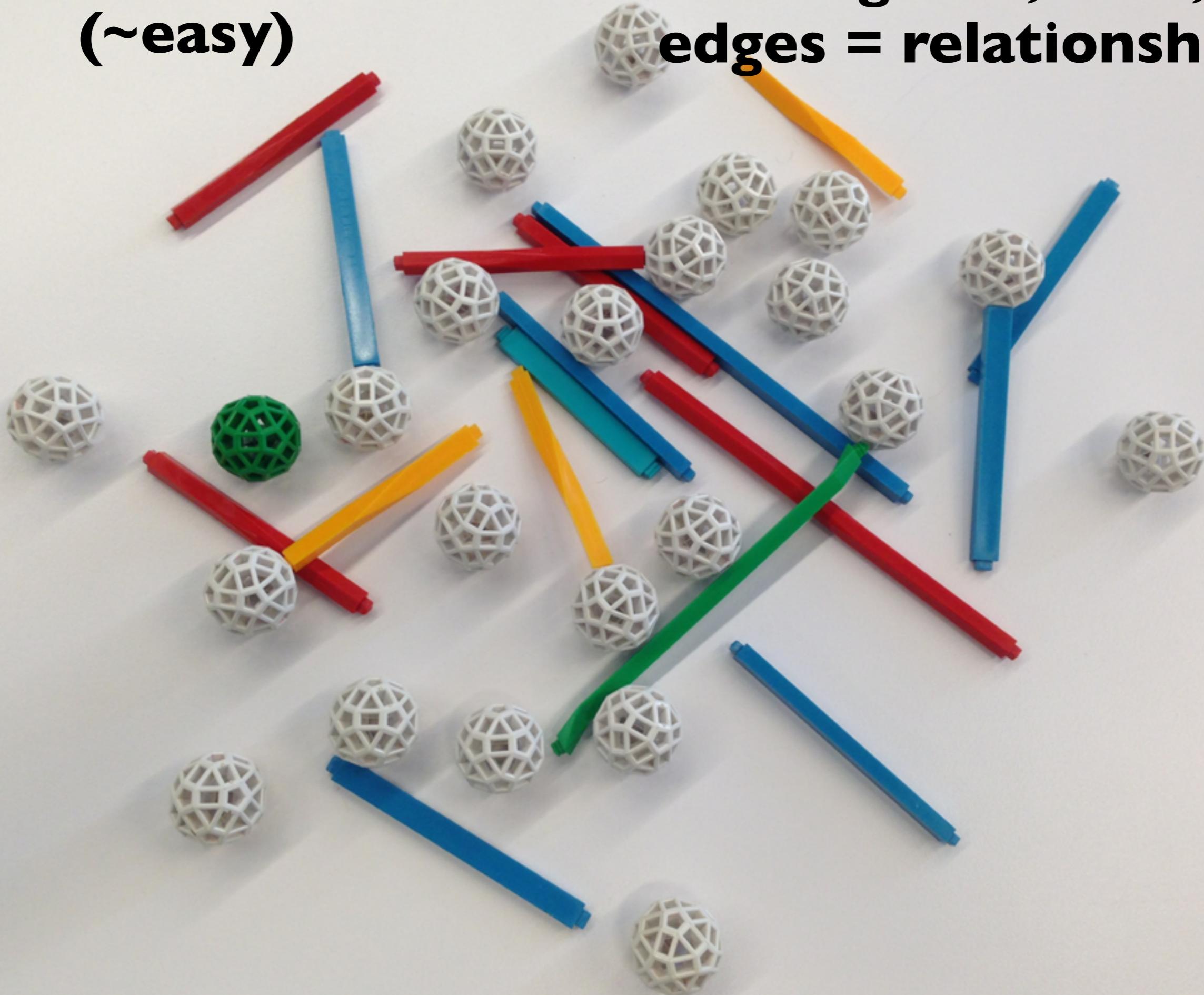


Andrea Choe

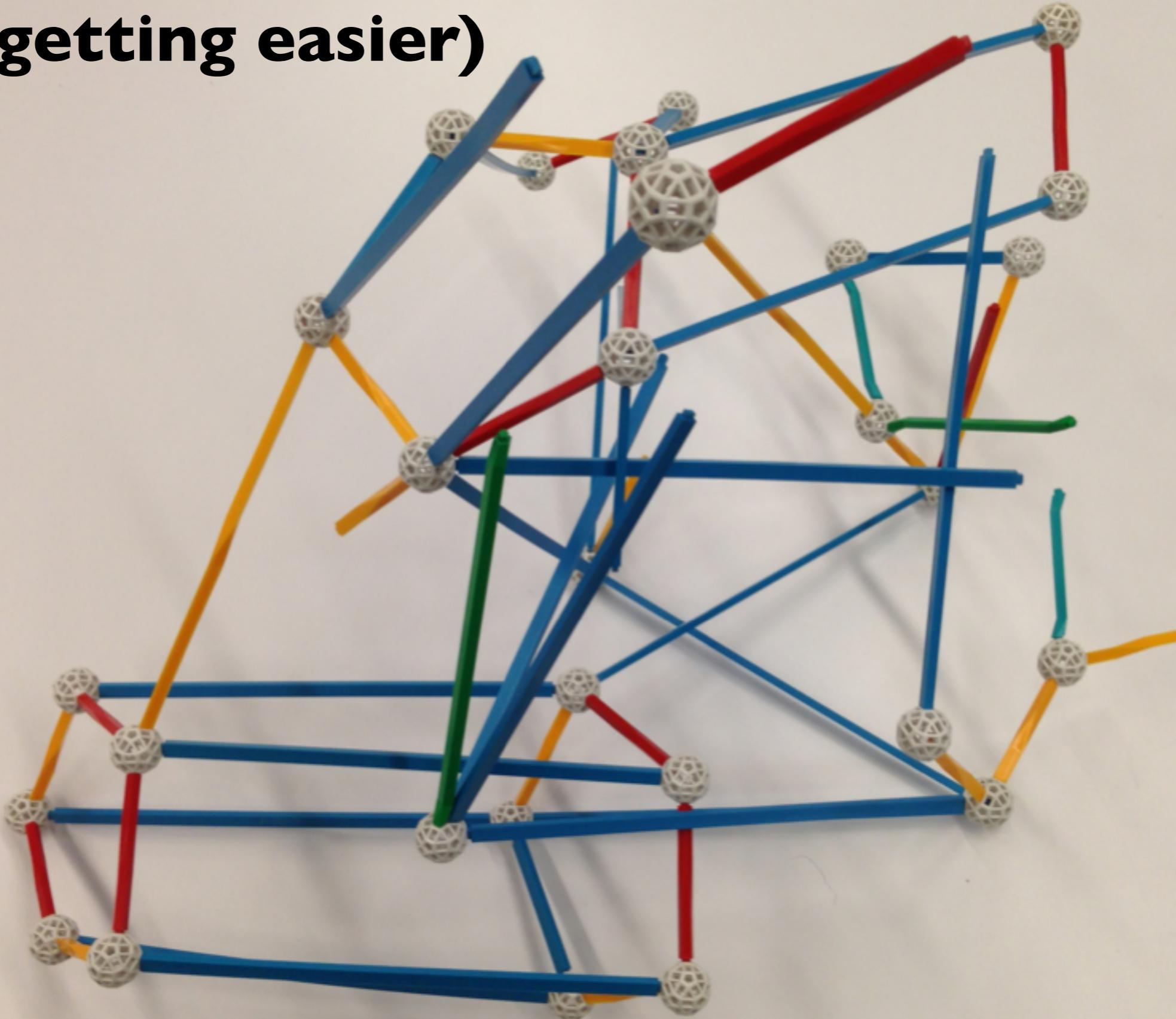
sexual attraction in free-living nematode *Panagrellus redivivus*

Network Parts (~easy)

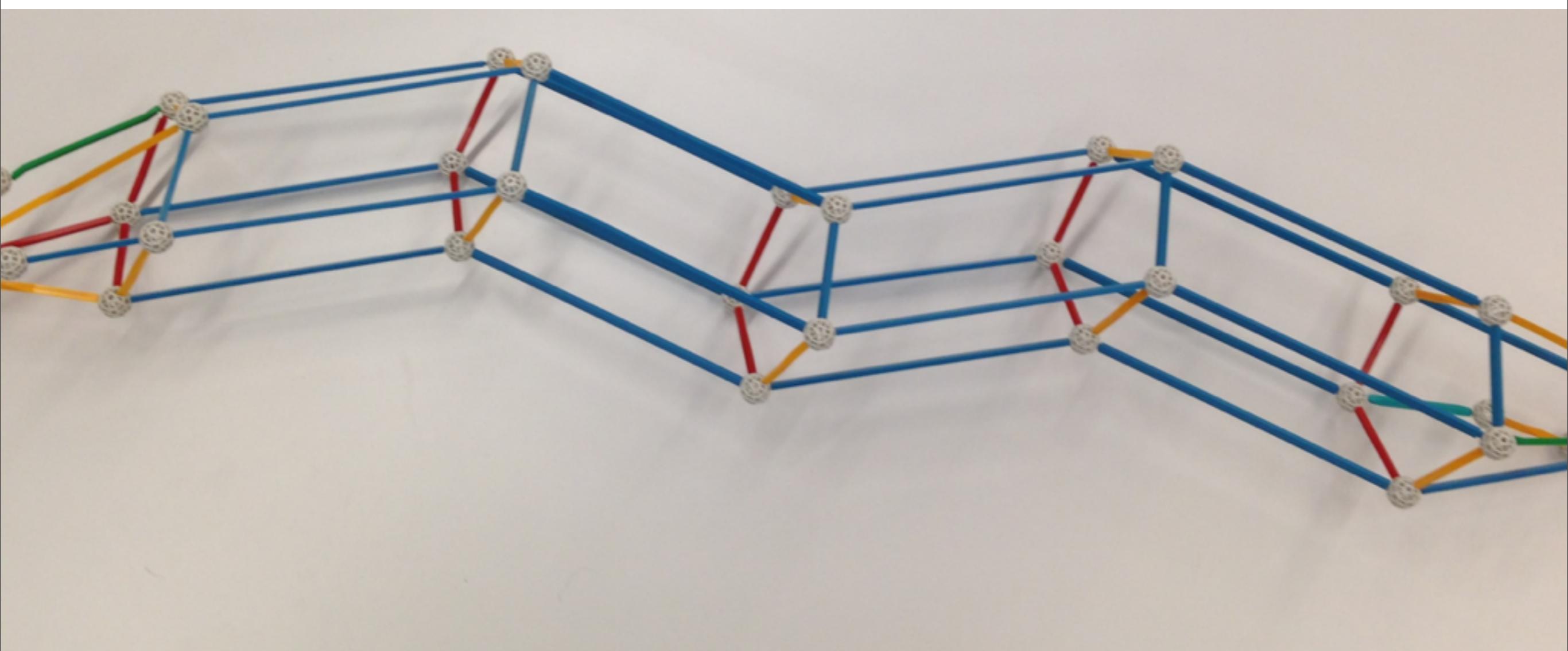
nodes = genes, cells, etc.
edges = relationships



