

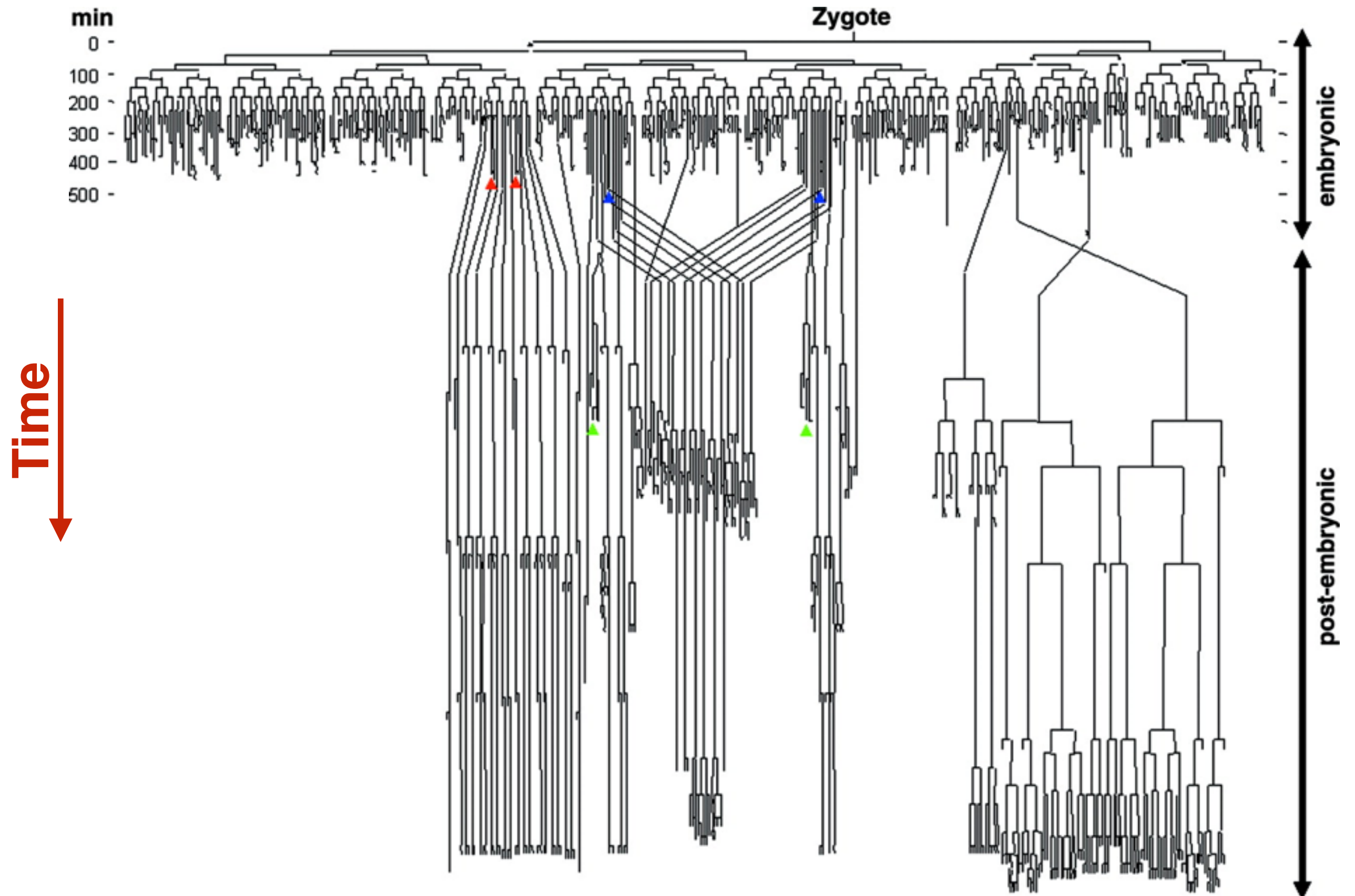
Bio393: Genetic Analysis

Developmental genetics I



C. elegans

The cell lineage of *C. elegans* is known and invariant



The cell lineage of *C. elegans* is known and invariant



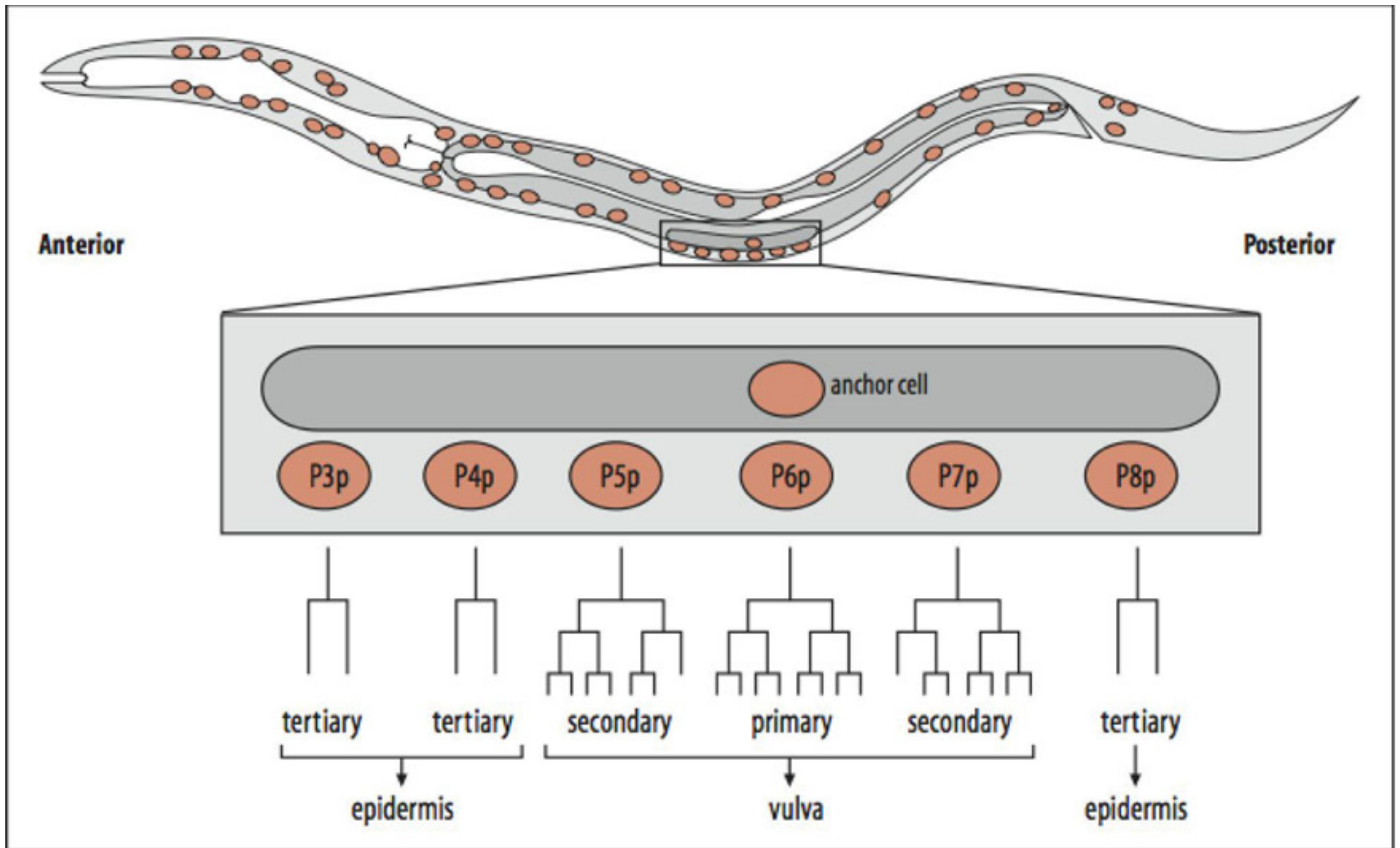
John Sulston

The cell lineage of *C. elegans* is known and invariant



John Sulston

C. elegans vulval development

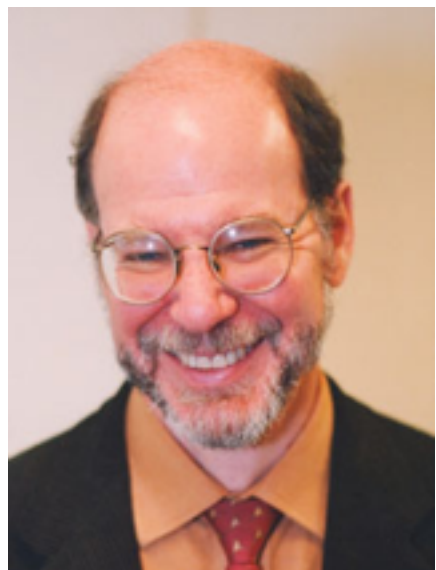
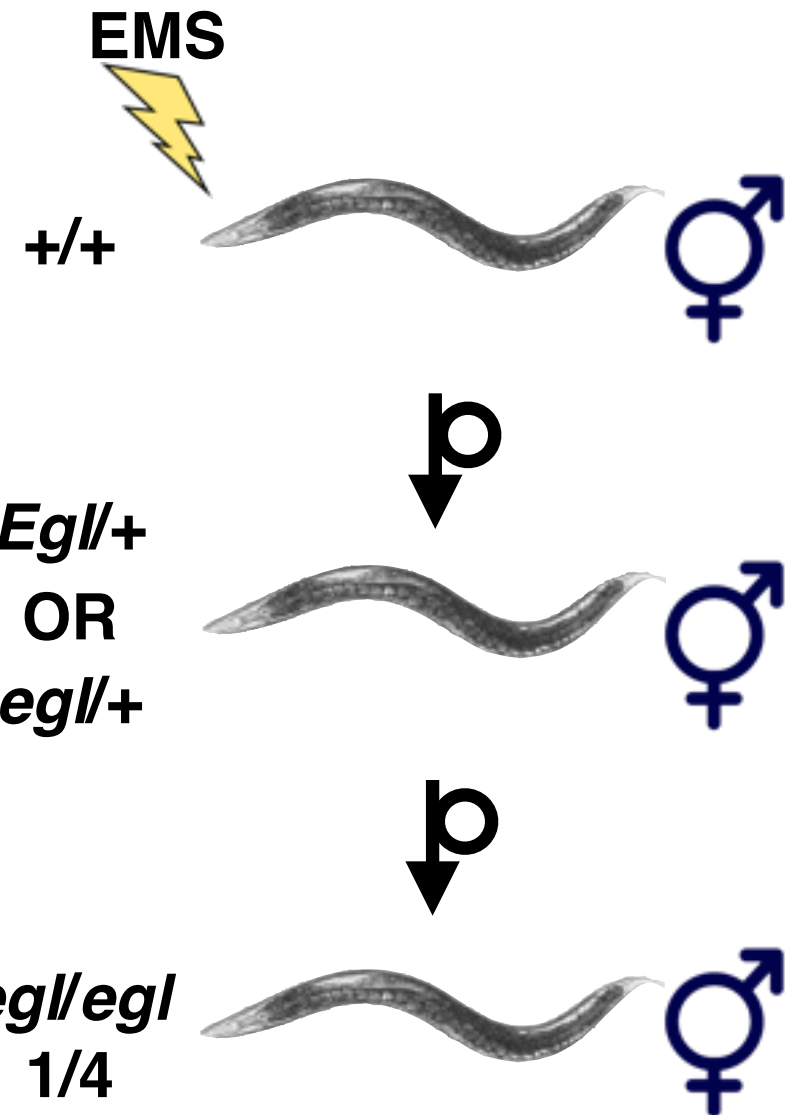
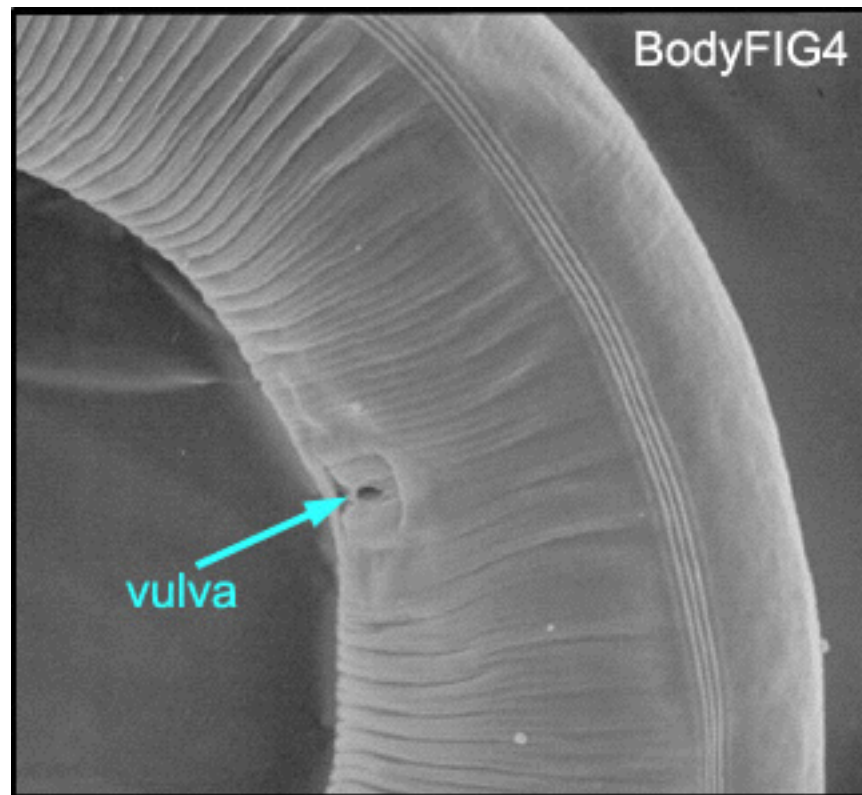


One of the best genetic screens ever



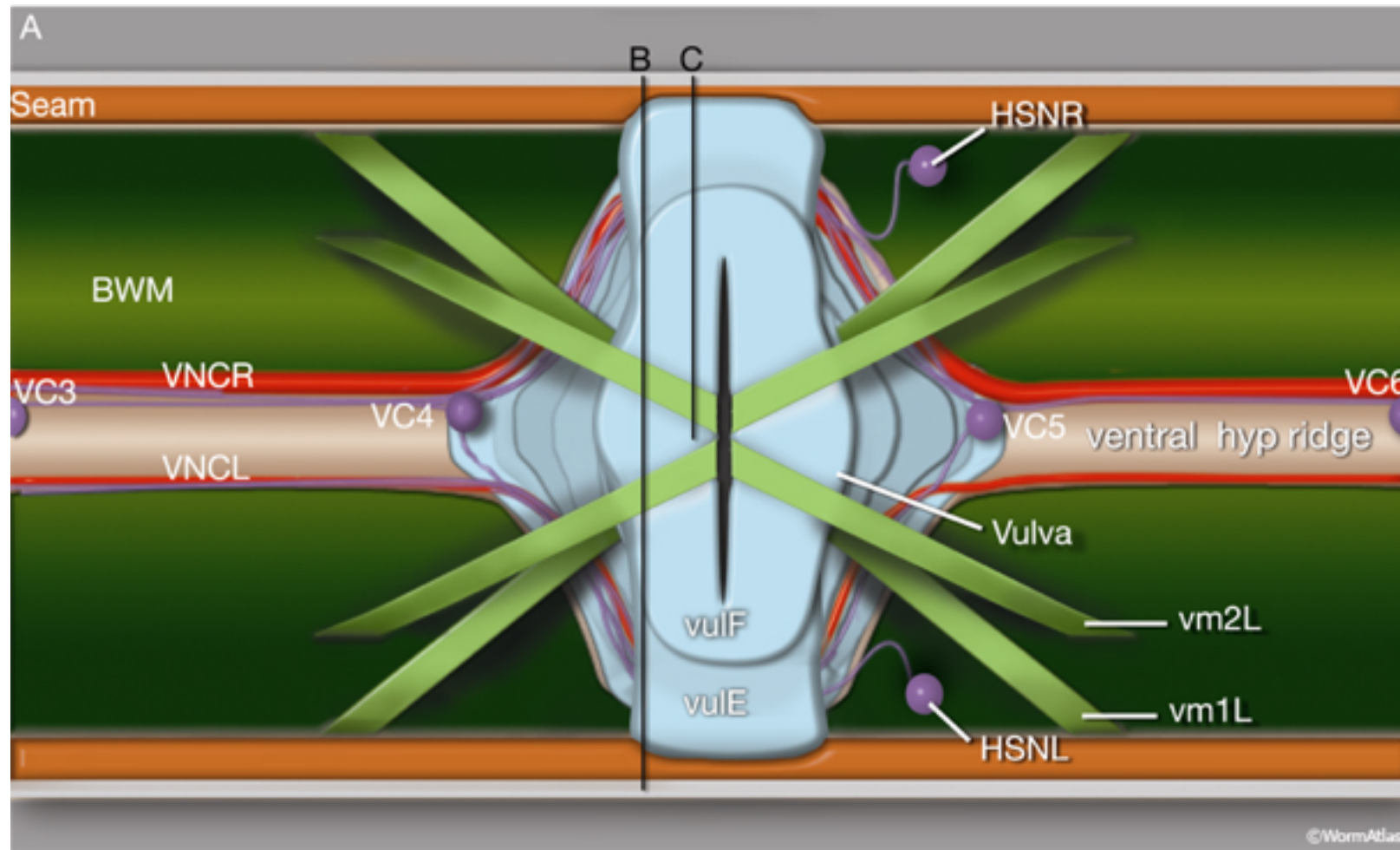
Let's say you
screened for mutants
that failed to lay eggs

Called Egl for egg-laying
defective



Bob Horvitz

One of the best genetic screens ever

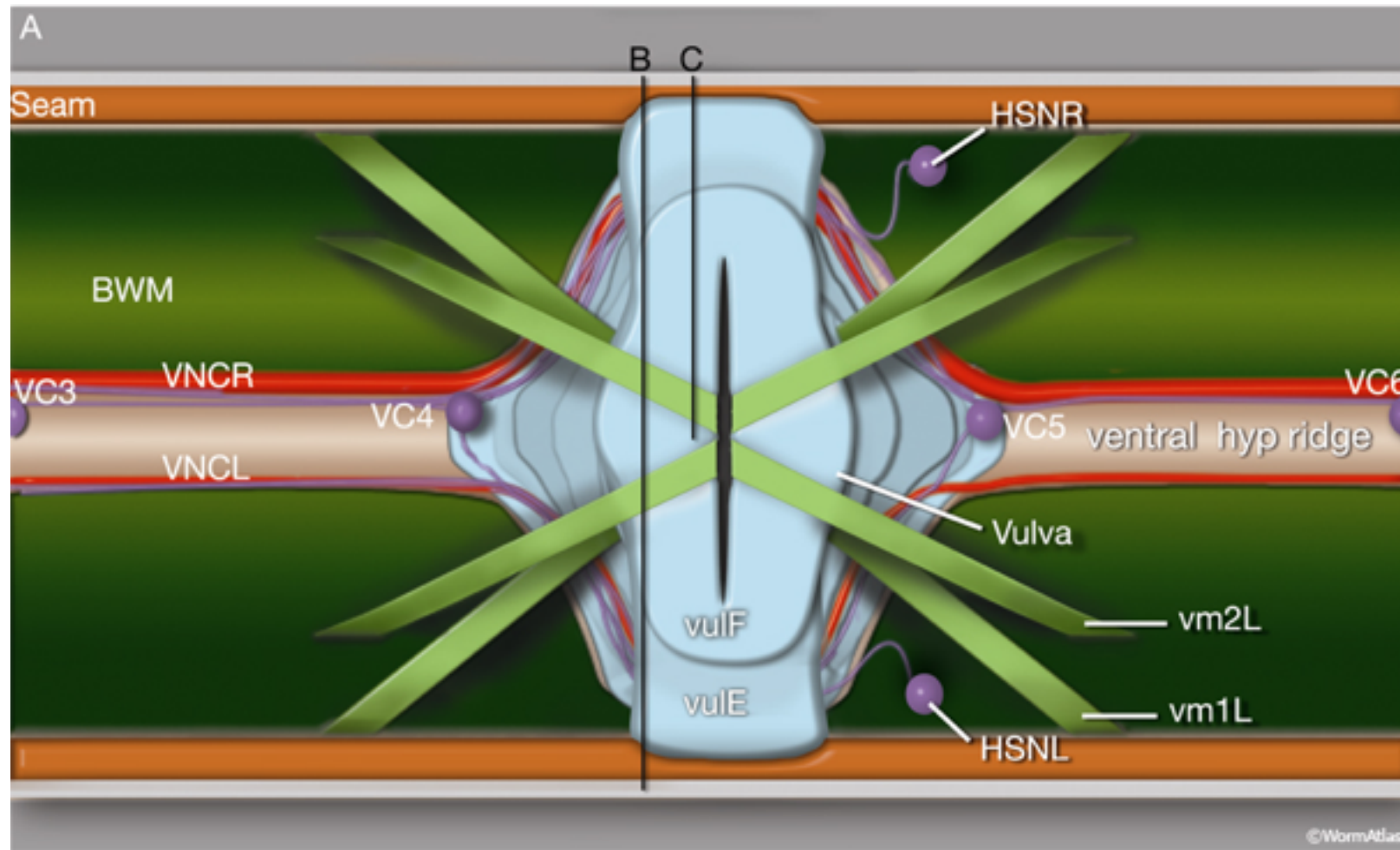


No neuron

egl-1 = inducer of programmed cell death

Hermaphrodite-Specific Neuron (HSN)
inappropriately dies

One of the best genetic screens ever

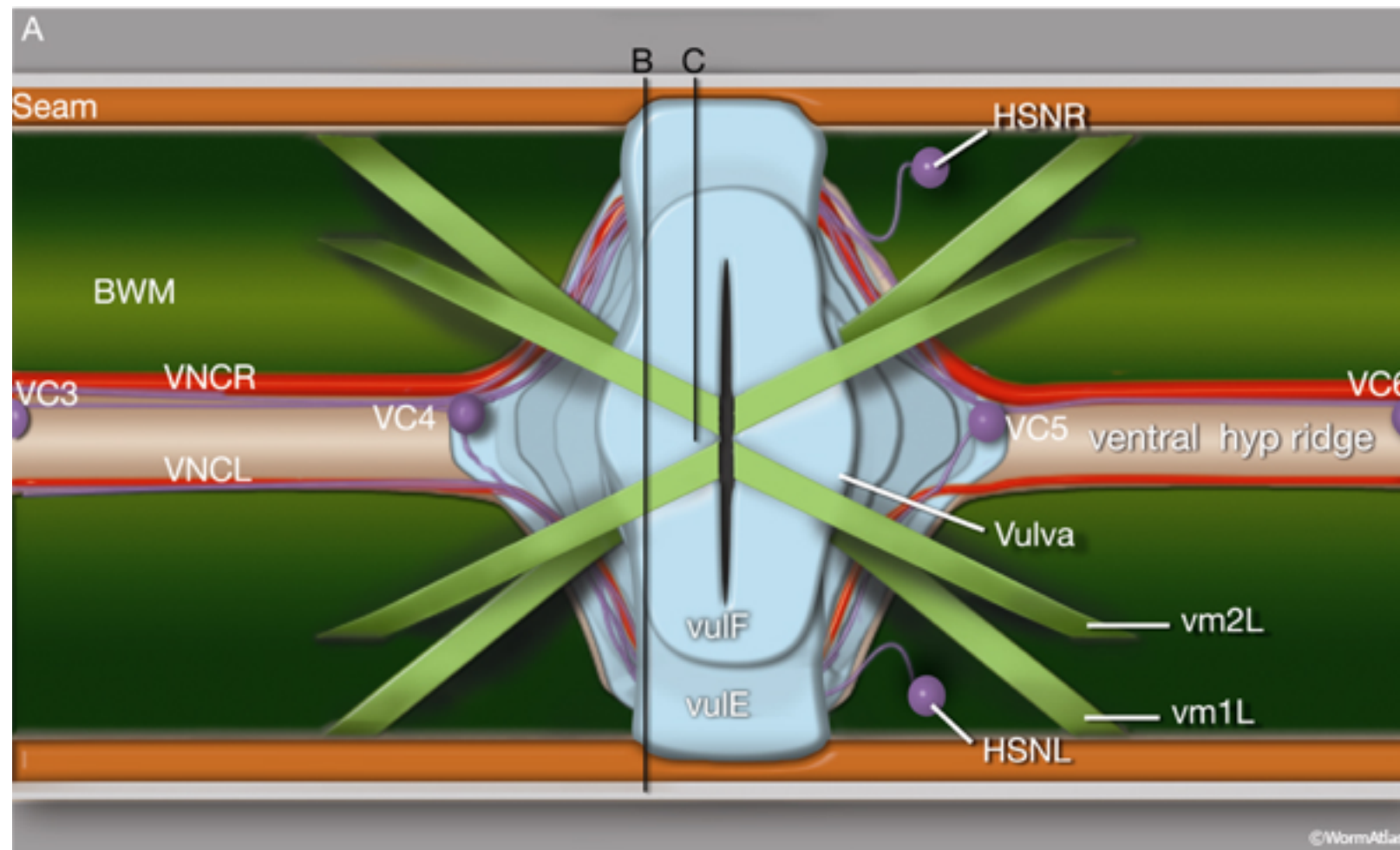


No neuron

tra-1 = inducer of sex determination

Mutants are partially male so HSNs die

One of the best genetic screens ever

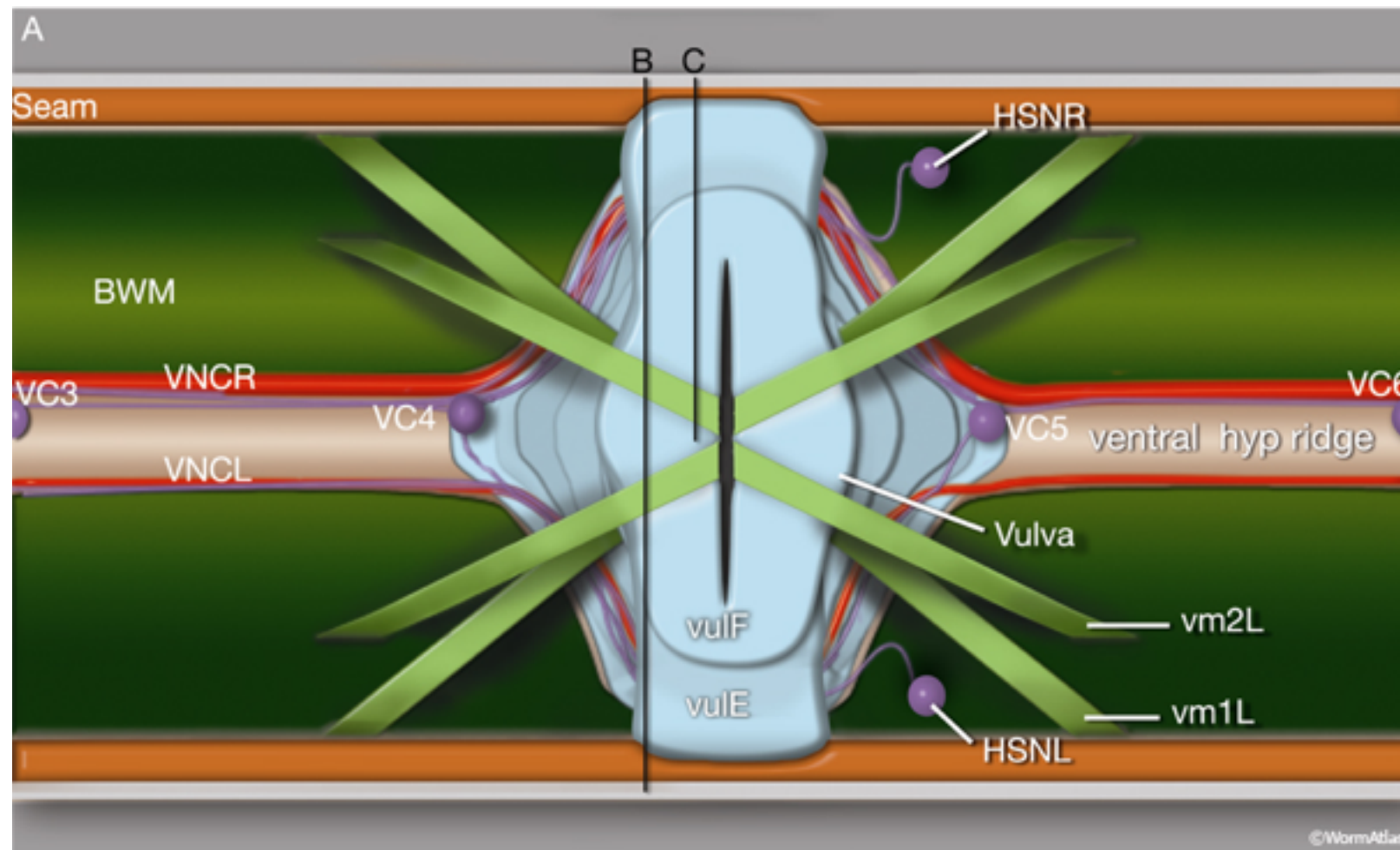


No neuron

**No neuronal
signaling**

egl-6 = serotonin signaling from HSN is defective

One of the best genetic screens ever



No neuron

**No neuronal
signaling**

No vulva

lin-3 = lineage defective gene 3

Vulval cells are not specified

One of the best genetic screens ever



C. elegans



Sydney Brenner

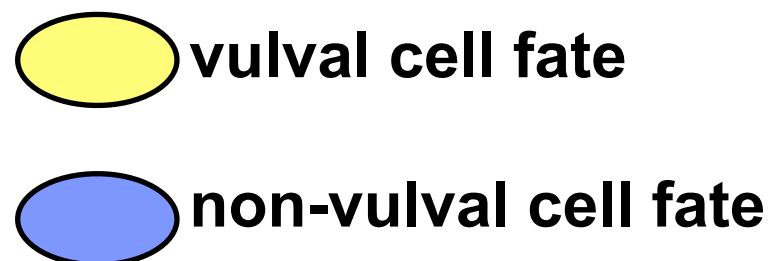
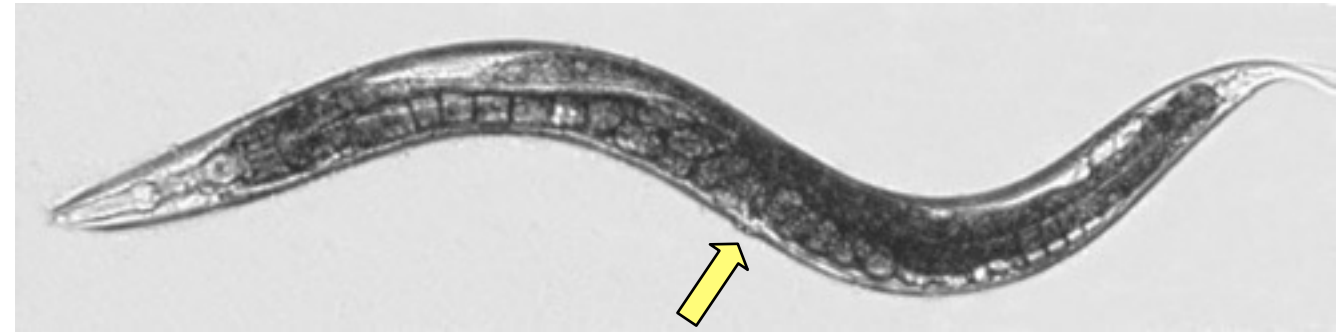
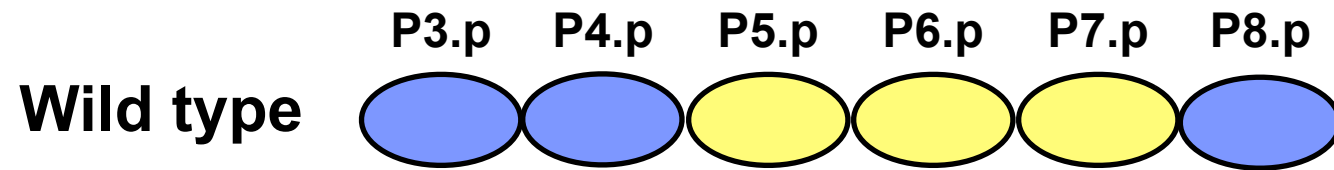


H. Robert Horvitz

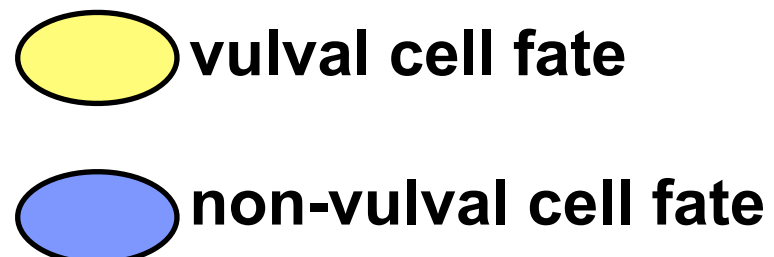
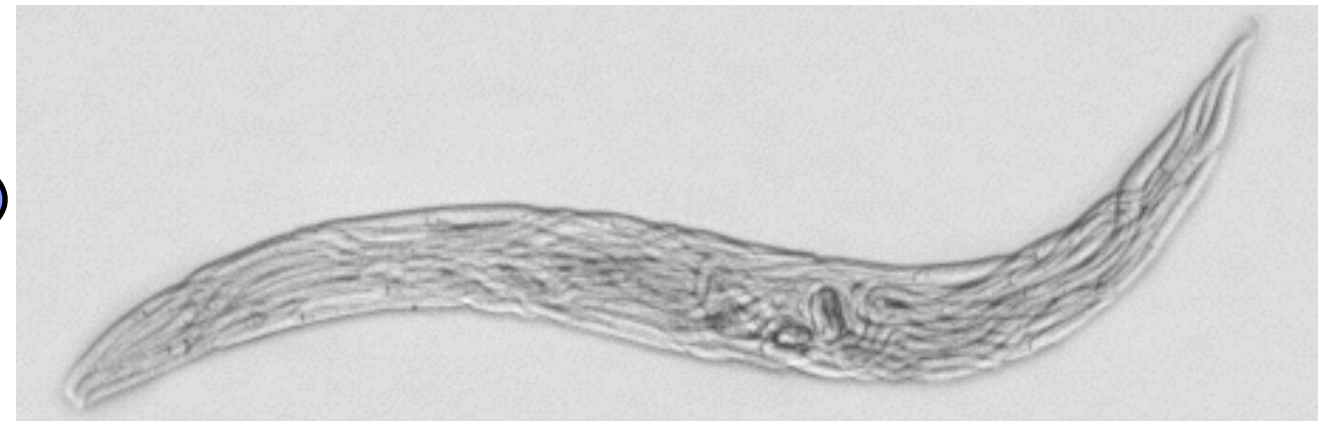
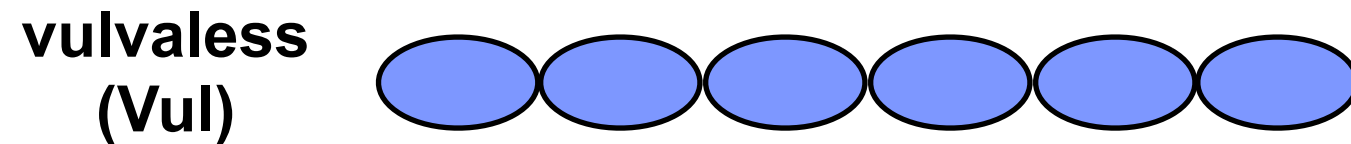
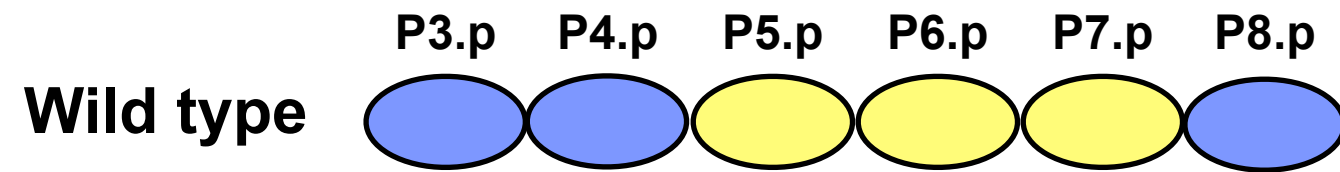