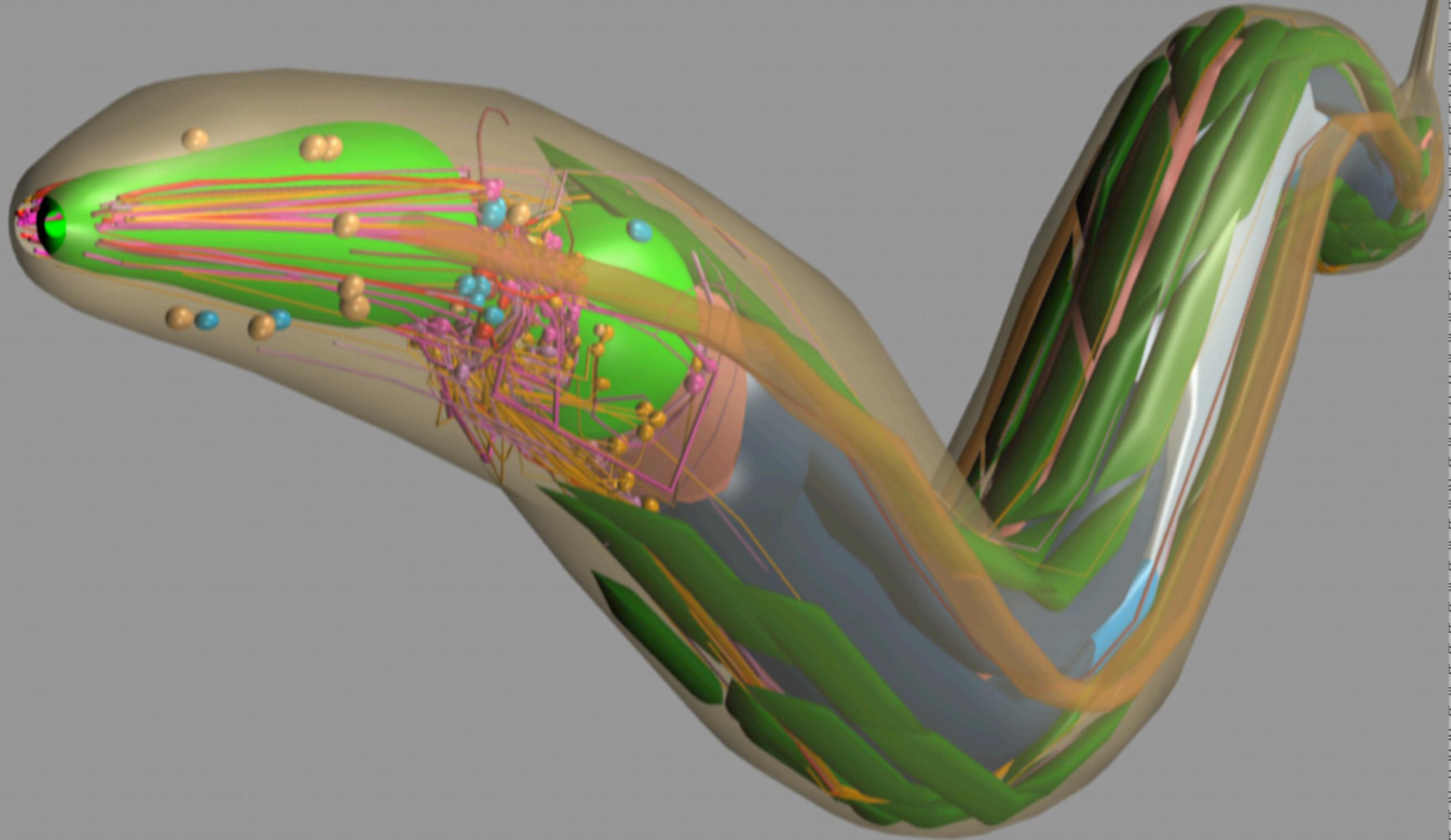
Network Relationships (getting easier)



Abstract the Relevant Biology (hard)



Systems Biology of an Animal



graphic by Chris Grove [WormBase-Caltech]

SCALE

4.5×10^8 interactions

30,000 genes (21K protein-coding)

10^5 regulatory elements

10^6 interactions

1000 cell types

1000 processes/physiological
responses/behaviors

3×10^{10} associations

Curate knowledge in computable form

WormBase.org



**Database of *C. elegans* & other nematodes
genomes, gene expression, phenotype, interactions**

**Gene Ontology Consortium
knowledge modeling across all organisms**



**new model (LEGO) : A does B to C in location D during
process E with input F, related to process G**

**Textpresso.org
semi-automated information extractions
C. elegans; Cancer; *Drosophila*; Mouse**



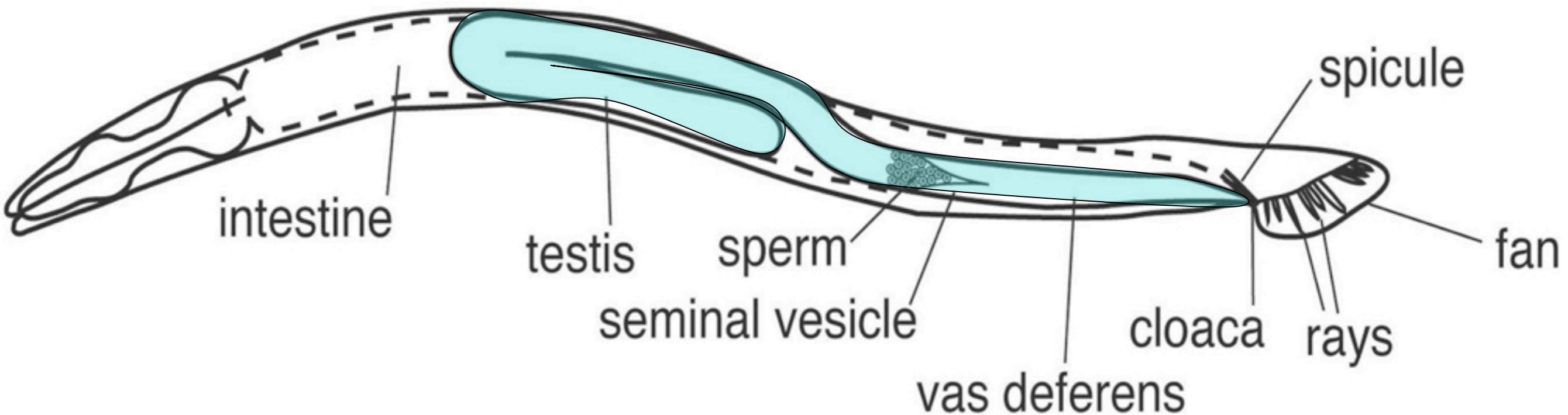
predicting genetic interactions (function)

**Data are produced
at many levels**

**There are knowledge gaps
at many levels**

**We need to represent and
model at many levels**

Nematode male gonadogenesis



C. elegans: Kimble & Hirsh (Dev Biol. 1979)

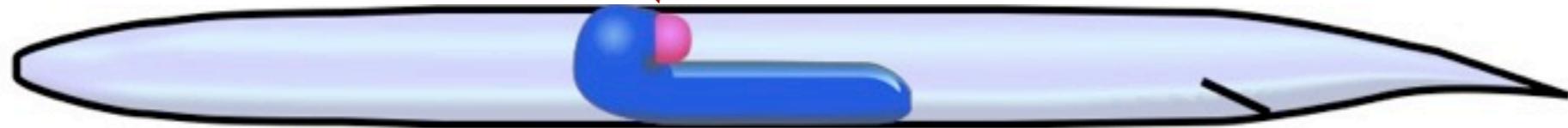
Panagrellus redivivus: Sternberg & Horvitz (Dev Biol. 1981)

Linker cell migration generates the male gonad morphology

25 hours

linker cell=LC

early L3 stage



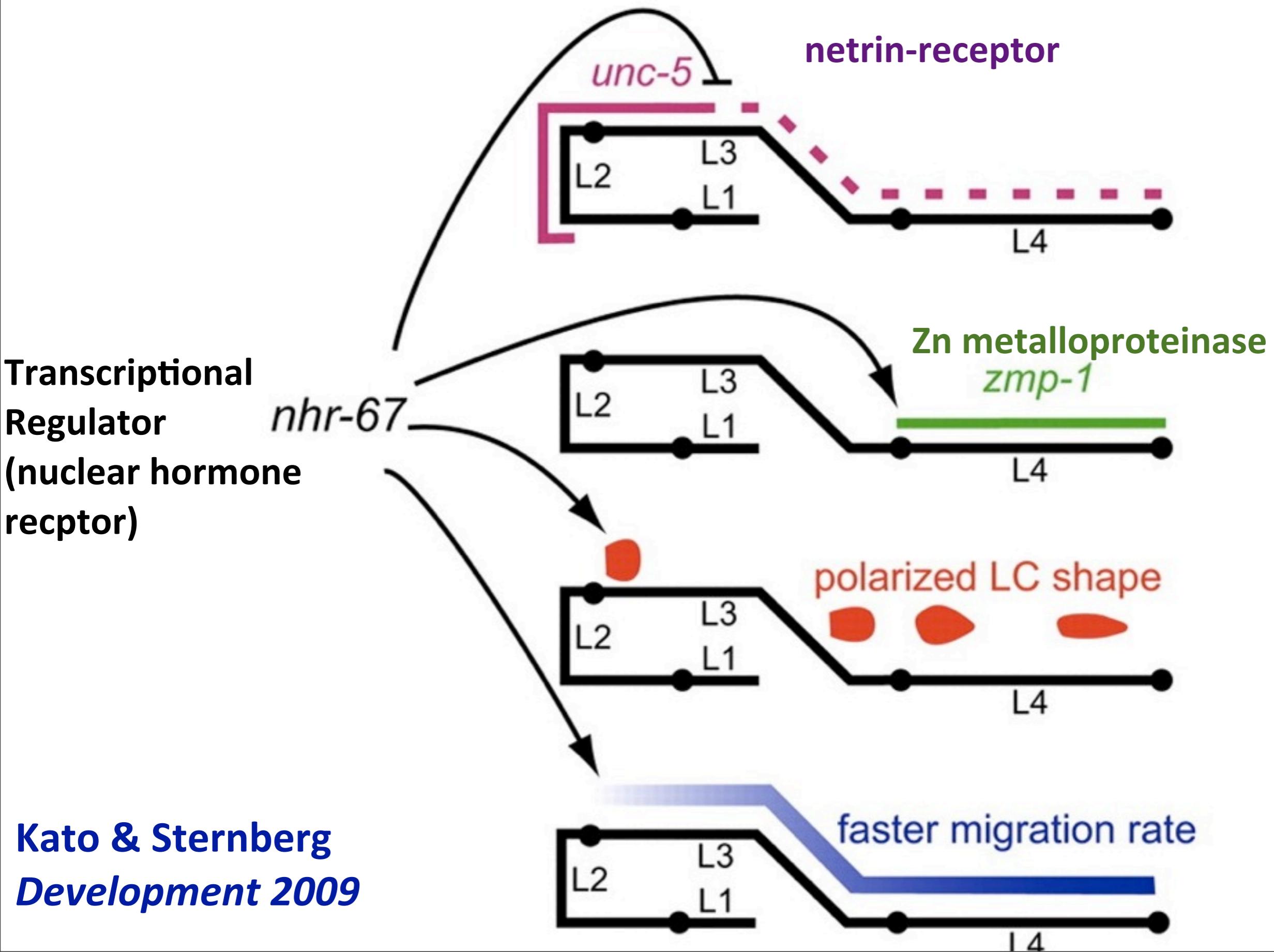
early L4 stage



mid-L4 stage



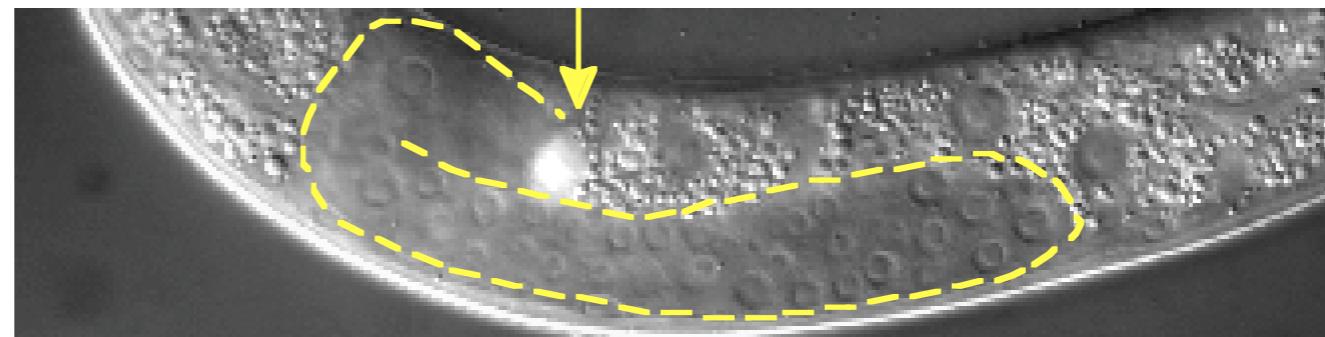
nhr-67 (Tlx/tailless) regulates LC migration