John E. Sulston

Three cells express vulval fates in wild-type animals

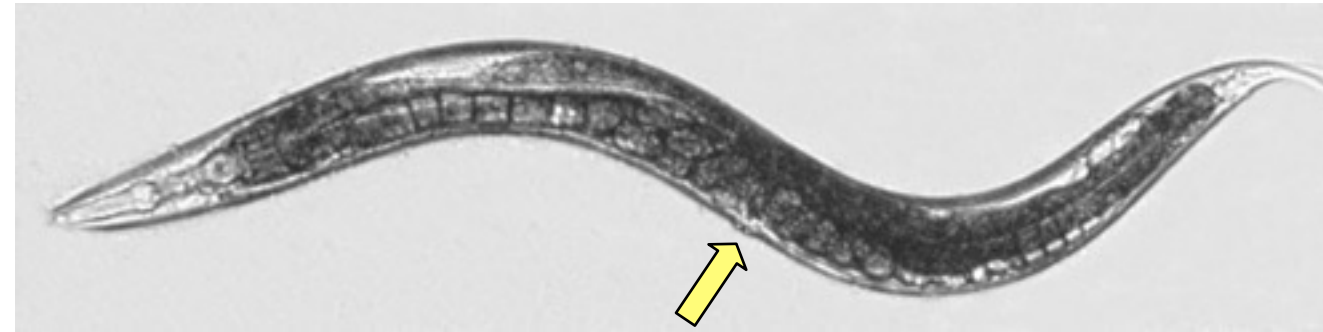
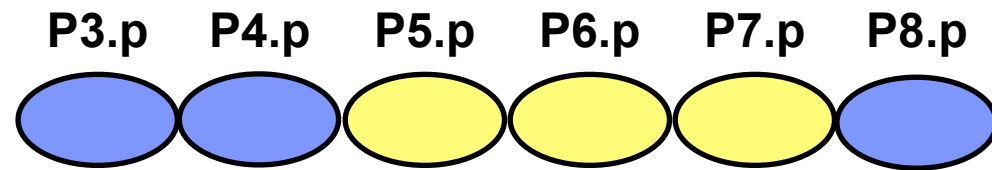


No cells express vulval fates in vulvaless mutants

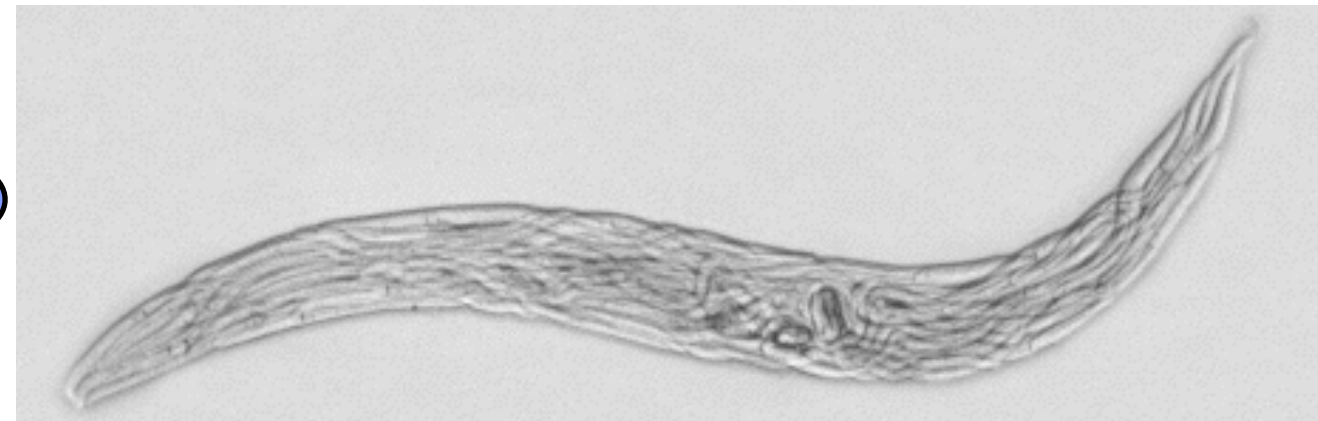
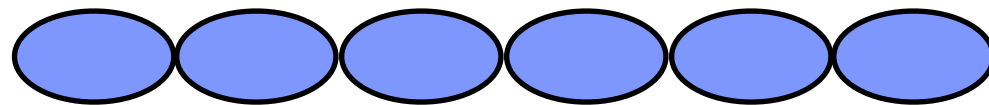


Six cells express vulval fates in multivulva mutants

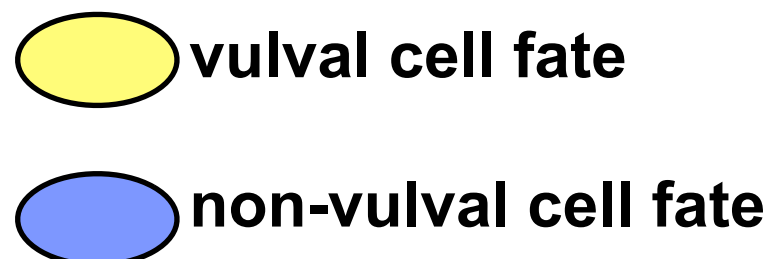
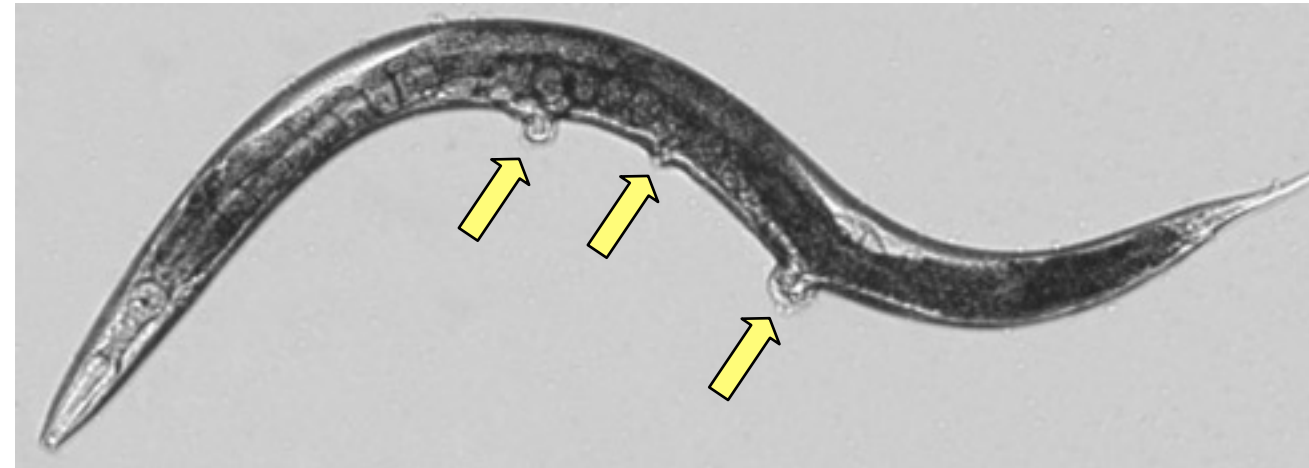
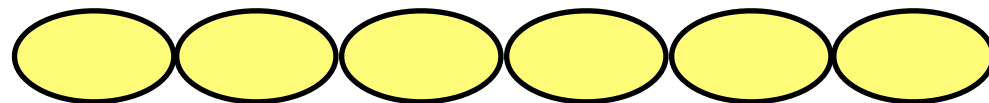
Wild type



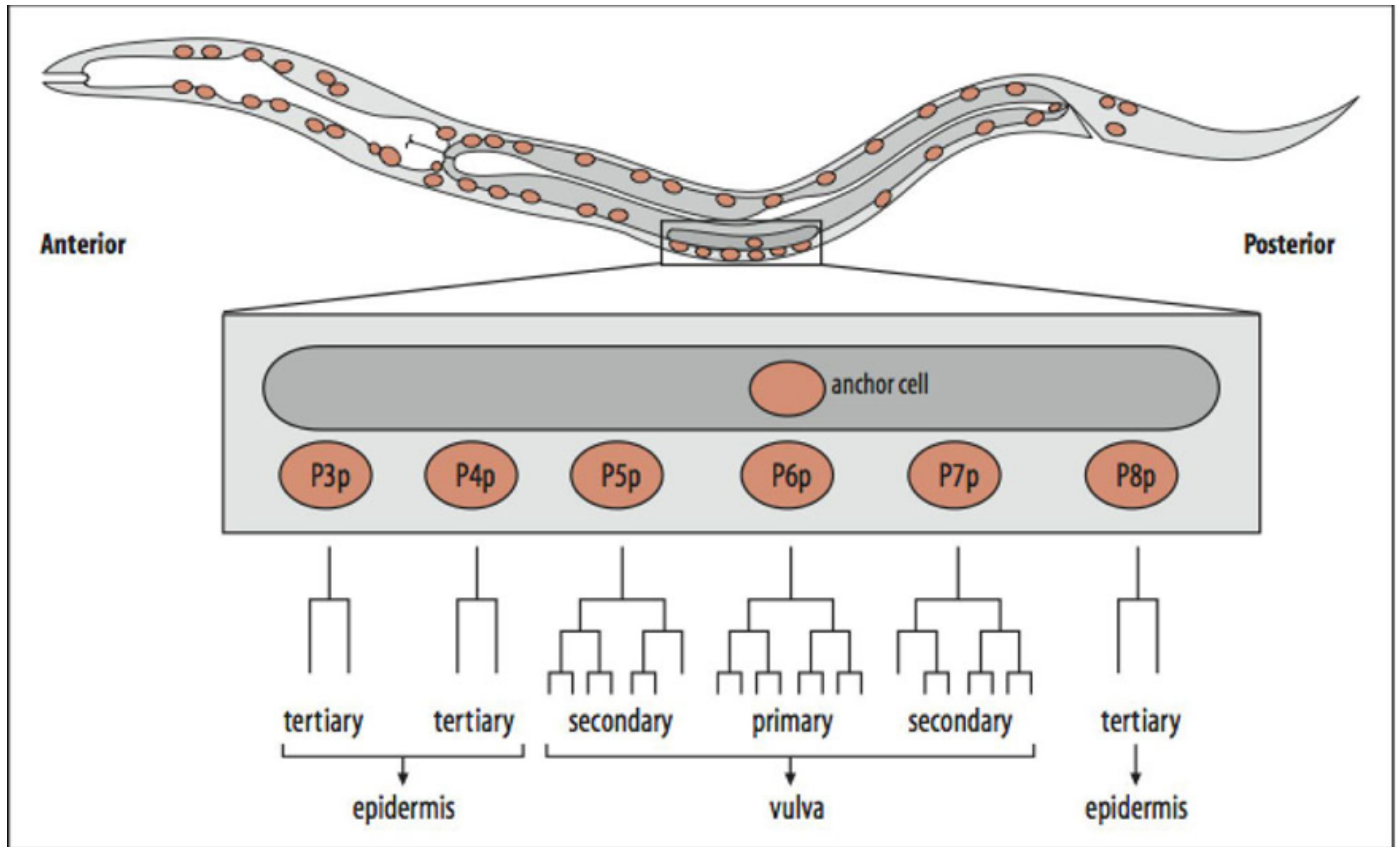
**vulvaless
(Vul)**



**multivulva
(Muv)**

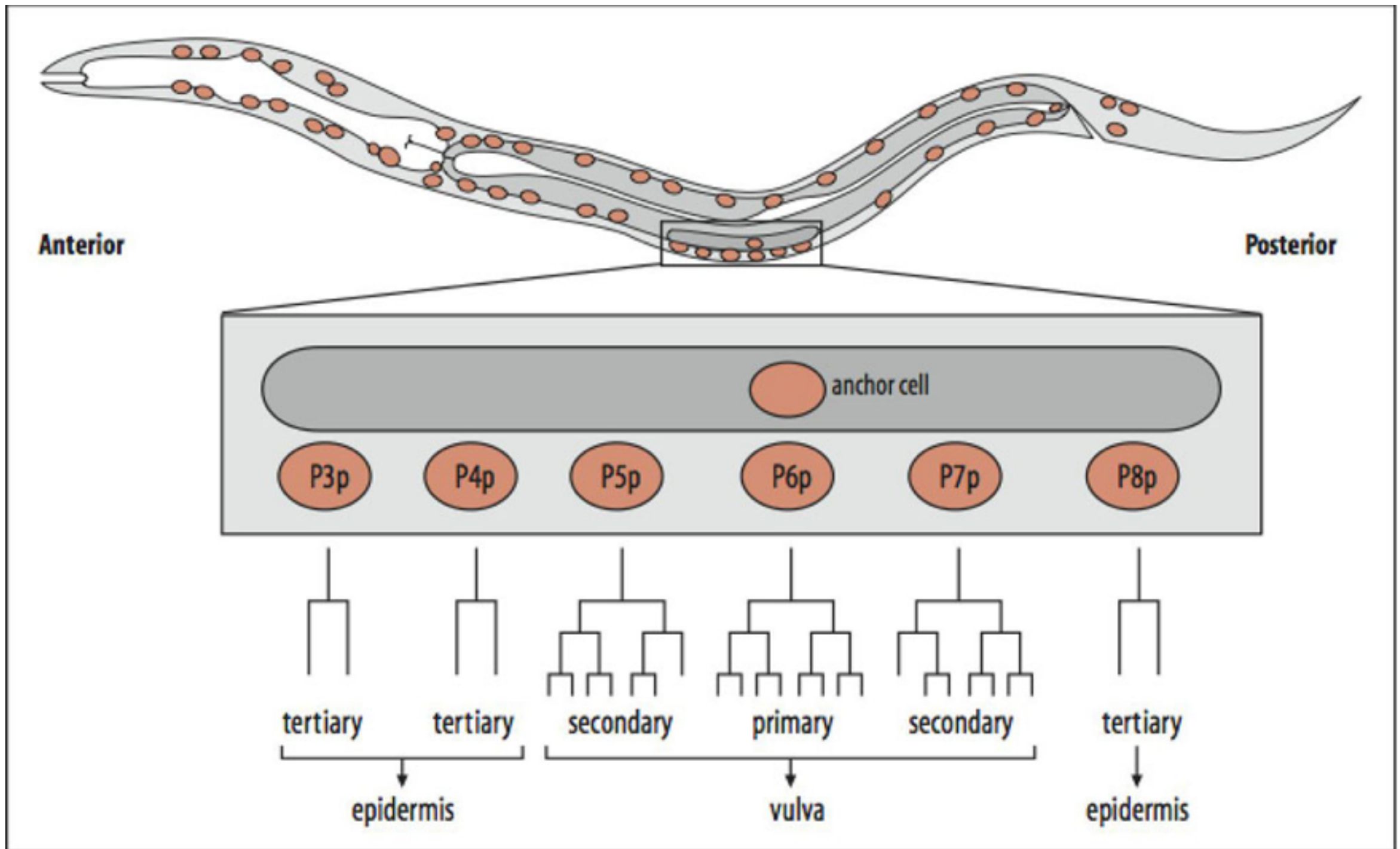


In developmental genetics, we seek to understand cell-cell interactions and tissue formation

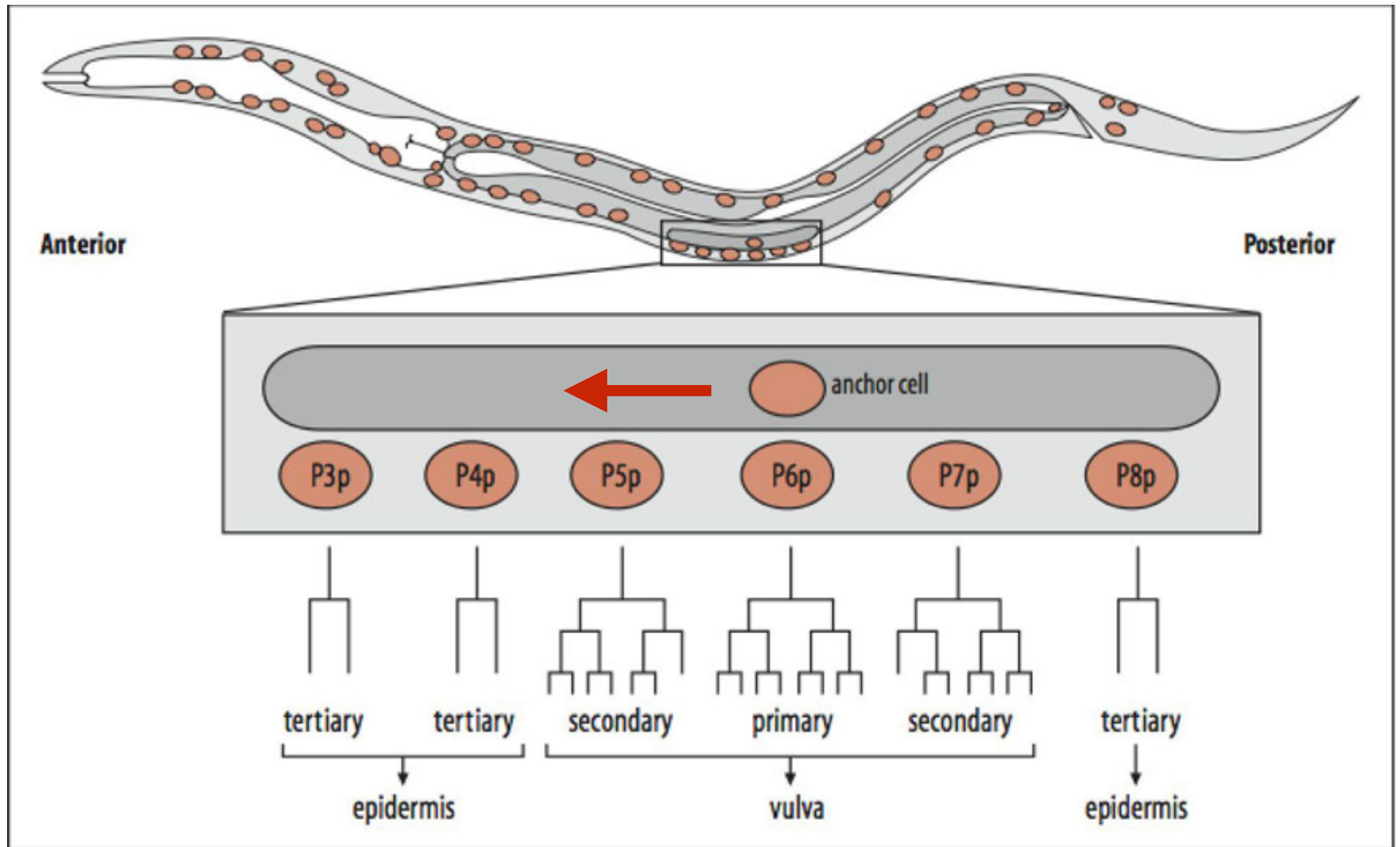


How do we perturb this system (in addition to genetics)?

The Pn.p cells are equally potent and induced to make vulval cells



The Pn.p cells are equally potent and induced to make vulval cells



dig-1 displaced gonad mutants

Vulval mutants

Mutant	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv

Double mutants defined

the basic vulval cell-fate specification pathway

Mutant genotypes	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-3(0); let-23(gf)</i>	Muv
<i>lin-3(0); let-60(gf)</i>	Muv
<i>let-23(0); let-60(gf)</i>	Muv
<i>let-23(gf); let-60(0)</i>	Vul
<i>let-60(0); lin-1(0)</i>	Muv
<i>let-23(0); lin-1(0)</i>	Muv

Double mutants defined

the basic vulval cell-fate specification pathway

Mutant genotypes	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-3(0); let-23(gf)</i>	Muv
<i>lin-3(0); let-60(gf)</i>	Muv
<i>let-23(0); let-60(gf)</i>	Muv
<i>let-23(gf); let-60(0)</i>	Vul
<i>let-60(0); lin-1(0)</i>	Muv
<i>let-23(0); lin-1(0)</i>	Muv

***lin-3* → *let-23* →**

vulval fate

Double mutants defined

the basic vulval cell-fate specification pathway

Mutant genotypes	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-3(0); let-23(gf)</i>	Muv
<i>lin-3(0); let-60(gf)</i>	Muv
<i>let-23(0); let-60(gf)</i>	Muv
<i>let-23(gf); let-60(0)</i>	Vul
<i>let-60(0); lin-1(0)</i>	Muv
<i>let-23(0); lin-1(0)</i>	Muv

***lin-3* → *let-23* → *let-60* →**

vulval fate

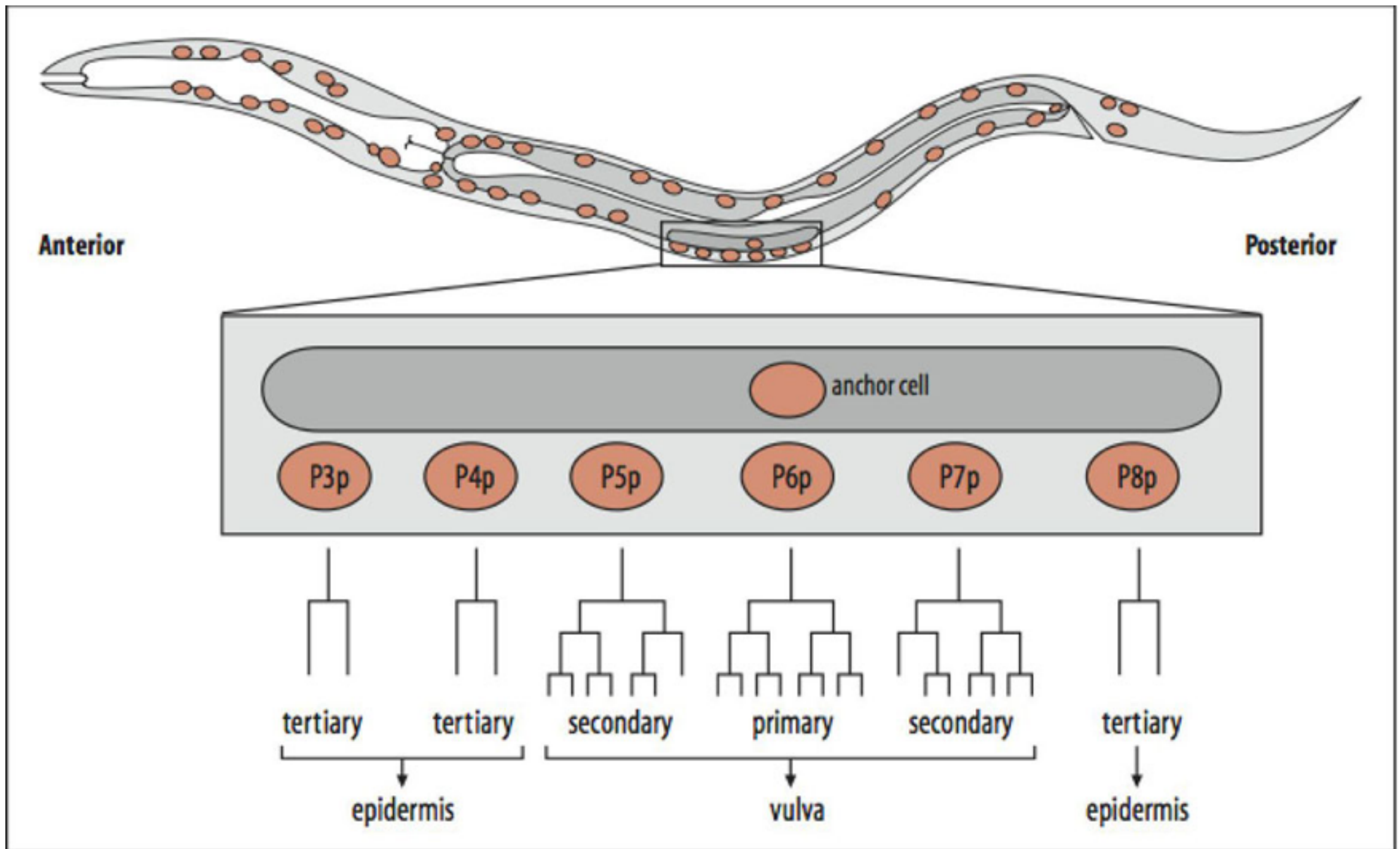
Double mutants defined

the basic vulval cell-fate specification pathway

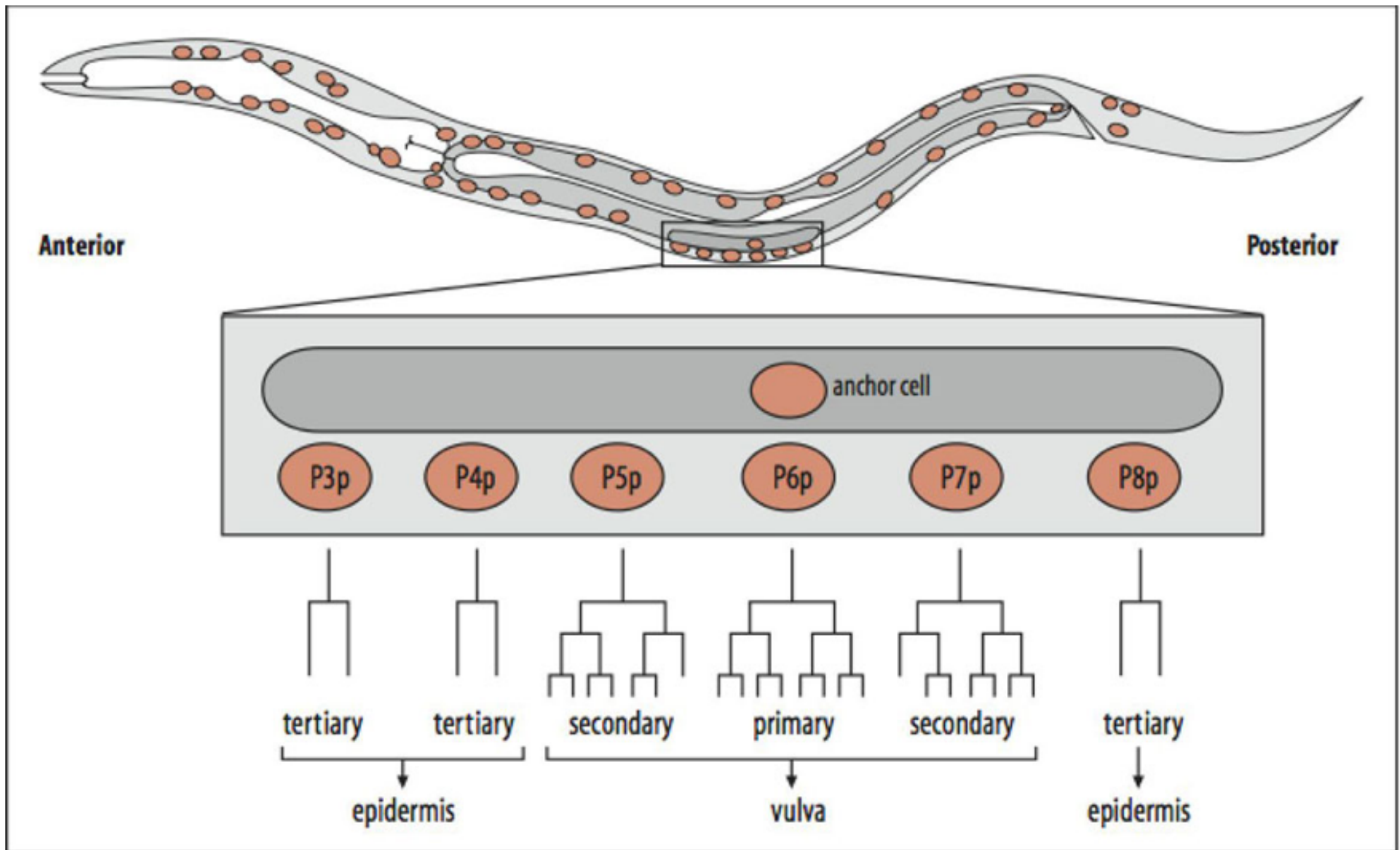
Mutant genotypes	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-3(0); let-23(gf)</i>	Muv
<i>lin-3(0); let-60(gf)</i>	Muv
<i>let-23(0); let-60(gf)</i>	Muv
<i>let-23(gf); let-60(0)</i>	Vul
<i>let-60(0); lin-1(0)</i>	Muv
<i>let-23(0); lin-1(0)</i>	Muv

***lin-3* → *let-23* → *let-60* — *lin-1* — vulval fate**

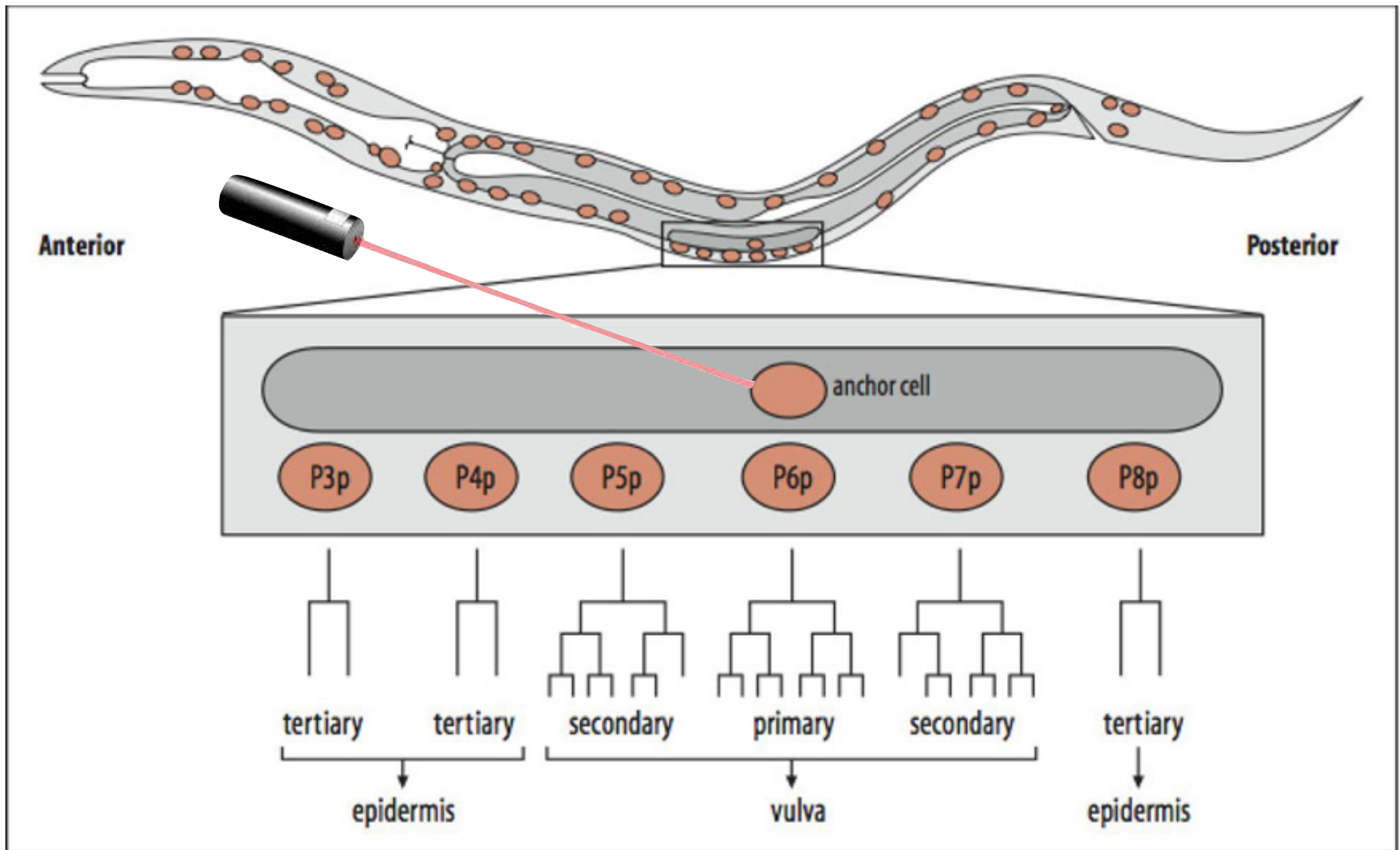
What is the source of the inductive signal?