Kato & Sternberg
Development 2009

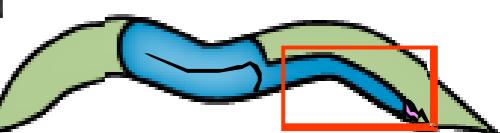
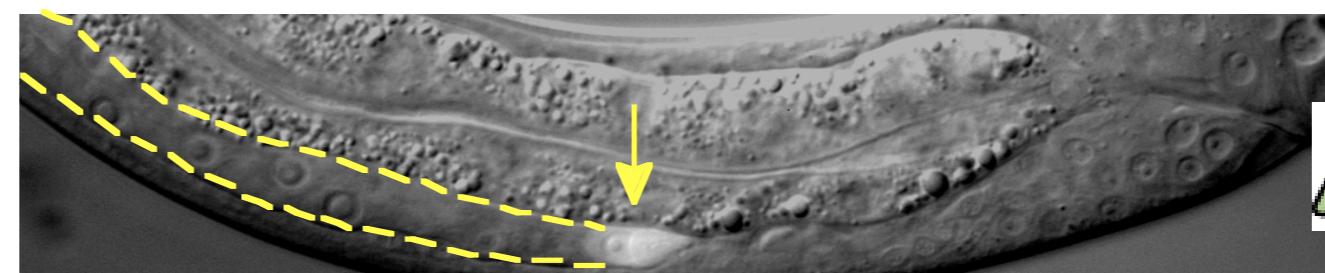
RNA-seq of single dissected LCs

L3 stage

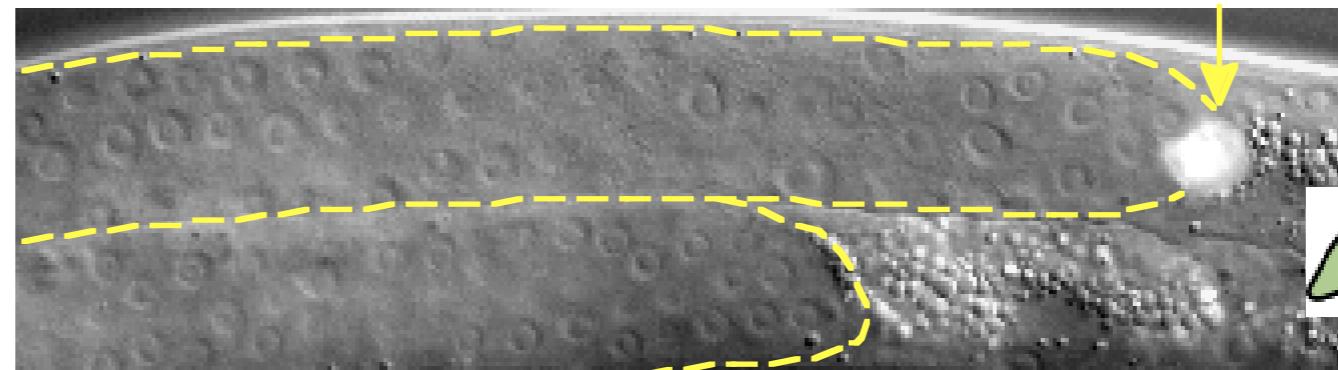


LC is labeled by YFP

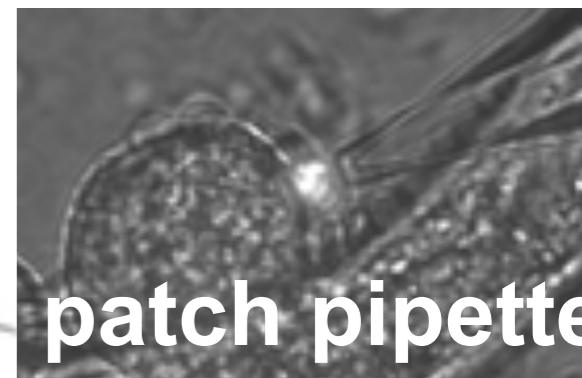
L4 stage



L4 stage
nhr-67(RNAi)
“acts like L3”

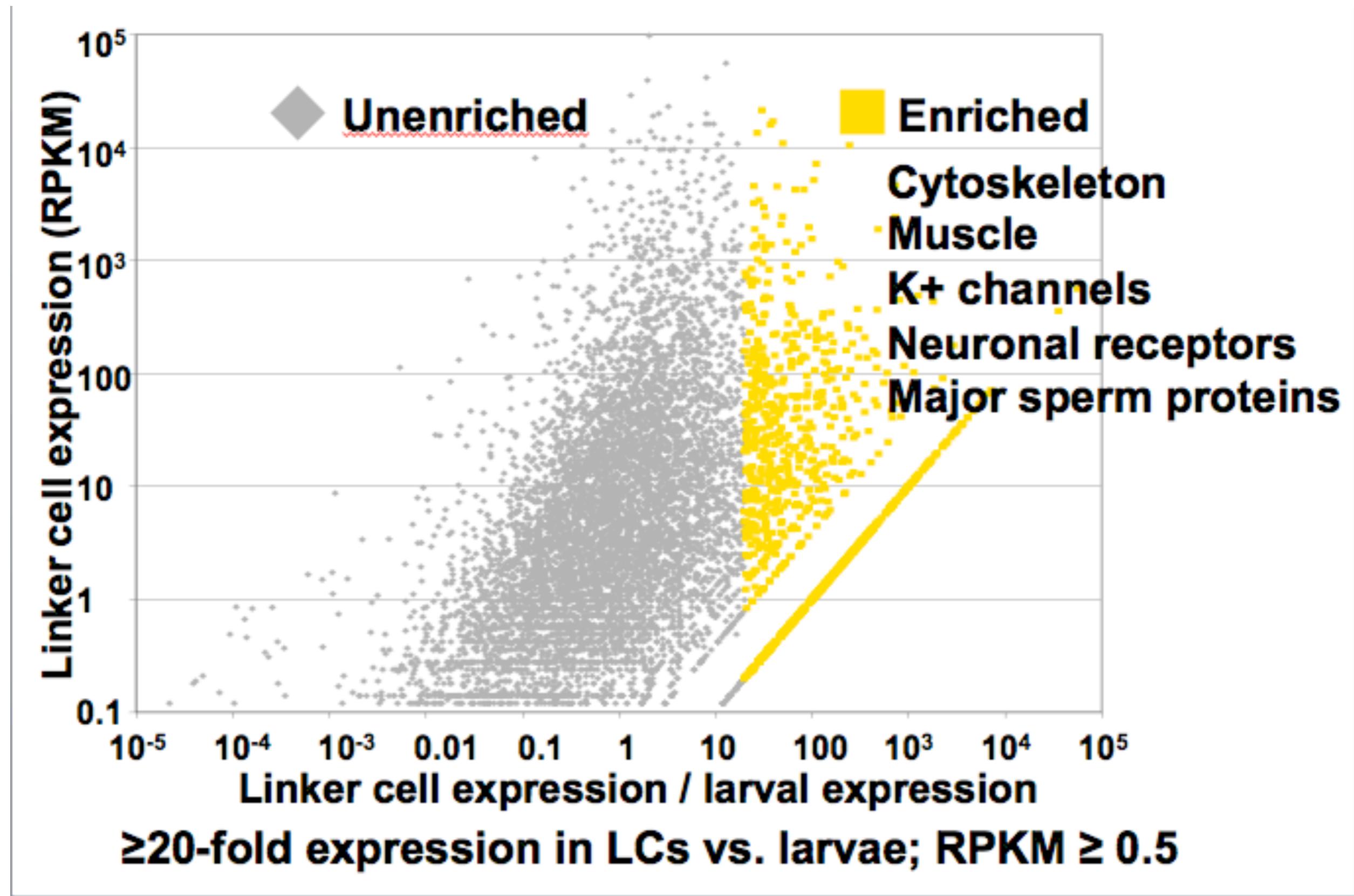


WT larval whole worm
(control)