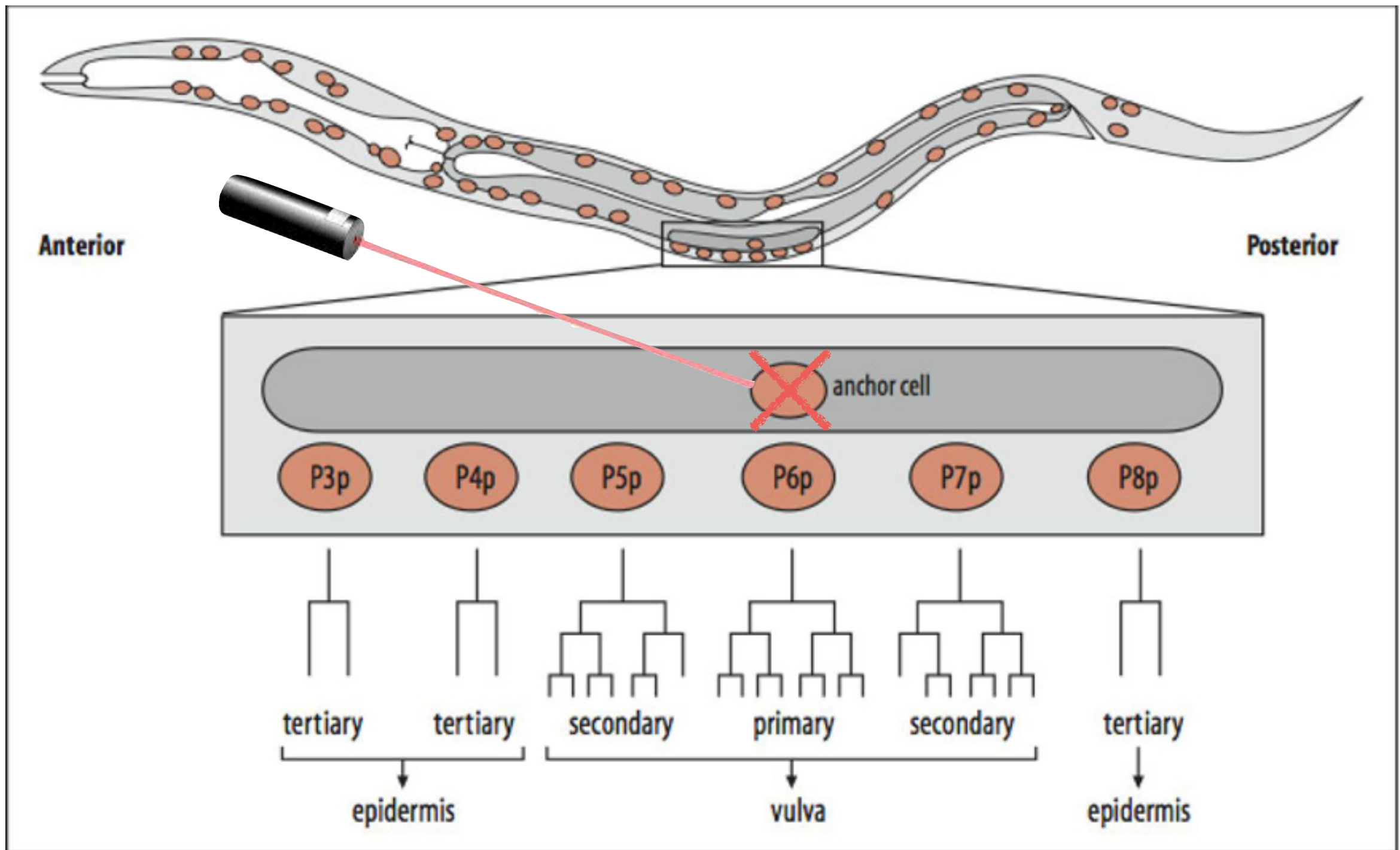
Ablation removes cells and probes cell requirements



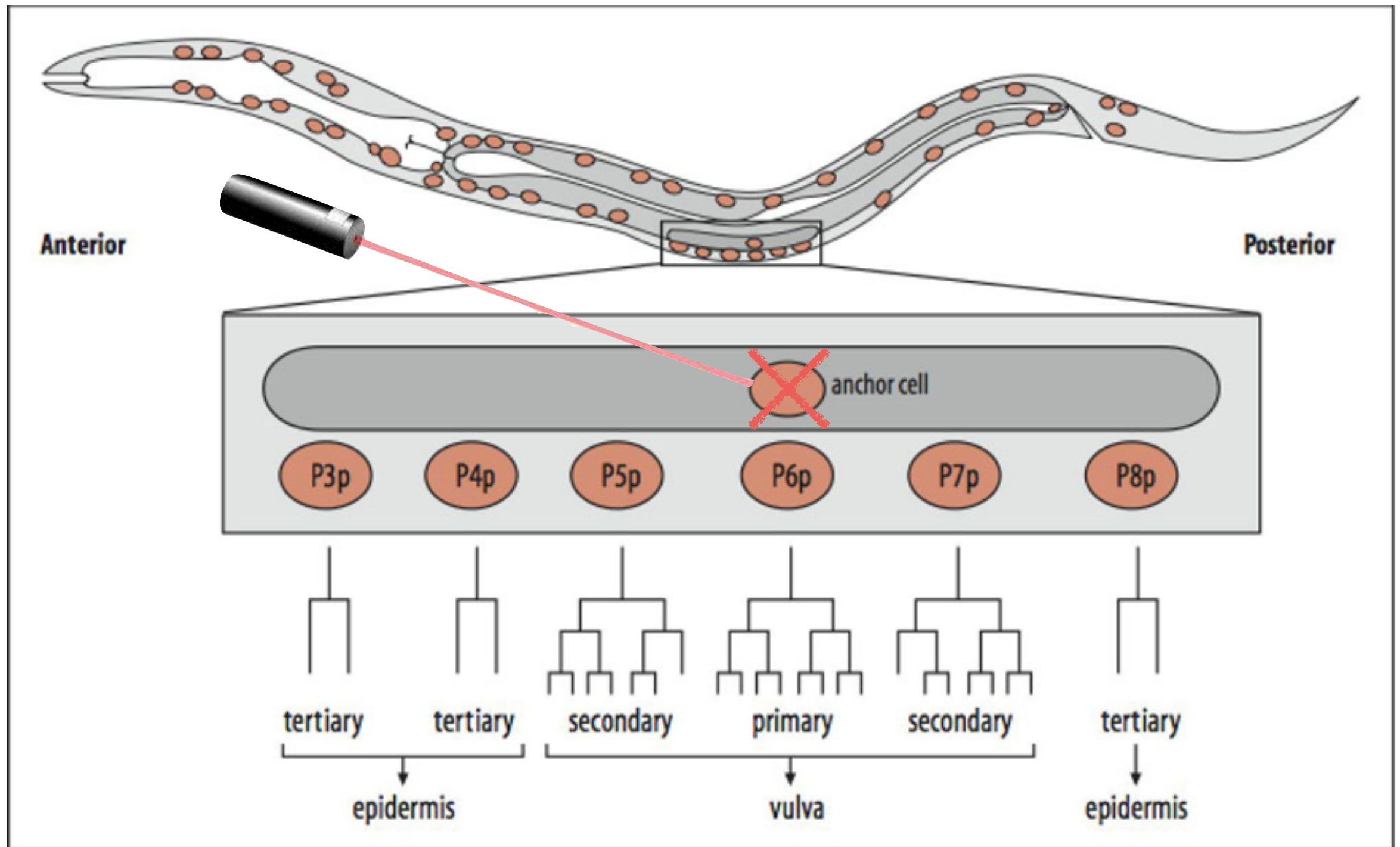
Ablation removes cells and probes cell requirements



Ablation removes cells and probes cell requirements



Ablation removes cells and probes cell requirements

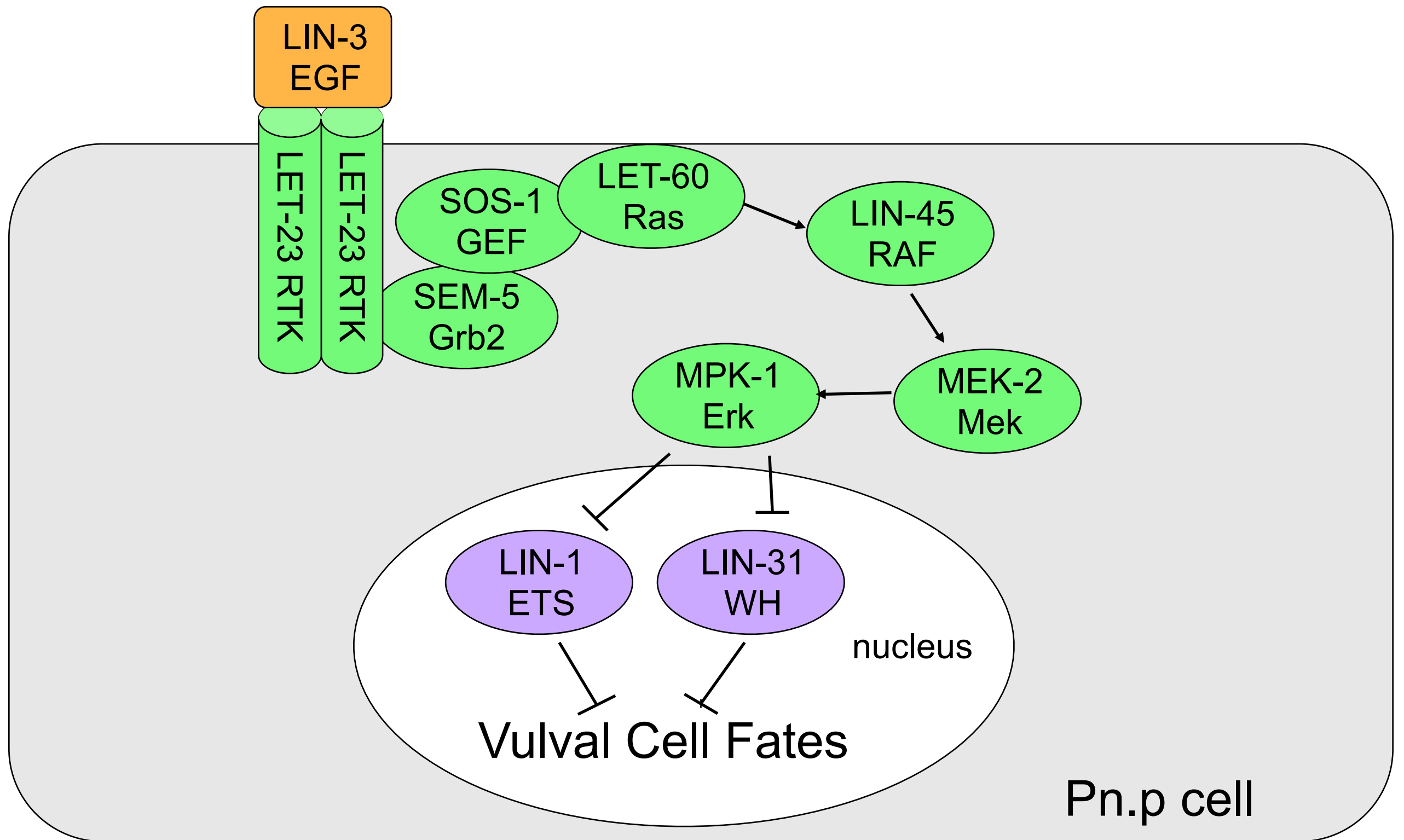


No AC leads to no vulval cell specification
and a vulvaless phenotype

Like *lin-3*, all other vulval mutants are epistatic to AC ablation

Mutant genotypes	Phenotype
AC ablation	Vul
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(gf)</i>	Muv
AC ablation; <i>let-23(gf)</i>	Muv
AC ablation; <i>let-60(gf)</i>	Muv
AC ablation; <i>lin-1(0)</i>	Muv

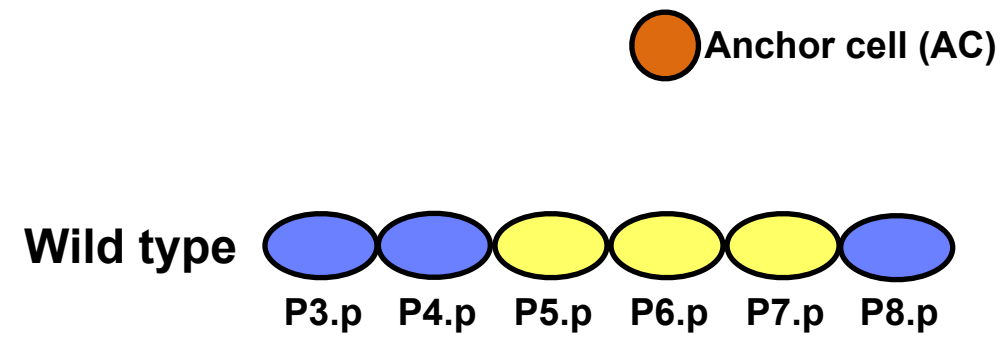
A Ras pathway promotes vulval fates



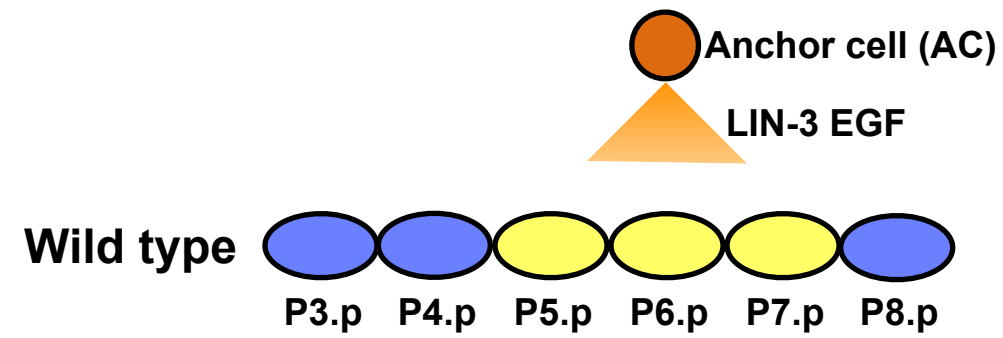
Vulval mutants

Mutant	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-2(0)</i>	~Vul
<i>lin-7(0)</i>	~Vul
<i>lin-10(0)</i>	~Vul

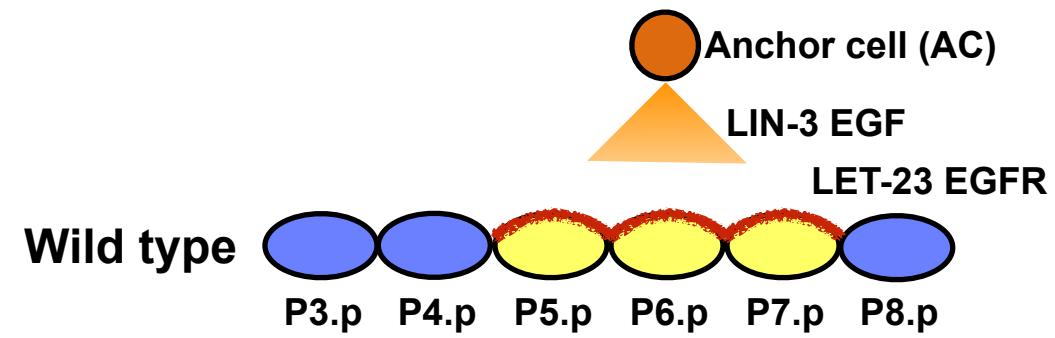
lin-2, *lin-7*, and *lin-10* act redundantly to localize LET-23 RTK



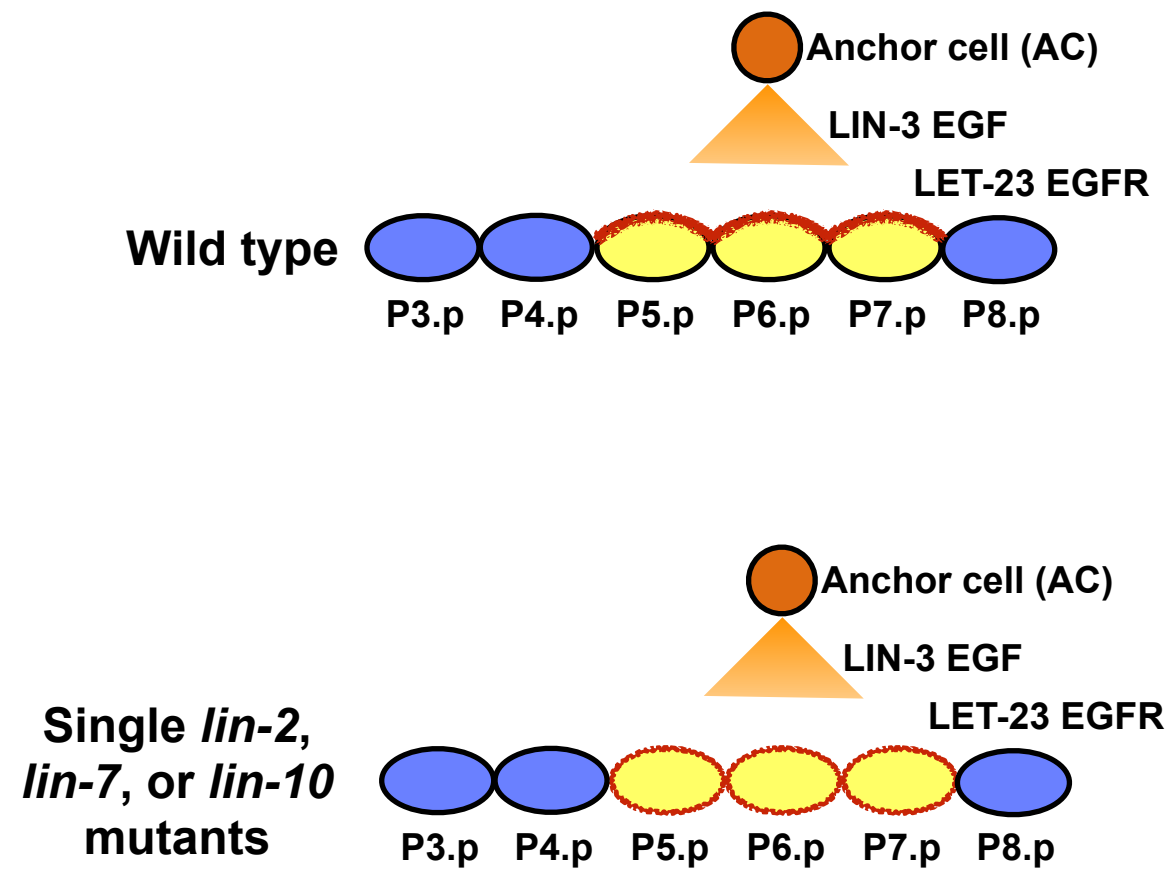
lin-2, *lin-7*, and *lin-10* act redundantly to localize LET-23 RTK



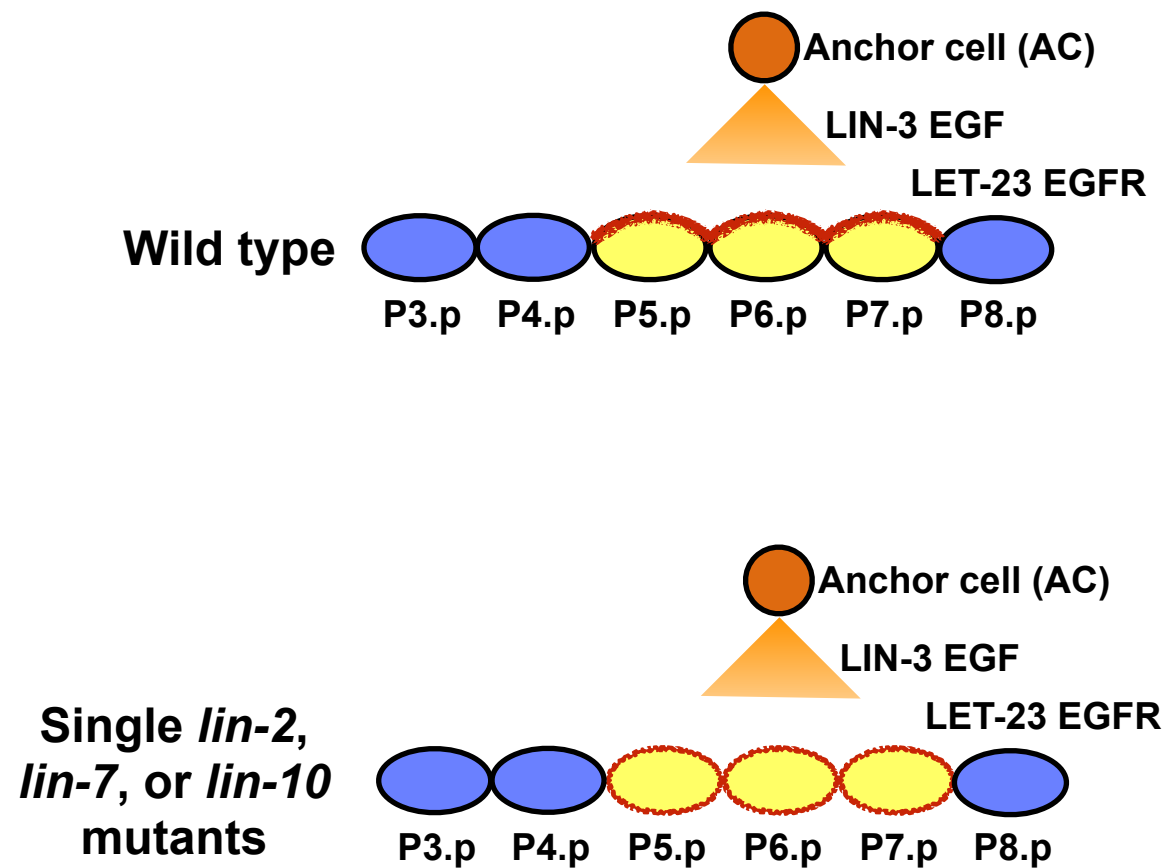
lin-2, *lin-7*, and *lin-10* act redundantly to localize LET-23 RTK



lin-2, *lin-7*, and *lin-10* act redundantly to localize LET-23 RTK

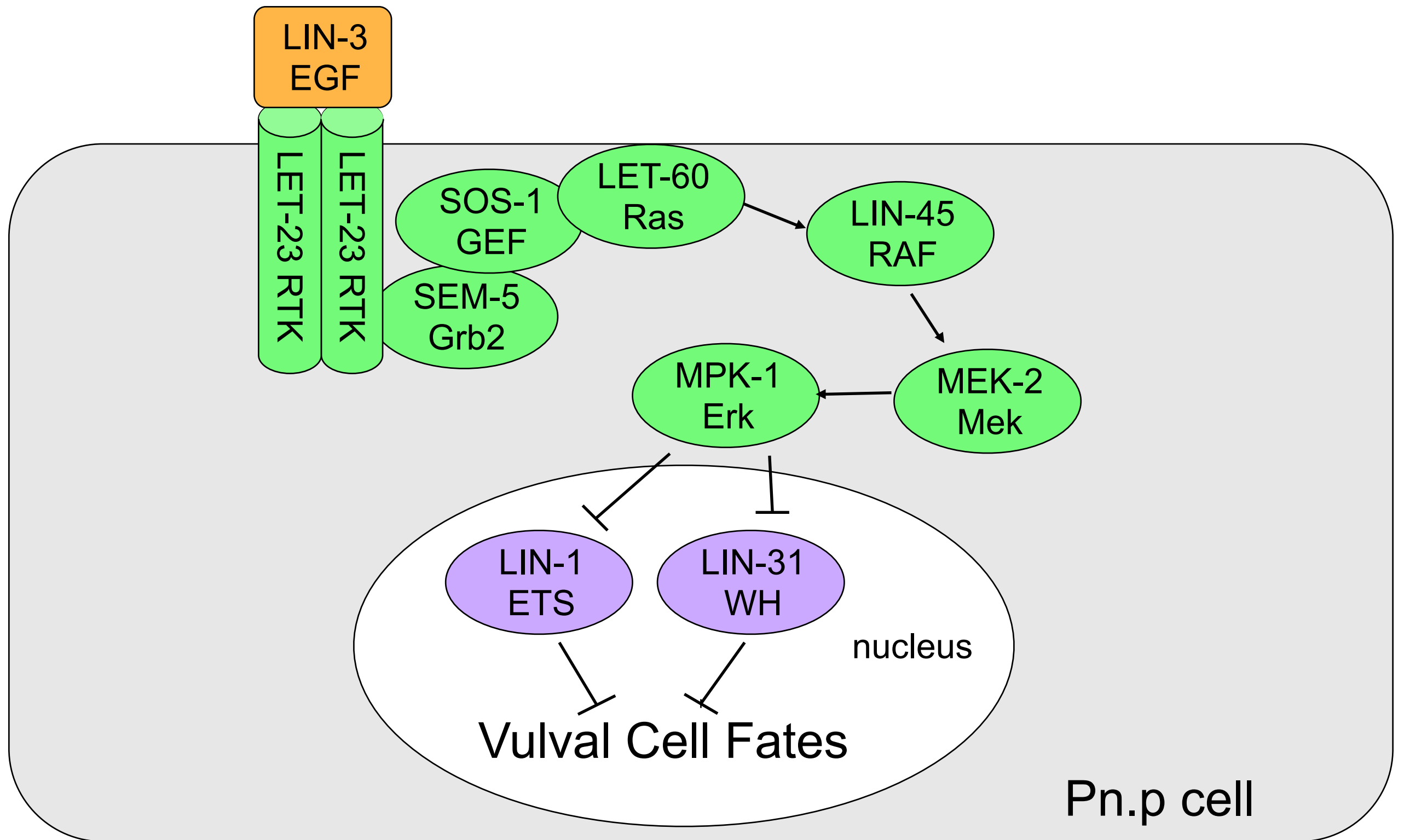


lin-2, *lin-7*, and *lin-10* act redundantly to localize LET-23 RTK

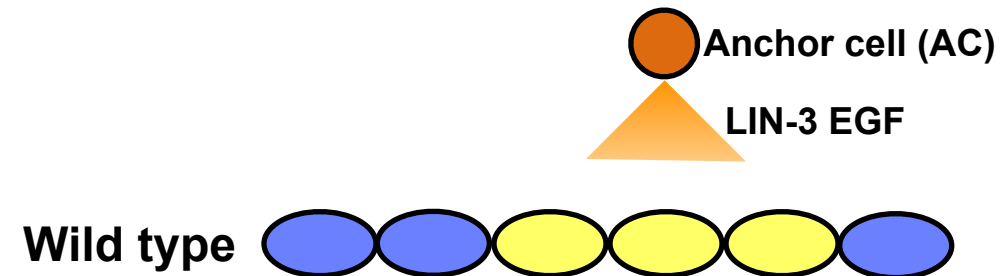


lin-3
↓
lin-2/7/10 → *let-23* → *let-60* → *lin-1* → vulval fate

A Ras pathway promotes vulval fates

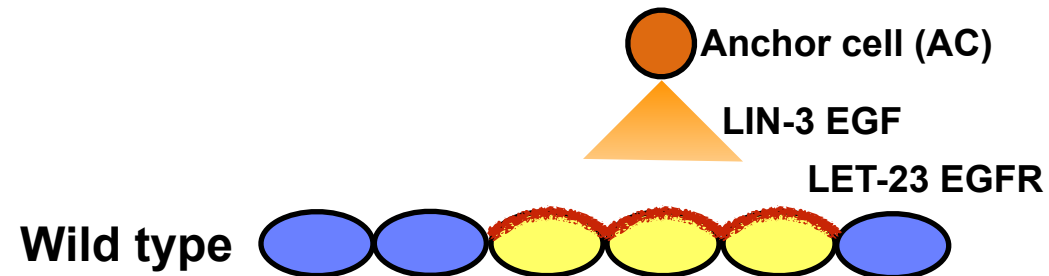


Cell autonomy of *let-60*



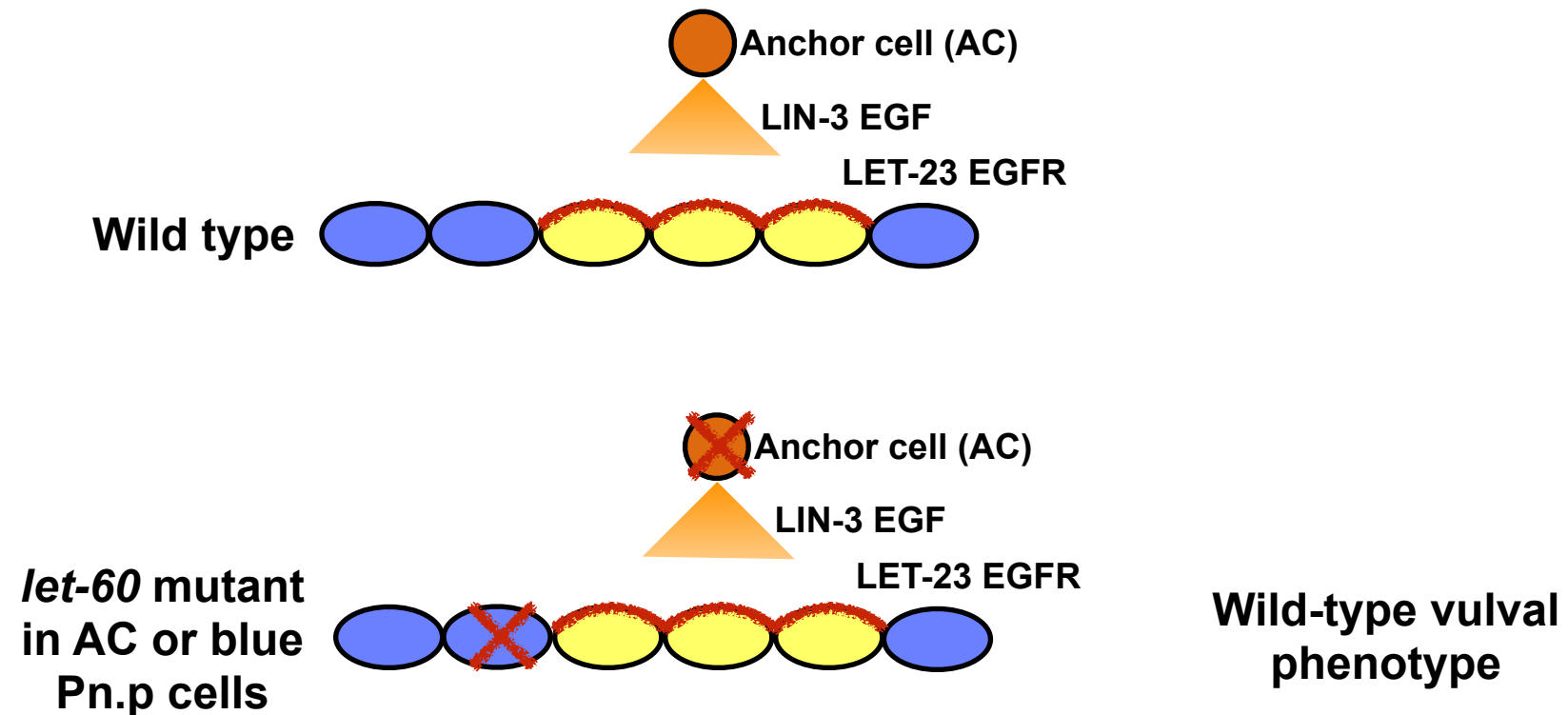
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *let-60*



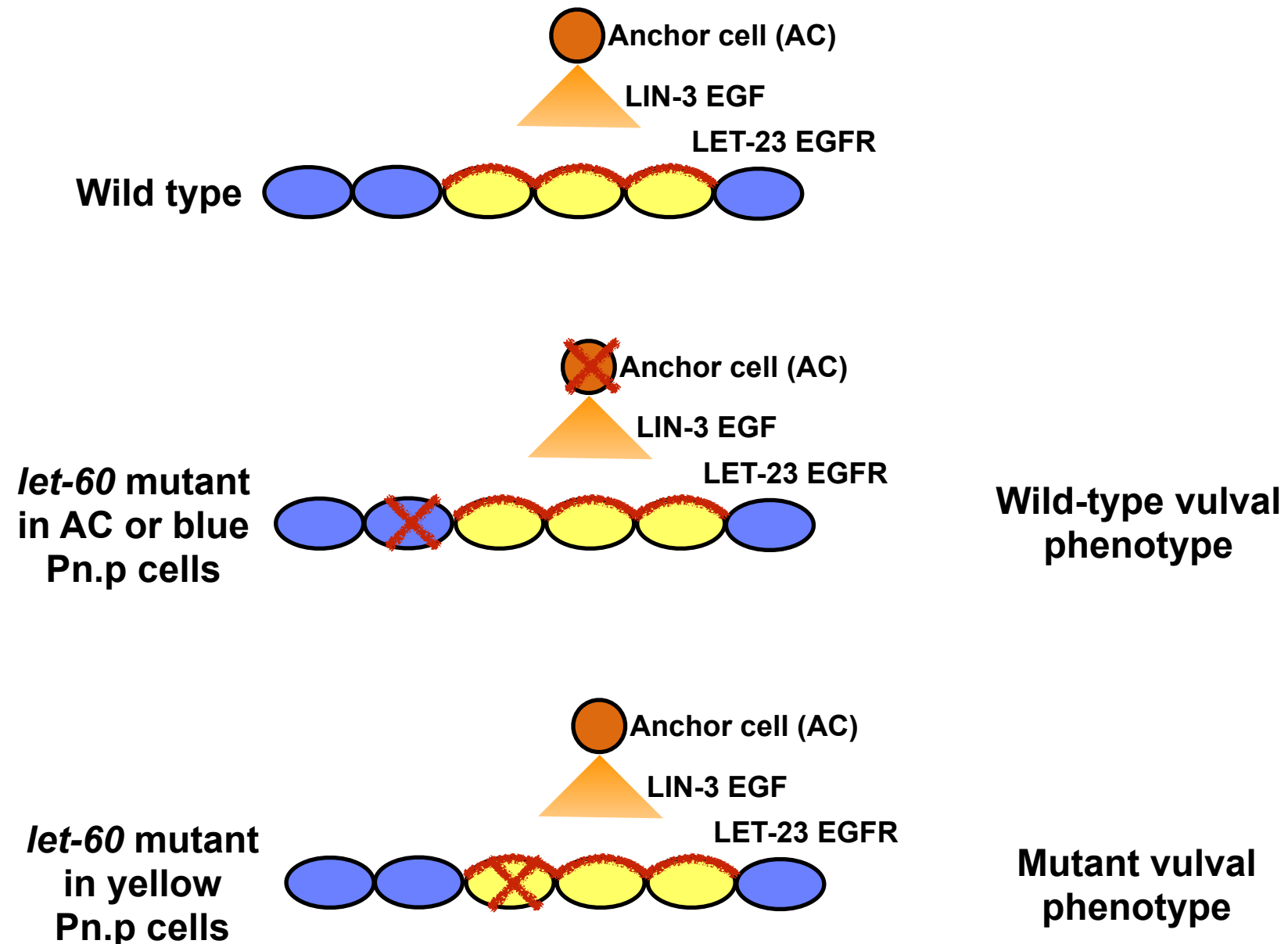
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *let-60*