patch pipette

963 LC-enriched genes (12% of 8,011)

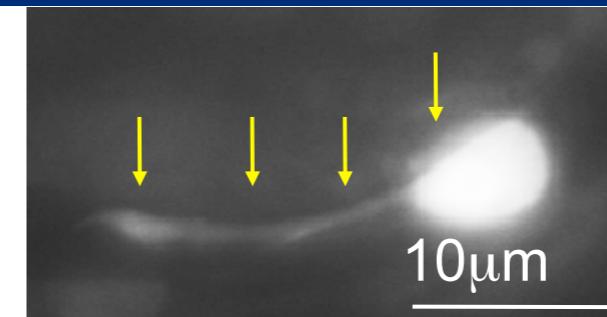


Erich Schwarz, Mihoko Kato

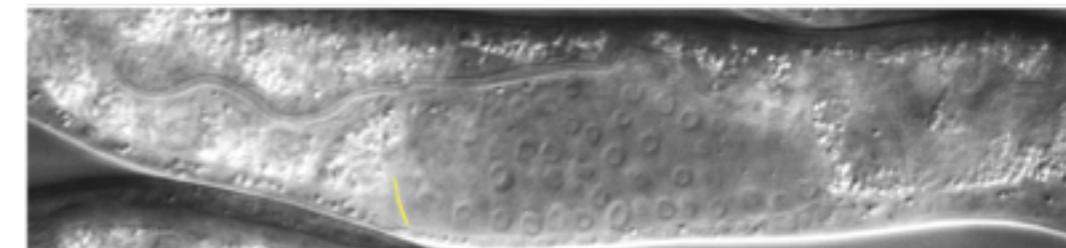
PNAS 2012

15% of 200 genes LC-enriched genes have abnormal phenotypes by RNAi

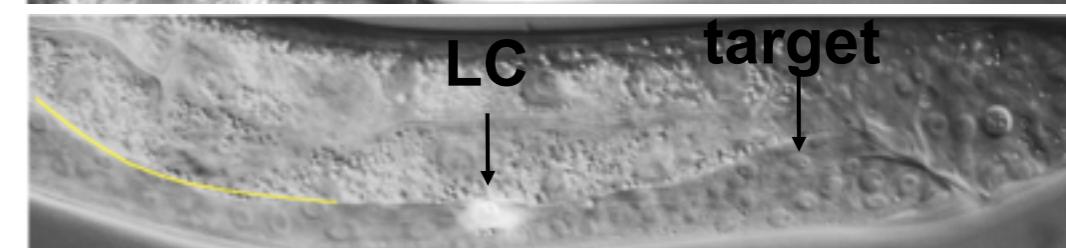
1. Abnormal LC shape



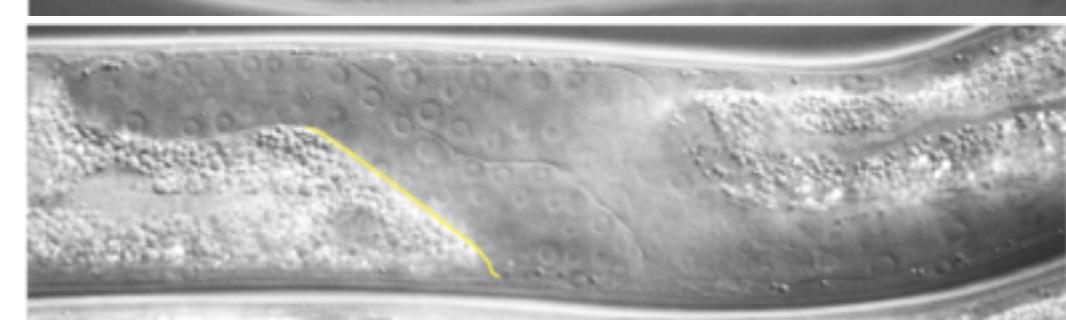
2. No LC specification



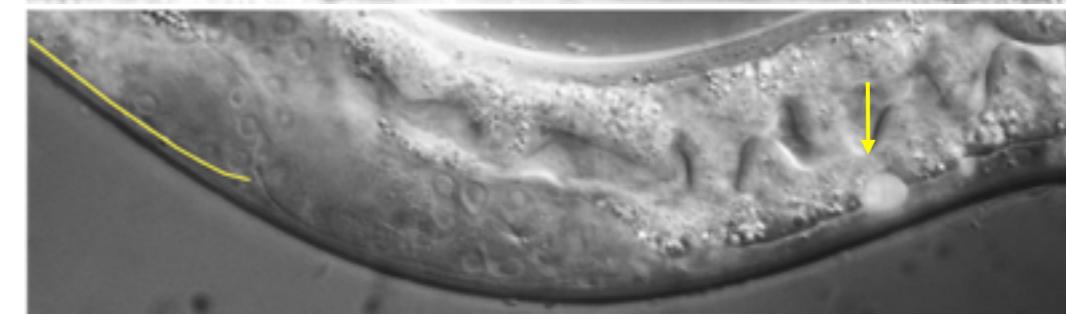
3. Slow migration



4. Abnormal path



5. Detached LC

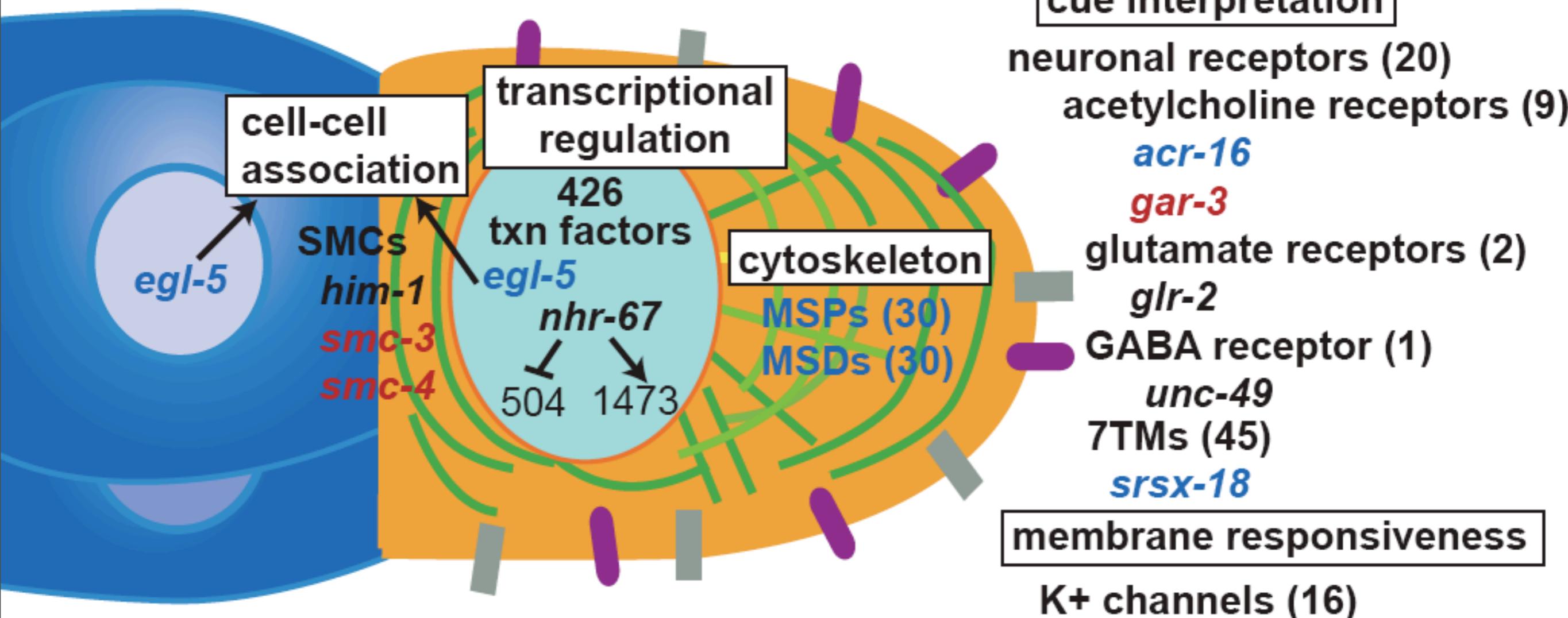


6. Stretched gonad



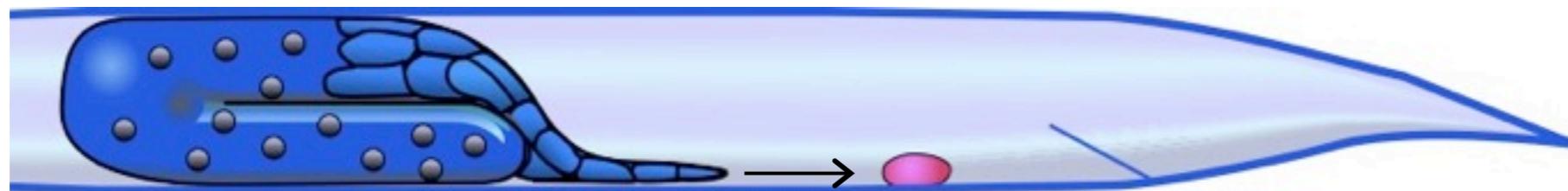
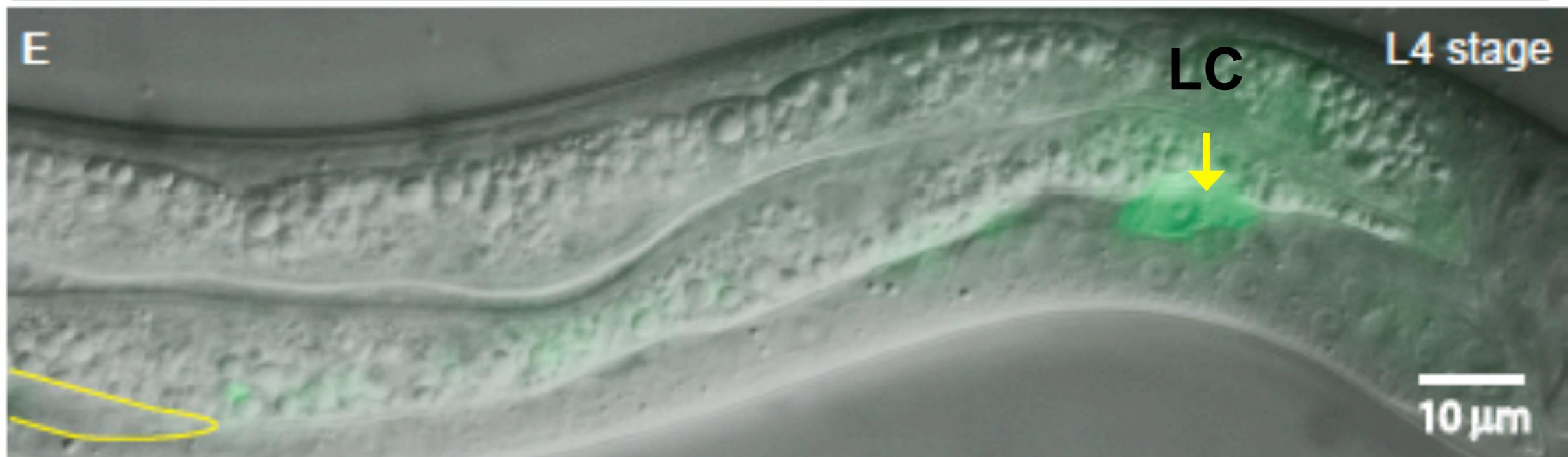
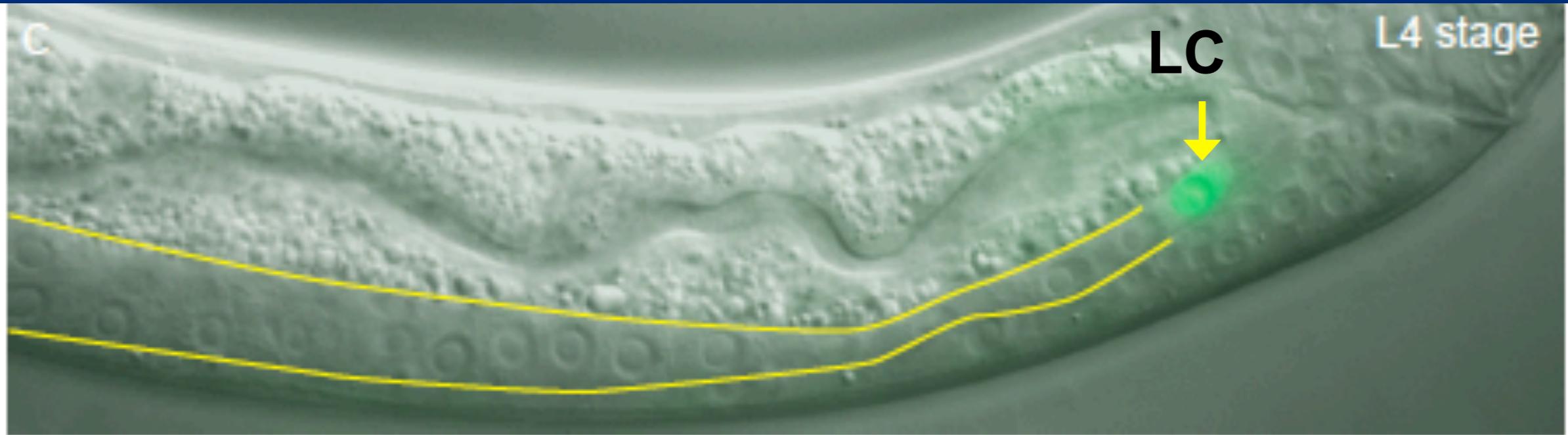
New genes involved in migration

2000 linker cell enriched, L4-enriched, NHR-67-regulated genes



Mihoko Kato, Erich Schwarz
PNAS 2012

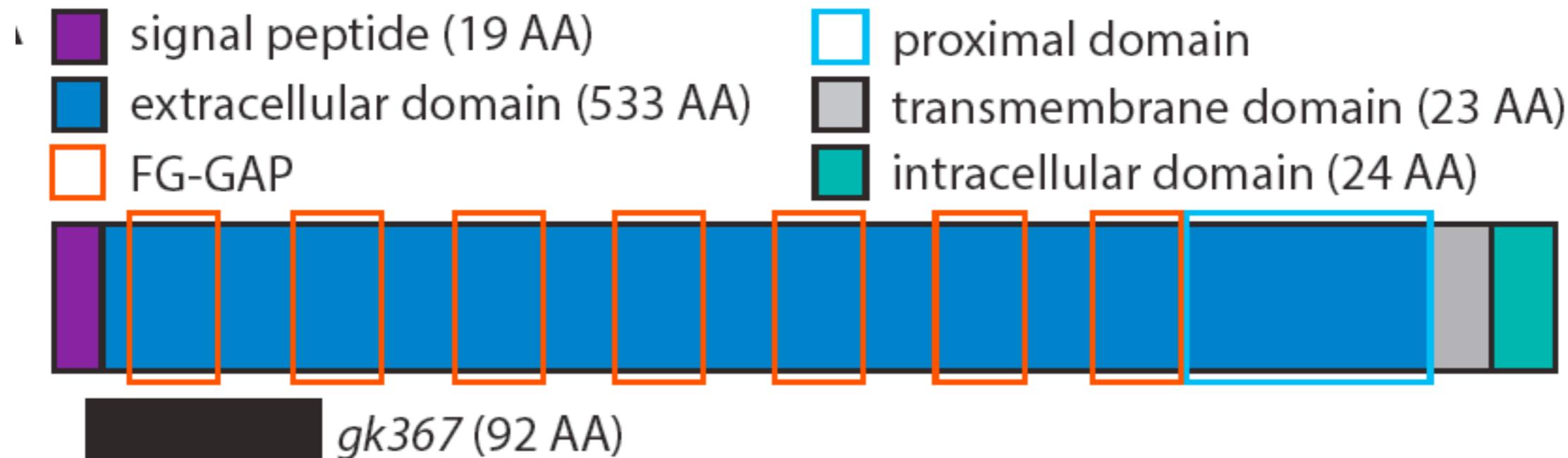
Inkn-1 mutants have a detached LC



LC detachment from gonad (96% males)

Hermaphrodites are sterile (100%)

LINKIN is a conserved protein



Conserved to human (ITFG1)

Fiscellla et al. Nat. Biotech. 2003

157/599
identical
(26%)