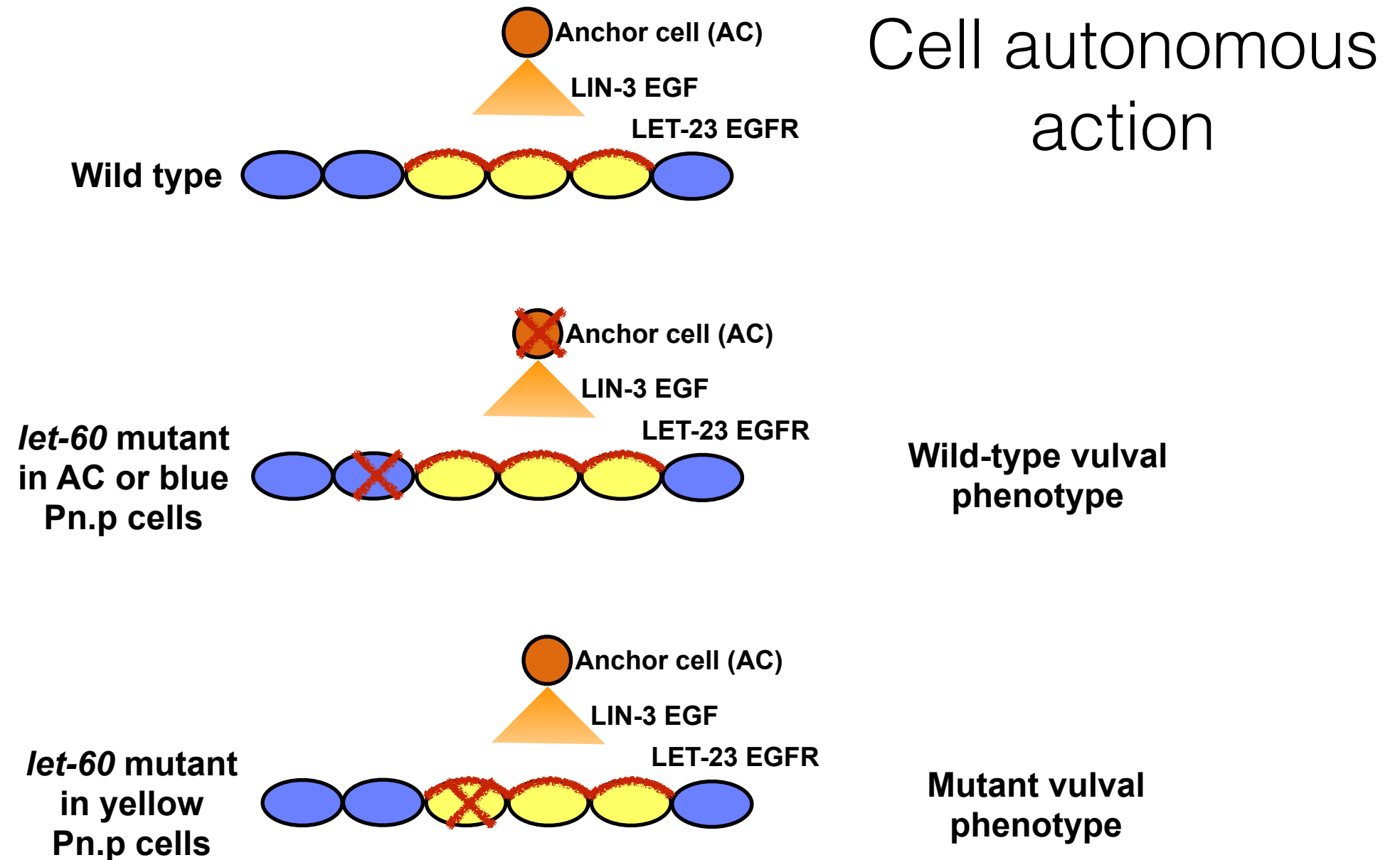
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *let-60*



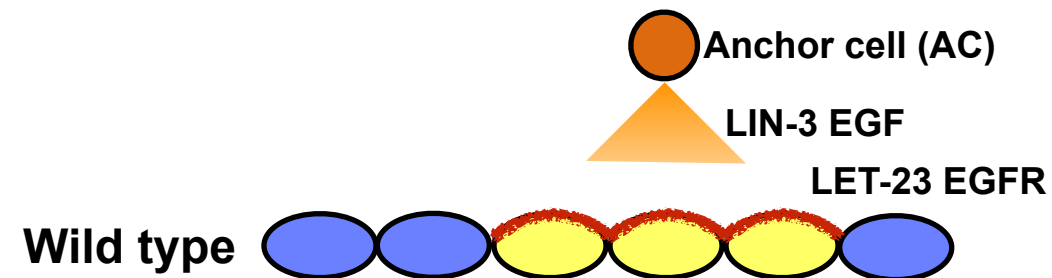
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *let-60*



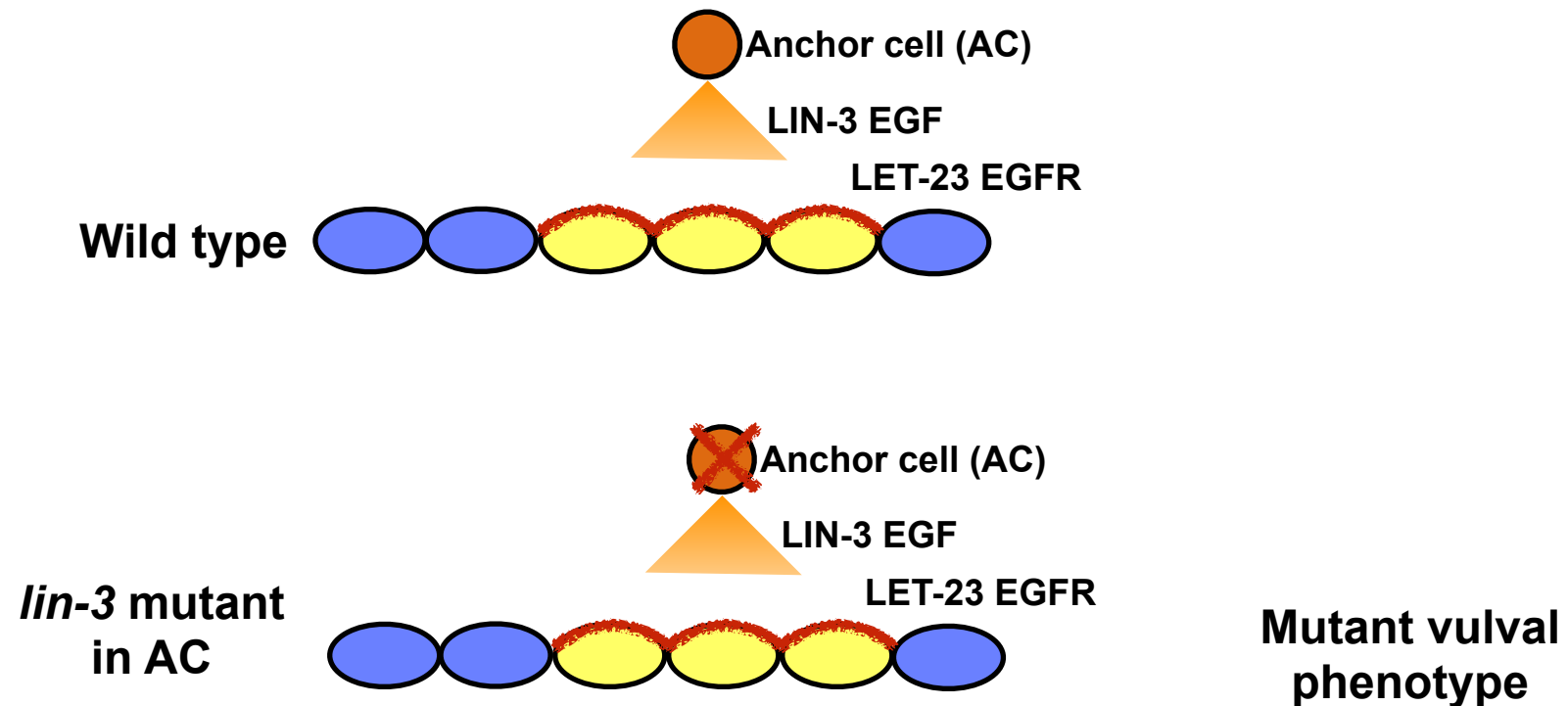
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *lin-3*



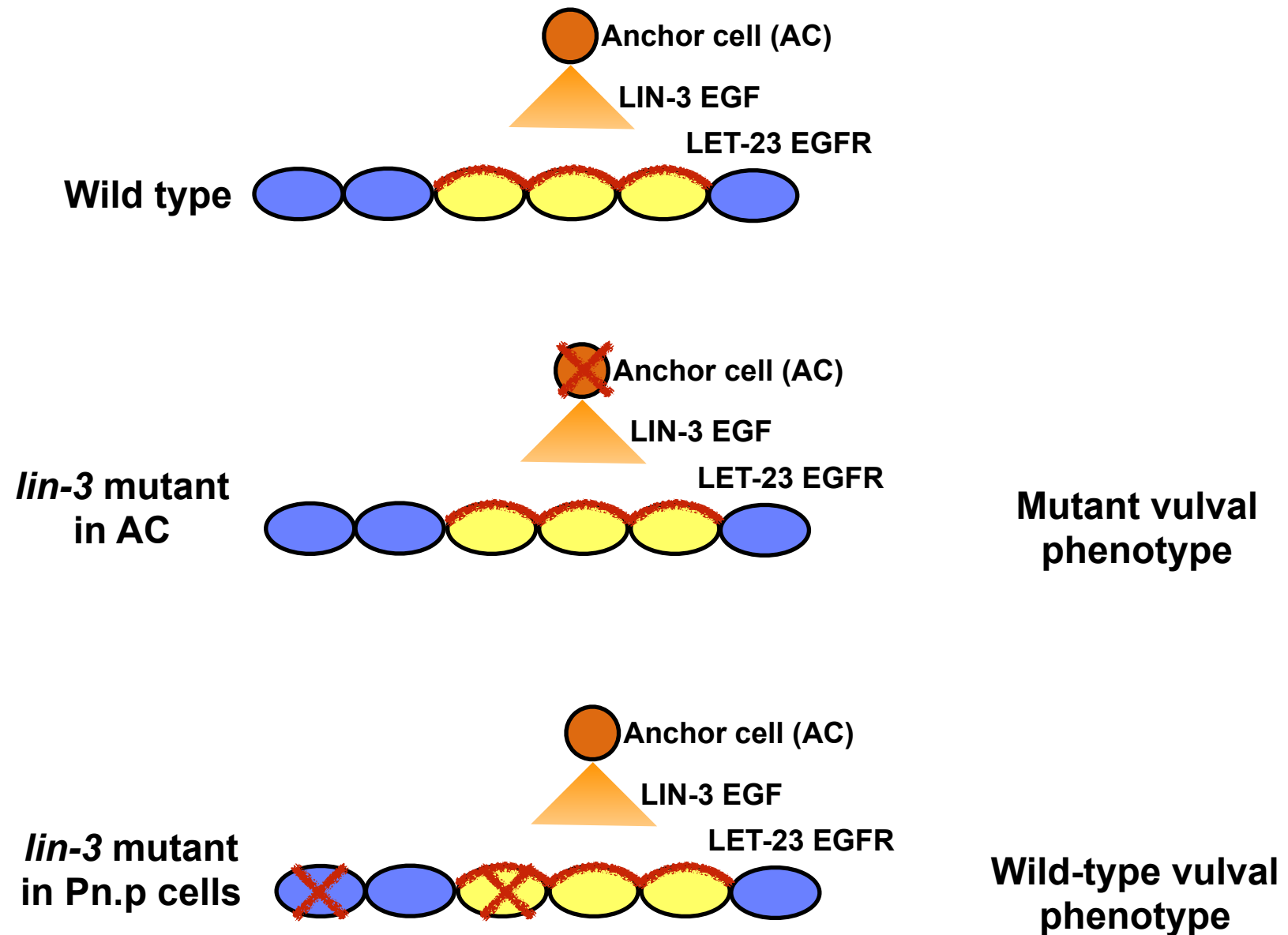
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *lin-3*



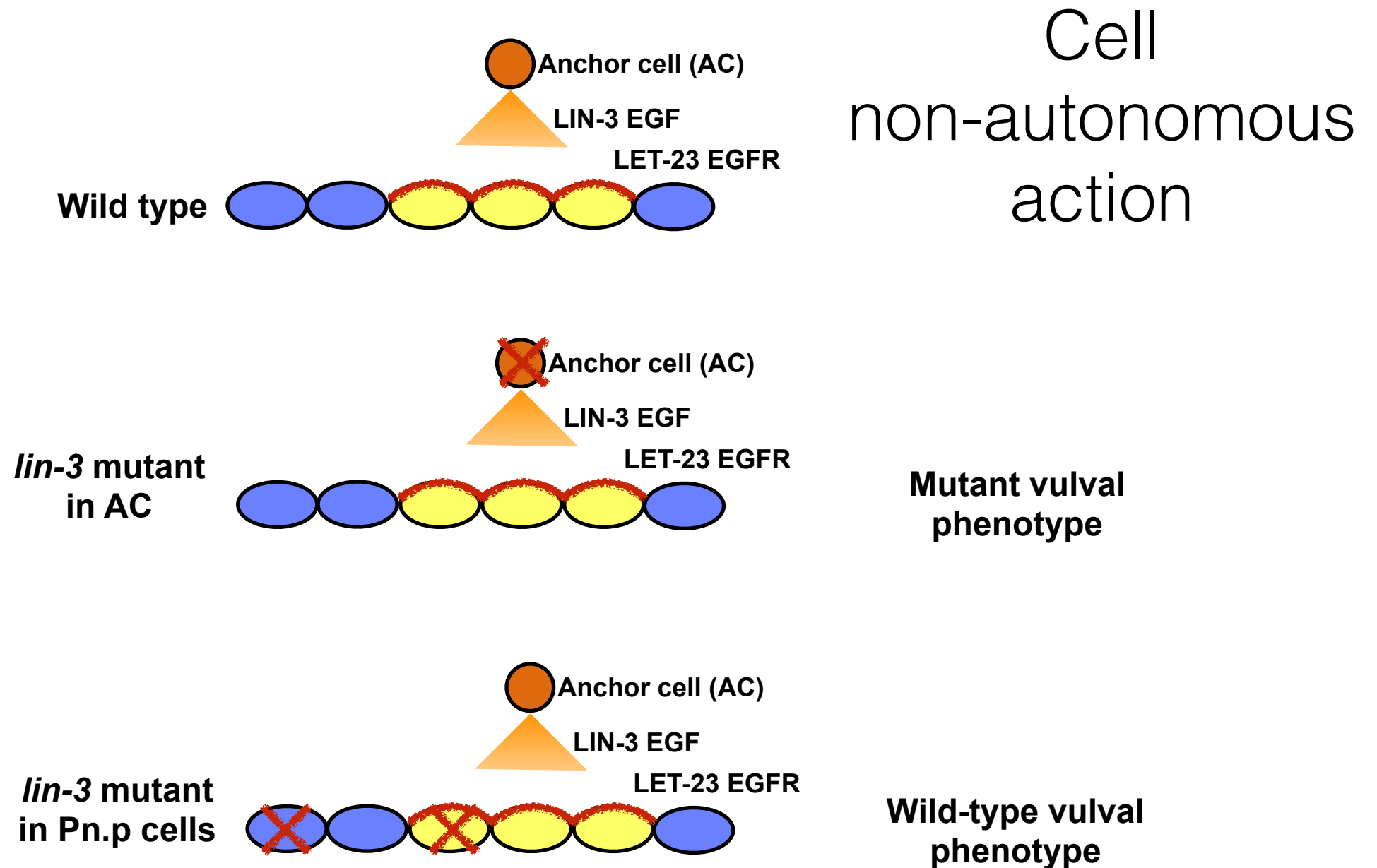
A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *lin-3*



A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

Cell autonomy of *lin-3*



A cell autonomous trait is a trait in a multicellular organism in which only genotypically mutant cells have the mutant phenotype

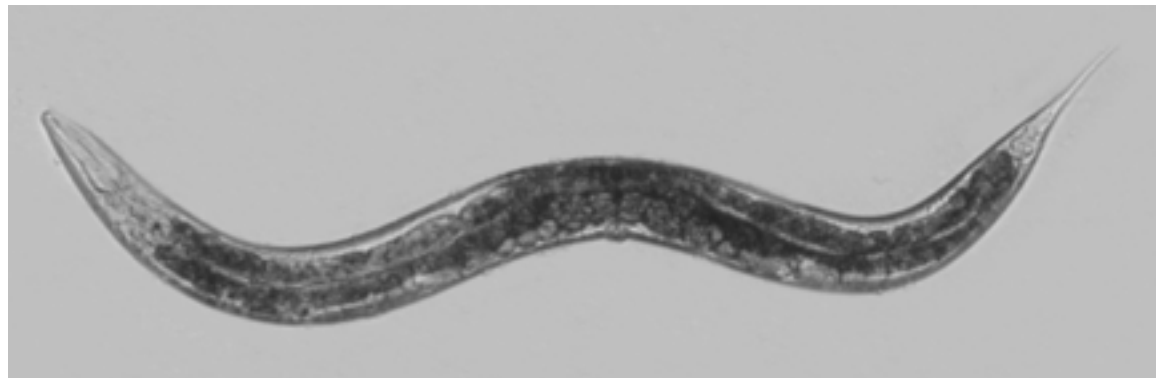
Vulval mutants

Mutant	Phenotype
<i>lin-1(0)</i>	Muv
<i>lin-3(0)</i>	Vul
<i>let-60(0)</i>	Vul
<i>let-60(gf)</i>	Muv
<i>let-23(0)</i>	Vul
<i>let-23(gf)</i>	Muv
<i>lin-2(0)</i>	~Vul
<i>lin-7(0)</i>	~Vul
<i>lin-10(0)</i>	~Vul
<i>lin-8(0); lin-9(0)</i>	synMuv