LINKIN ortholog

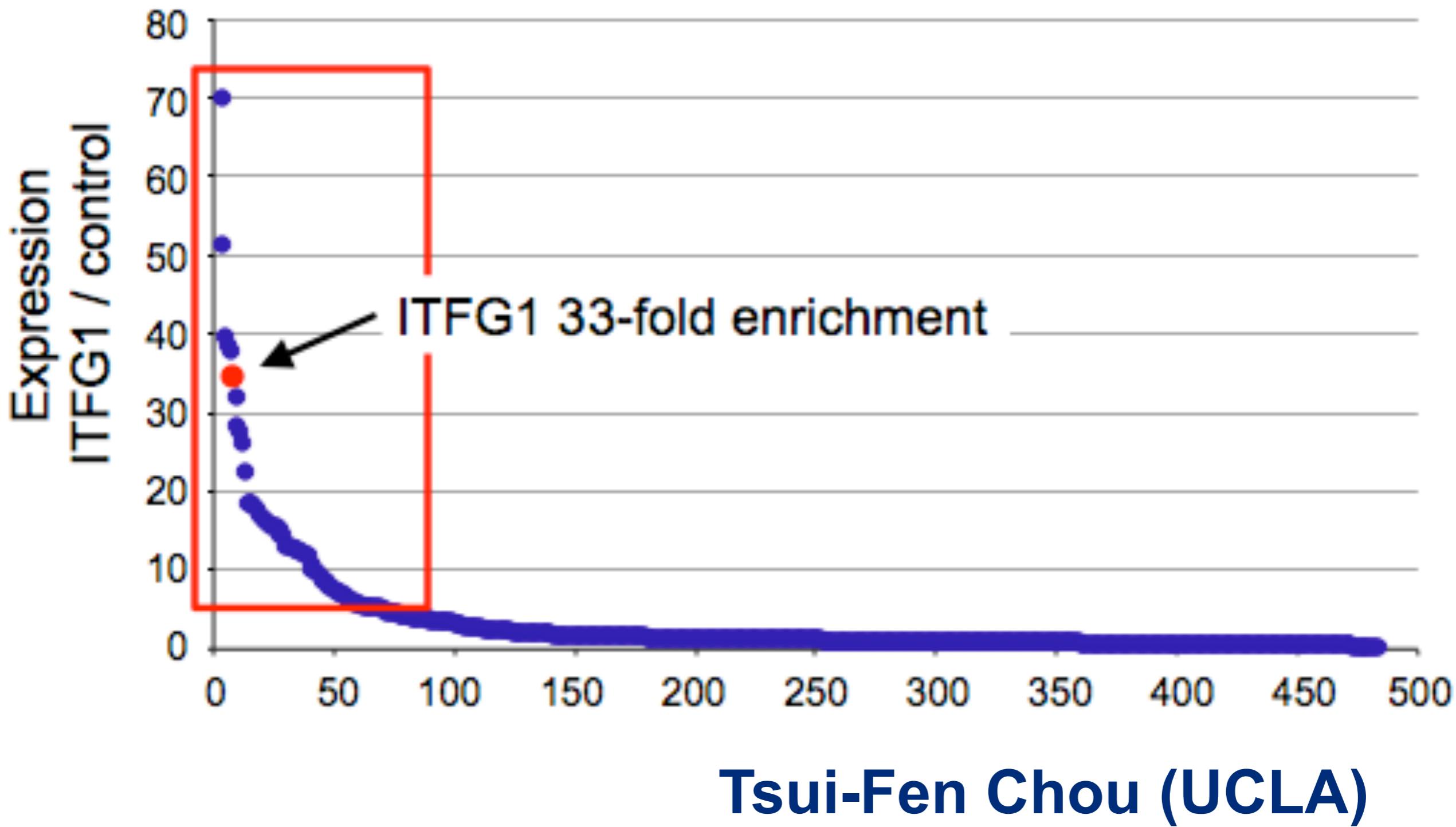
human
mouse
fly
worm

AIALIGVCVFILAIIGILHWQEKKADDREKQEAHRFHFDAM
AVALIGVCIFILAIIAILHWQEKKADDREKQEAHRFHFDAM
VVALG3TCLVIVFIIILVLYIKEKREDKQERLQESHRFHFDAM
LAVIALVCCMLLMVVVFLHYREKKEDRYERQQQSHRFHFDAM

← transmembrane intracellular

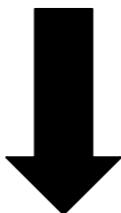
SILAC mass spectrometry of human ITFG1

67 proteins with >5-fold enrichment



Identifying the *C. elegans* orthologs for human Linkin interactors

46/66 (70%) of the human Linkin interactors have *C. elegans* orthologs



46 *C. elegans* genes were tested by RNAi for male gonadal defects and hermaphrodite sterility

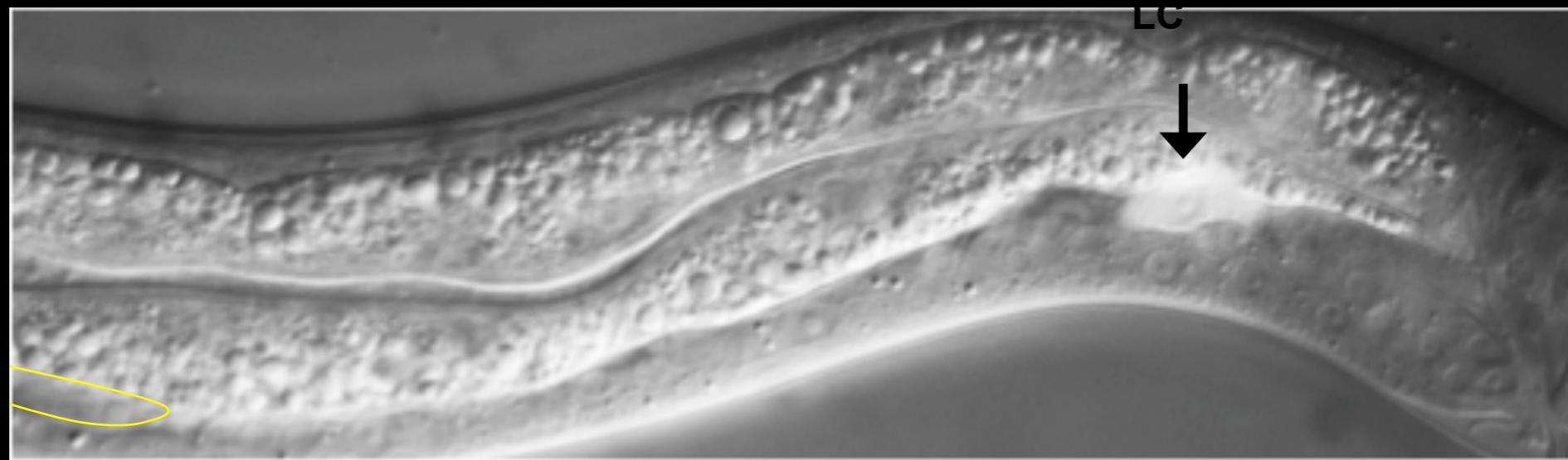


3 with Phenotype, positive on Western blot

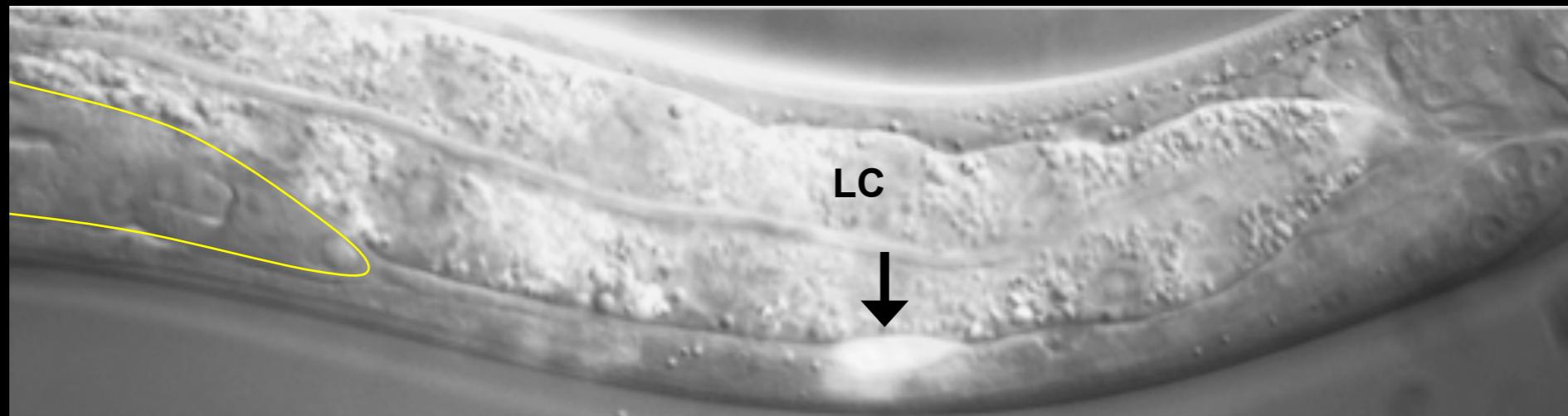
Mihoko Kato, Tsui-Fen Chou

Three LINKIN interactors have same detached LC phenotype

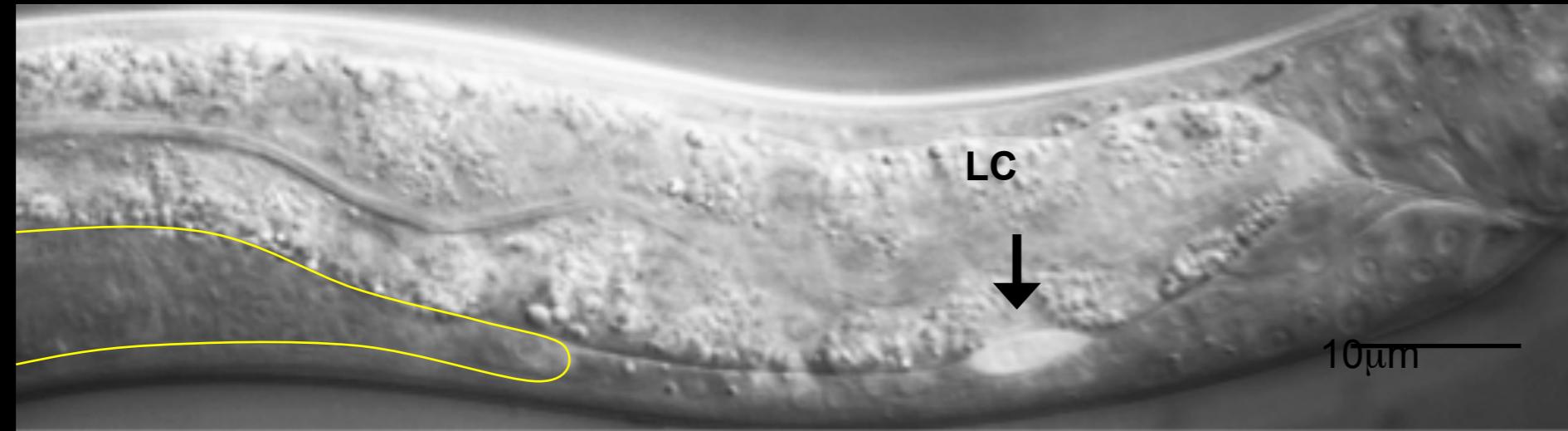
Inkn-1
mutant



tba-2/
Tubulin- α
RNAi

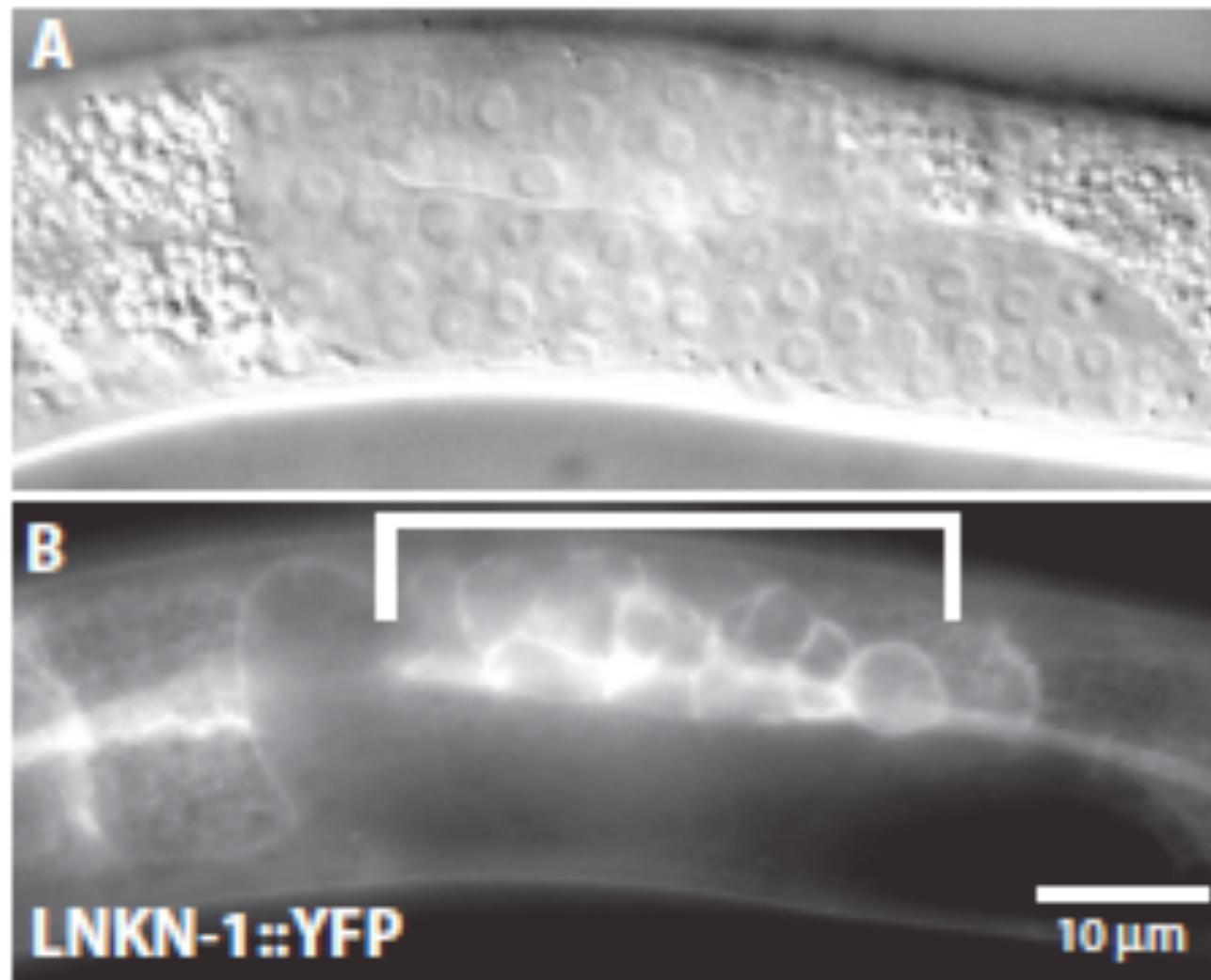


rvvb-1 or
rvvb-2
Ruvb1-like
RNAi

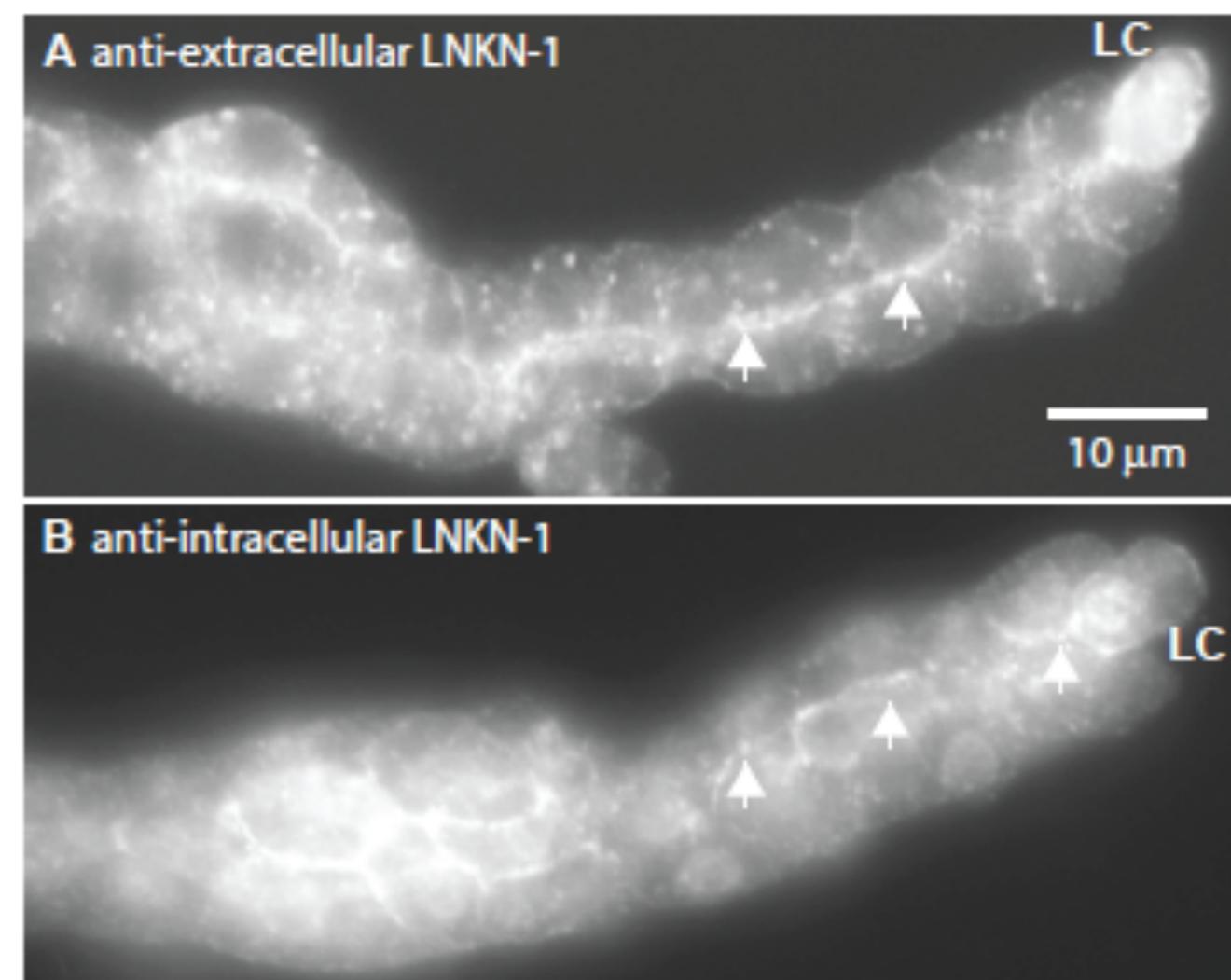


LINKIN is in plasma membrane of many cells, enriched in apical domains

TRANSLATIONAL YFP



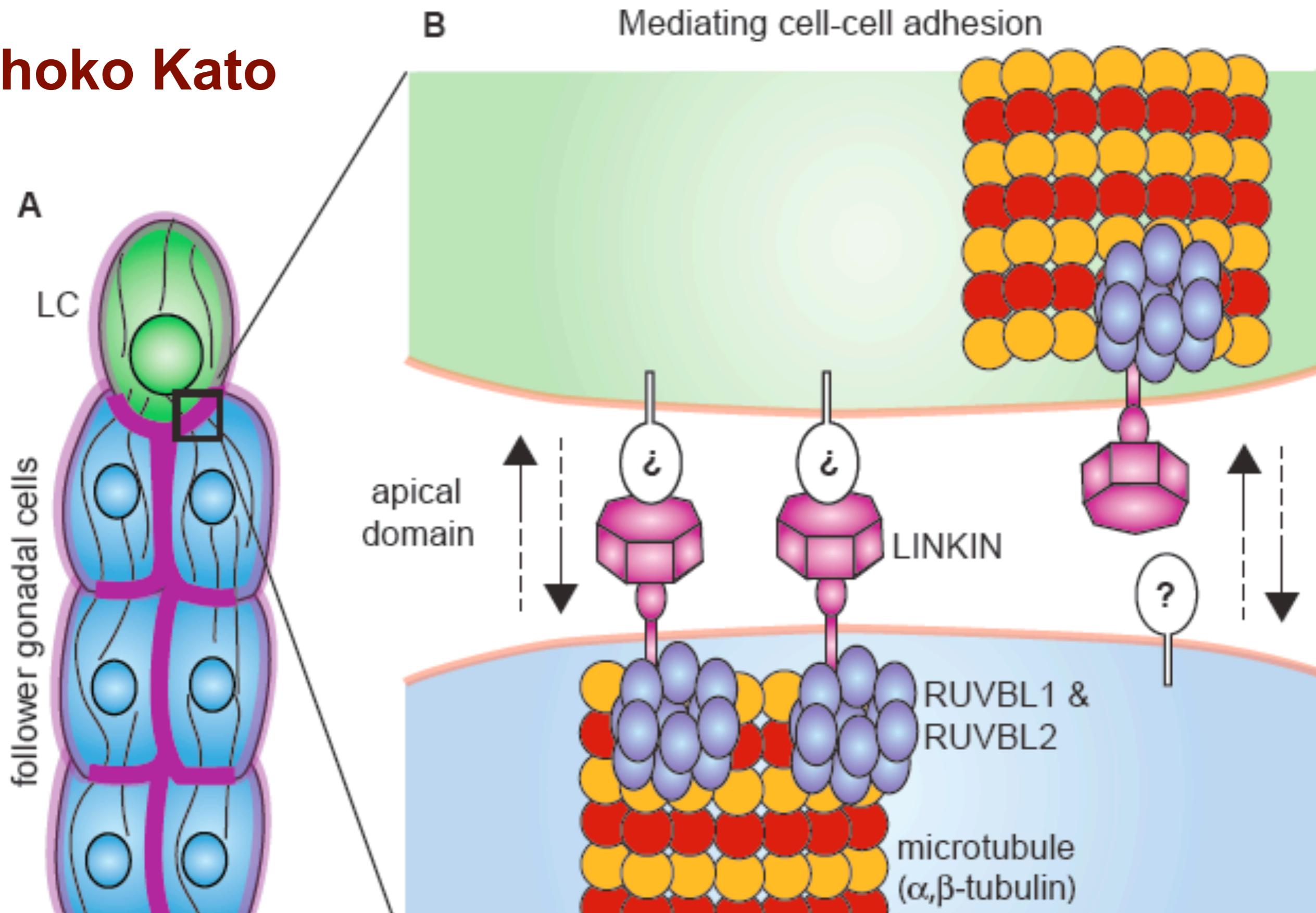
antisera to N or C
terminal domains



Mihoko Kato

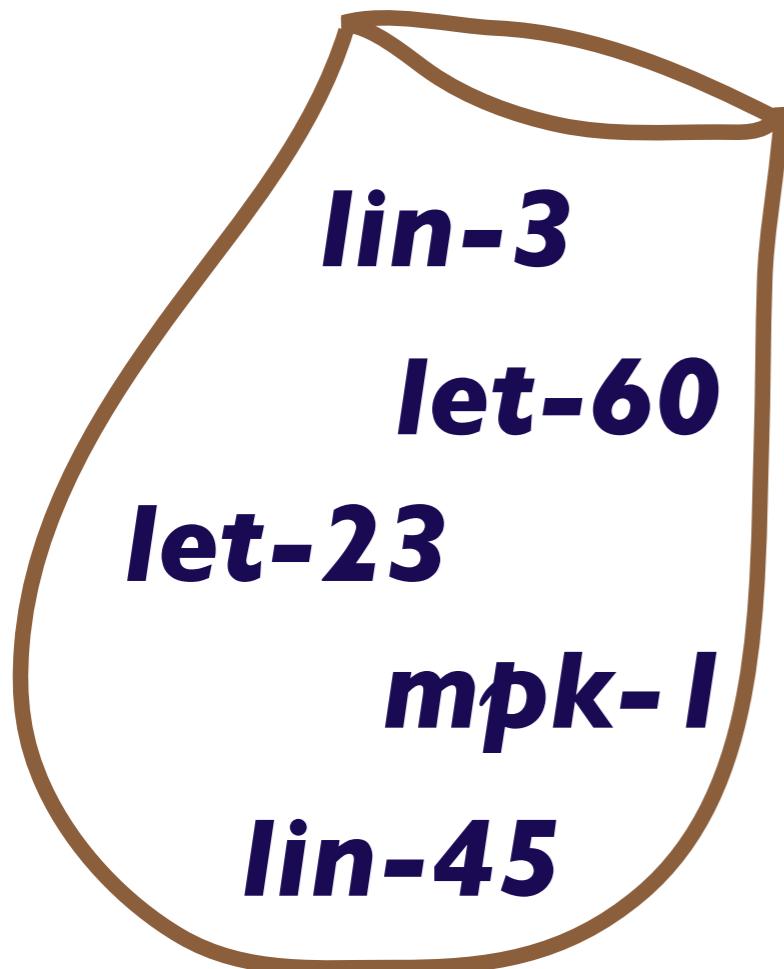
Hypothesis: LINKIN•RUVB complex organizes microtubules and leads to tight cell association

Mihoko Kato

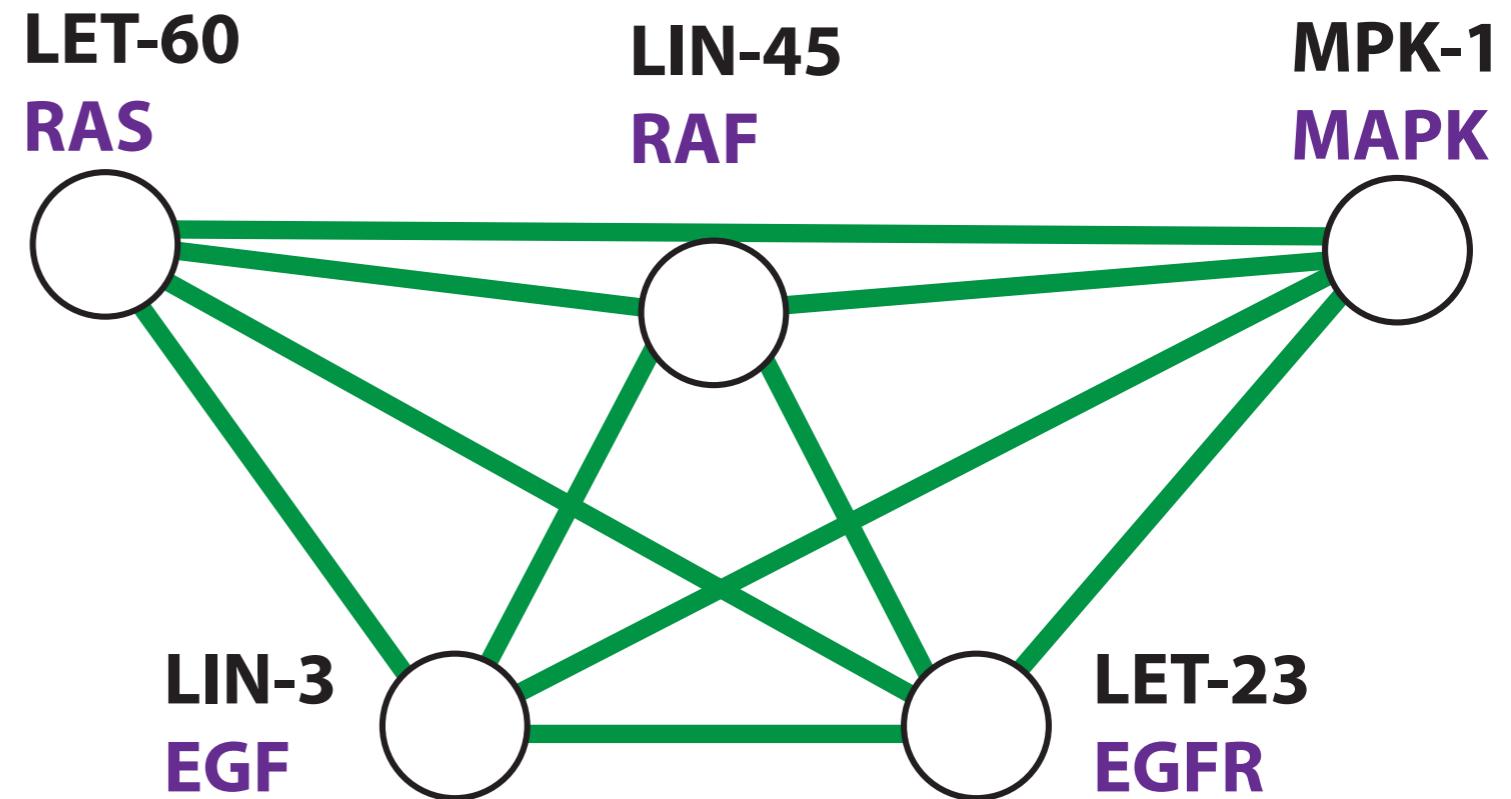


Bag of genes

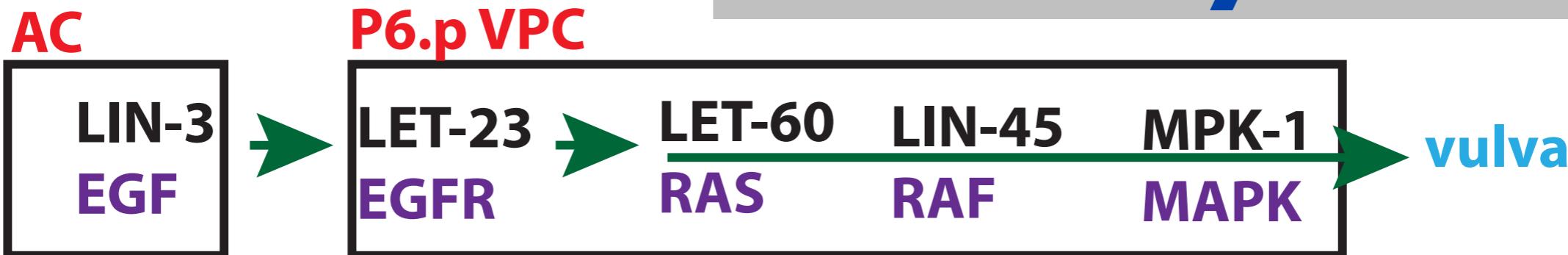
GO:0040026



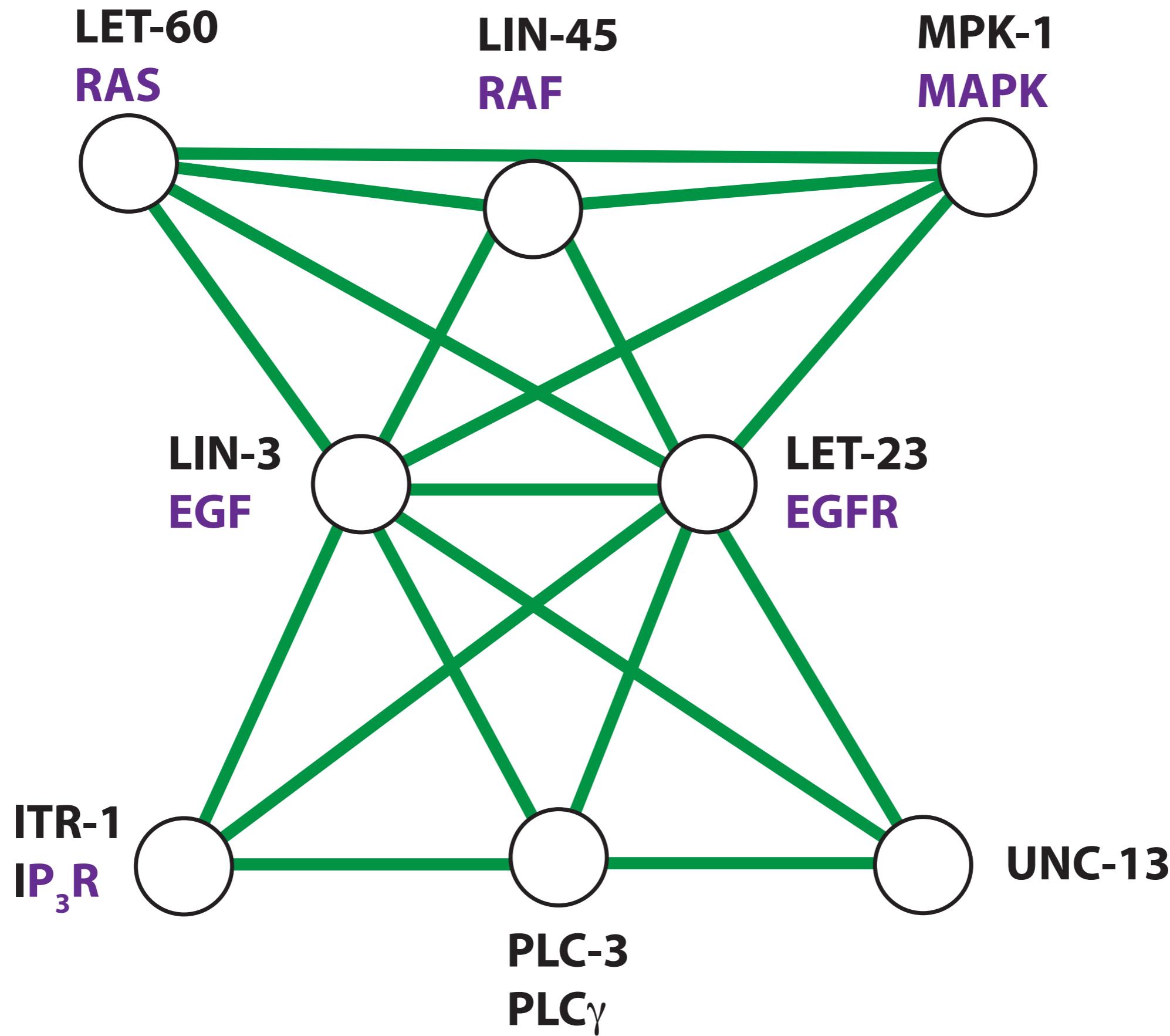
Network



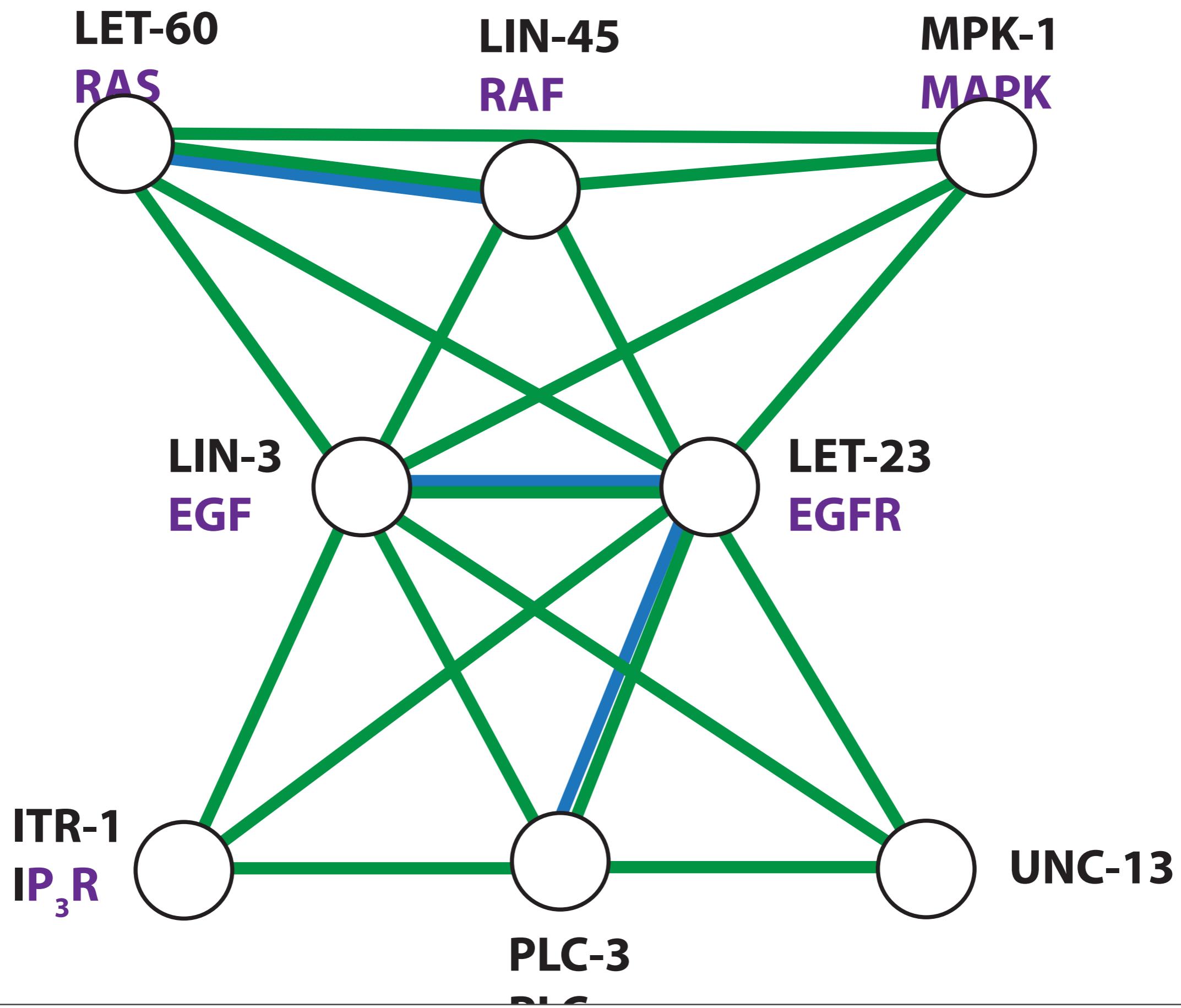
Pathway/Circuit



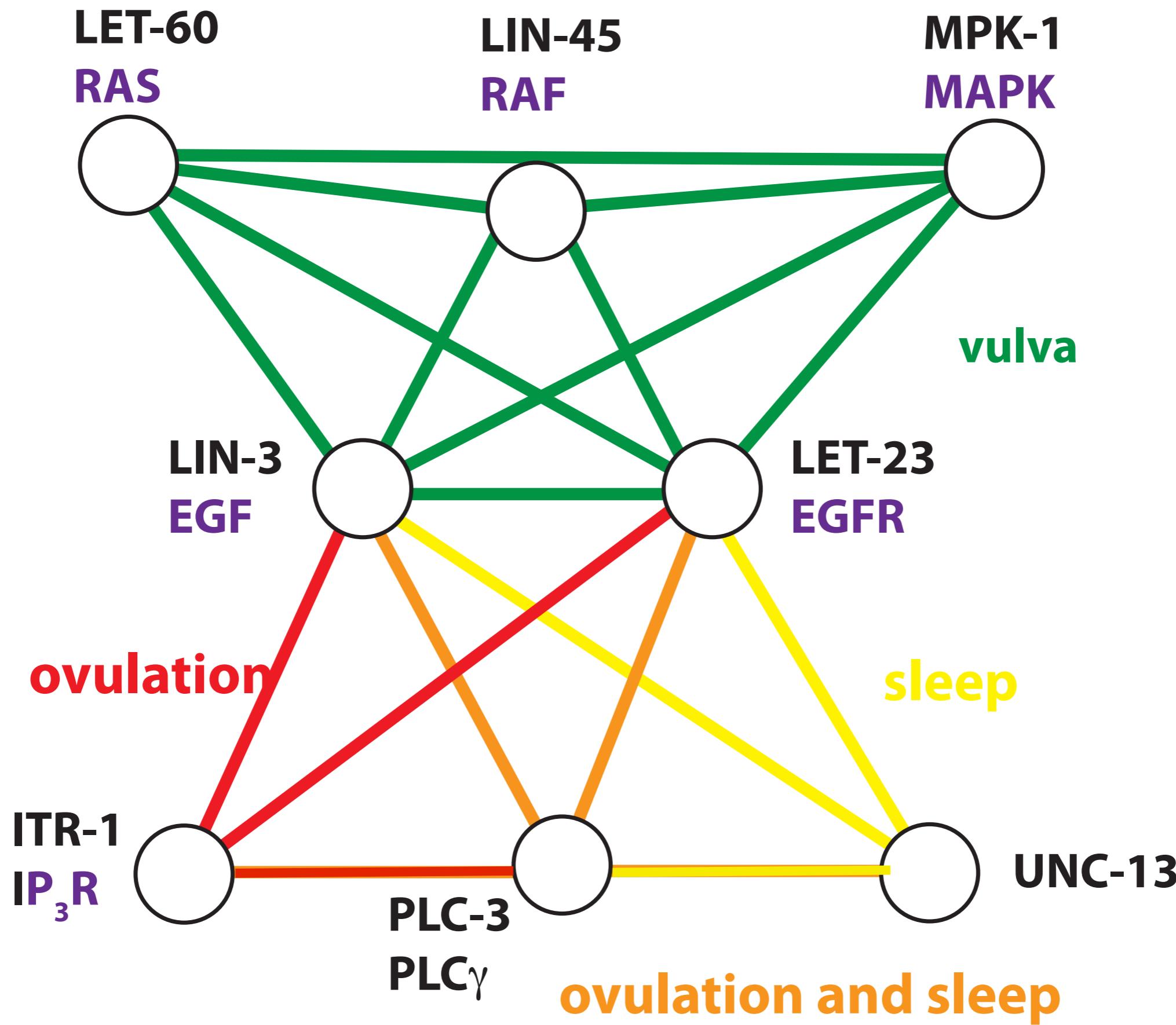
Network of Genetic Interactions



...with Physical Interactions



Network of Process/Phenotypes

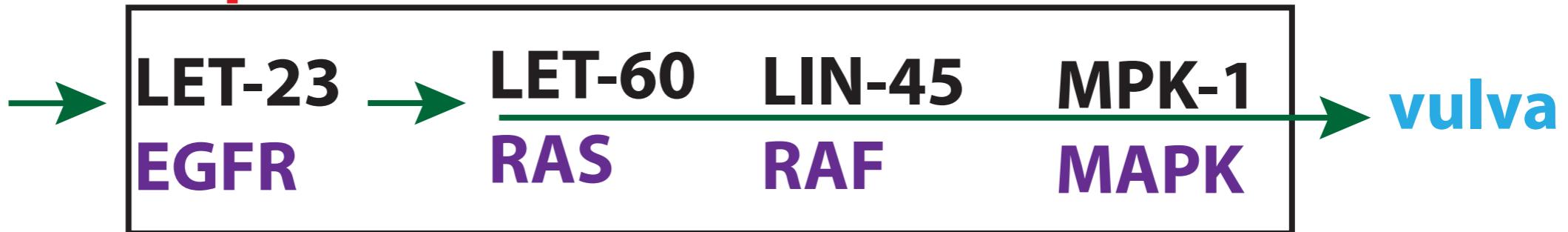


Context dependence

AC



P6.p VPC



?



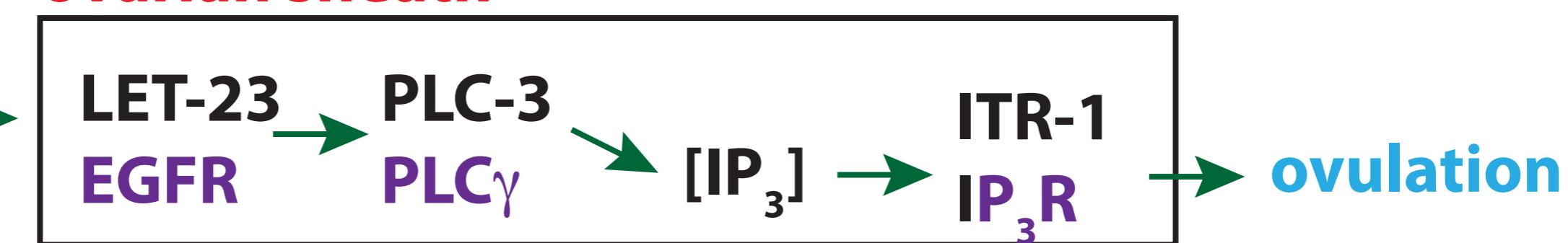
ALA neuron



germline



ovarian sheath

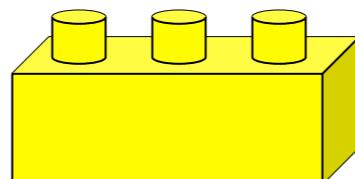


LEGO: Logical Extension of Gene Ontology

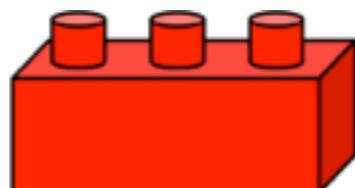


**Increased expressivity for GO annotations
Pathway-like representation
LEGO annotation tool**

**gene product A does molecular function B
to gene product C in location D during process E
with input F, related to process G**



**Seth Carbon
Chris Mungall
Anushya Muruganujan**



**Huaiyu Mi
Paul Thomas
Gene Ontology Consortium**

Gene Pages at WormBase

Concise Description (hand-written + automated)

Gene Ontology terms

James Done

Interactions (genetic, physical, regulatory)

Phenotypes

Human Disease relevance

Topic Displays at WormBase

Genes

Gene Ontology terms

Interactions (genetic, physical, regulatory)

Phenotypes

Gene expression clusters (microarray, RNA-seq)

Pathways

Karen Yook, WormBase Consortium

Link to WikiPathways: [h](#)

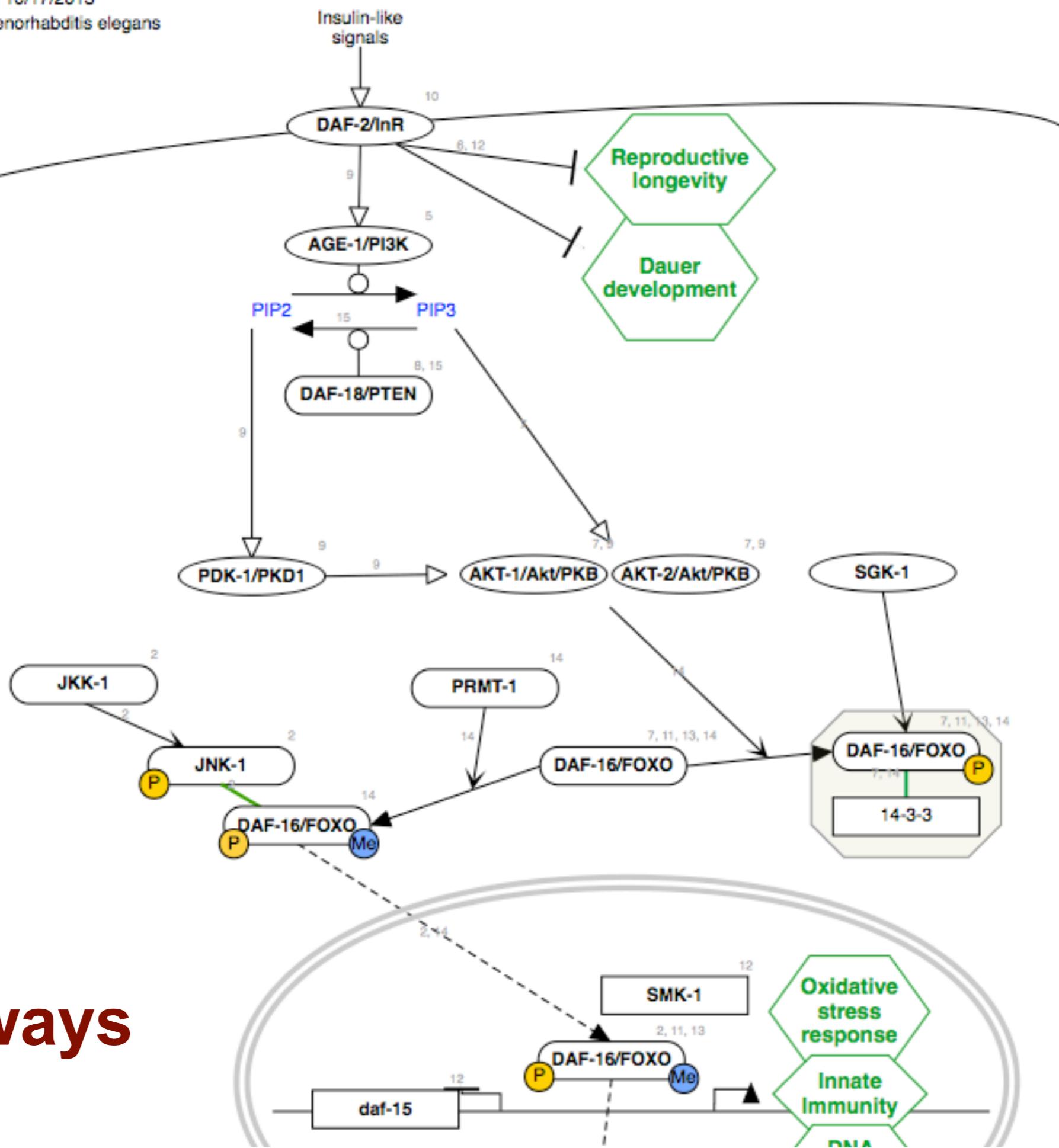
Aging

Title: Aging
 Last modified: 10/1
 Organism: Caenorhabditis elegans

C

WikiPathways

[View at WIKIPATHWAY](#)



[Download](#)

**There are knowledge gaps
at many levels**

**We need to represent and
model at many levels**

**The models can be used to
prioritize experiments to fill
knowledge gaps**