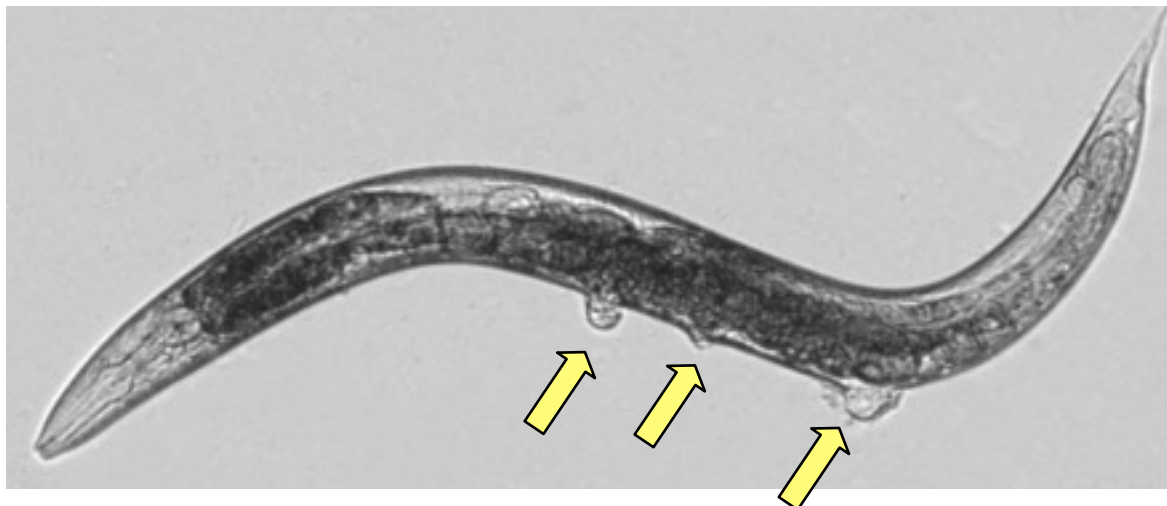
The synMuv phenotype is caused by mutations in both class A and B genes



class A single mutant



class B single mutant

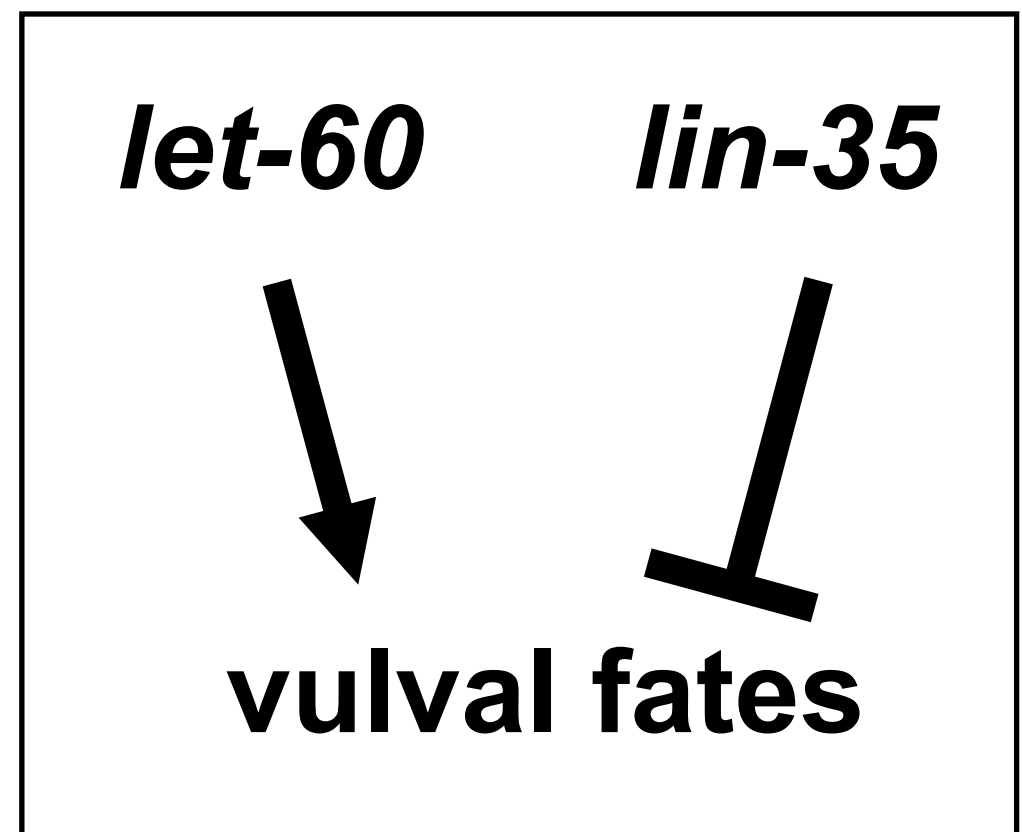
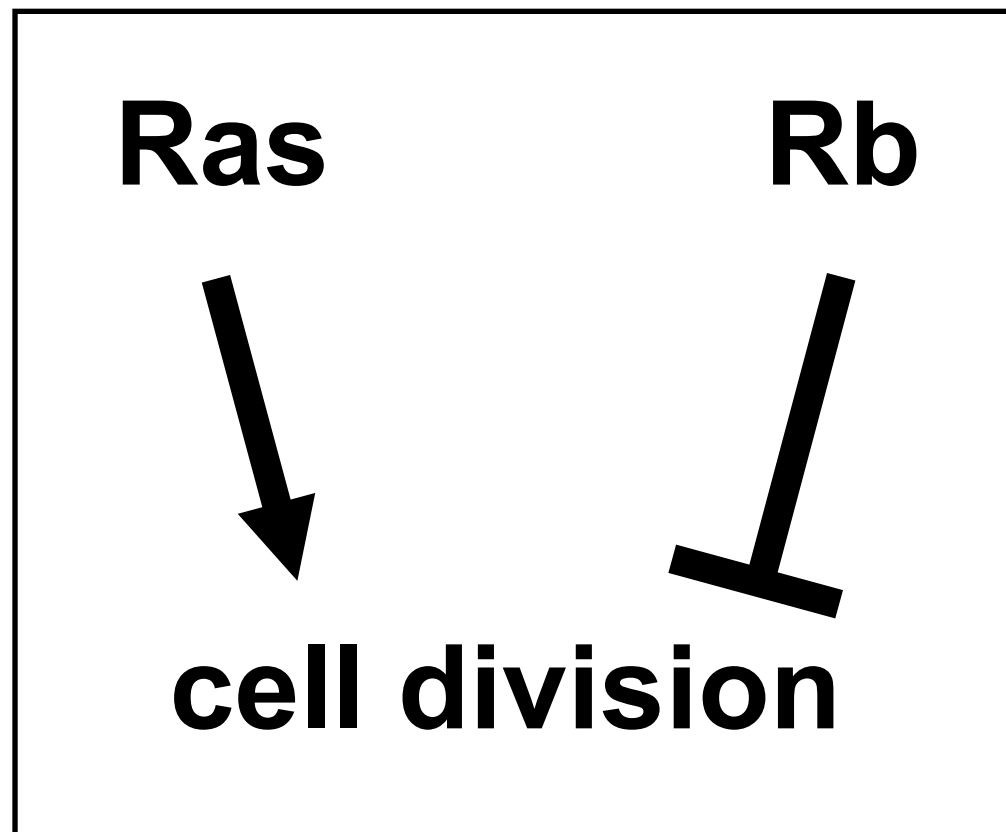


class AB double mutant

Double mutants within the same class have been reported to be non-Muv

	Class A	Class B
Class A	non-Muv	Muv
Class B		non-Muv

The vulval cell-fate decision models cell-fate decisions involved in carcinogenesis



The synMuv genes

class A

lin-8 novel
lin-15A THAP
lin-38 Zn finger
lin-56 THAP

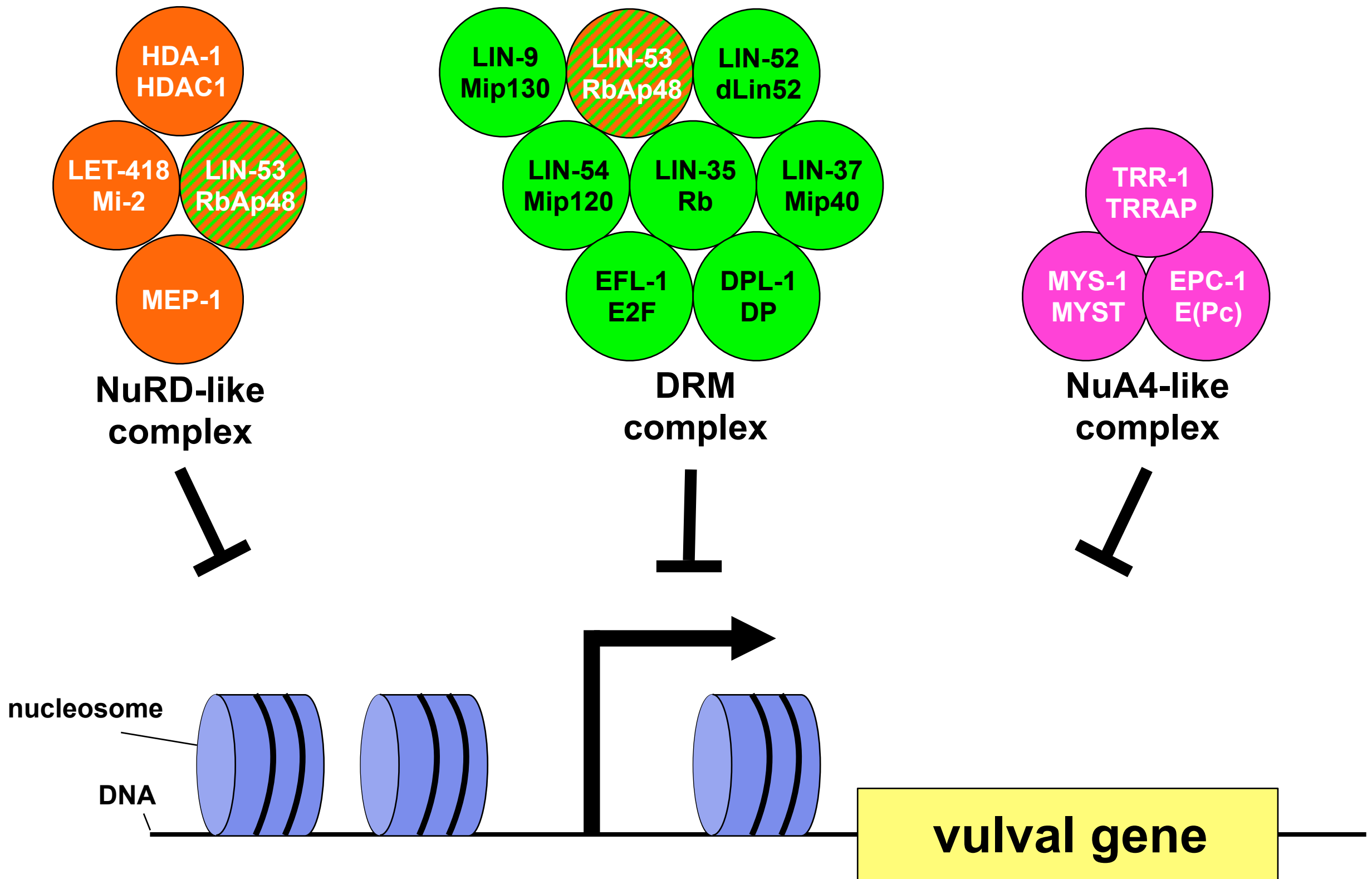
lin-9 Mip130/ALY
lin-13 Zn fingers
lin-15B THAP
lin-36 THAP
lin-37 Mip40
lin-52 dLin52
lin-54 Mip120
lin-61 I(3)MBT
lin-65 novel
tam-1 RING finger

class B

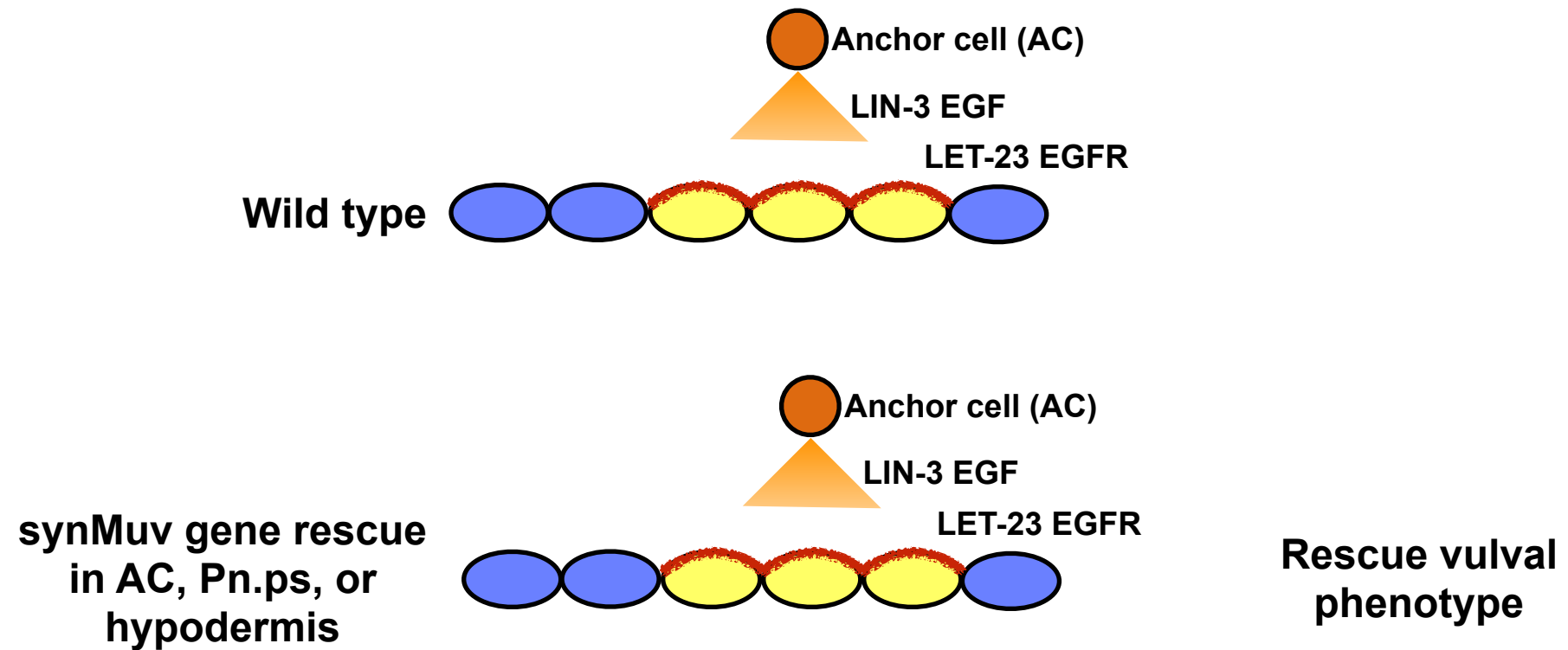
dpl-1 DP
efl-1 E2F4
lin-35 Rb
lin-53 RbAp48
hda-1 HDAC1
let-418 Mi-2
mep-1 Zn fingers
hpl-2 HP1
gap-1 RasGAP
sli-1 c-Cbl
ark-1 Ack

trr-1 TRRAP
mys-1 HAT
epc-1 E(Pc)

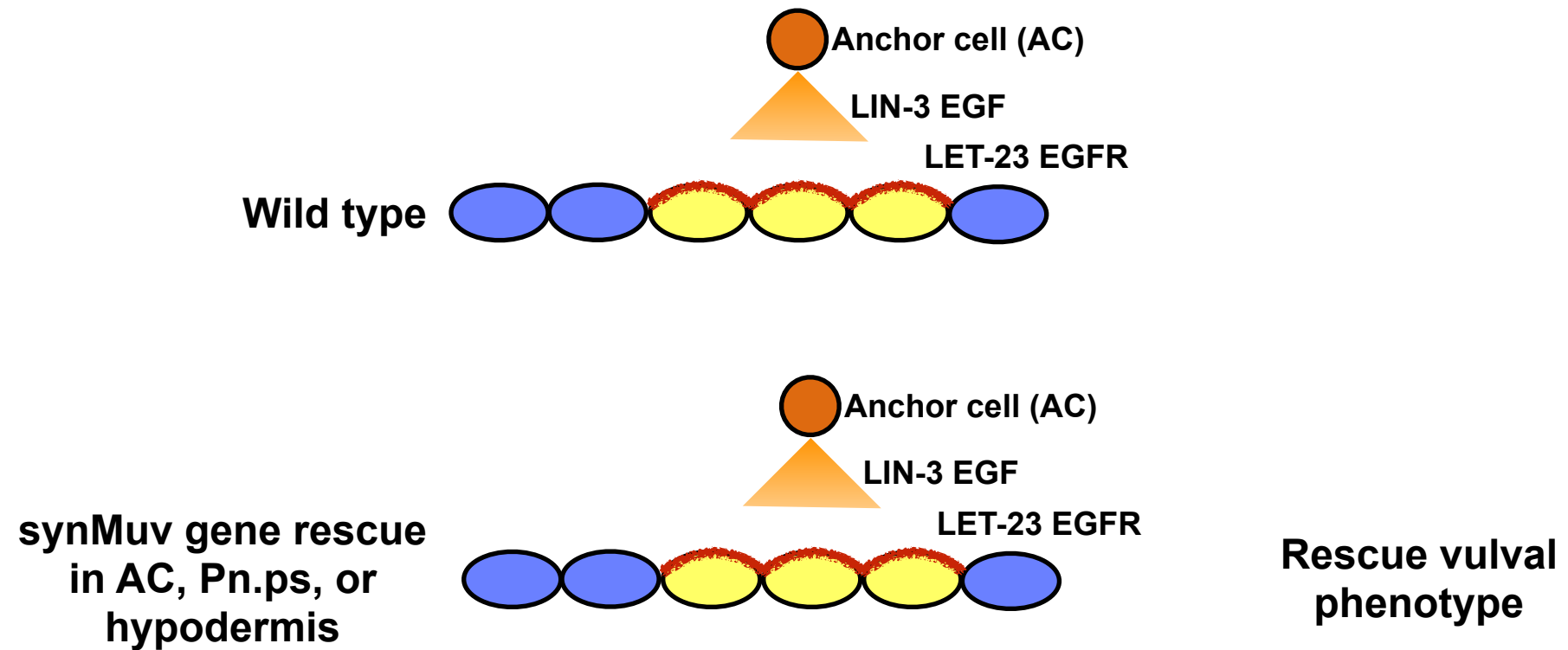
NuRD-like, DRM and NuA4-like complexes affect the transcription of vulval genes



Cell autonomy of synMuv genes

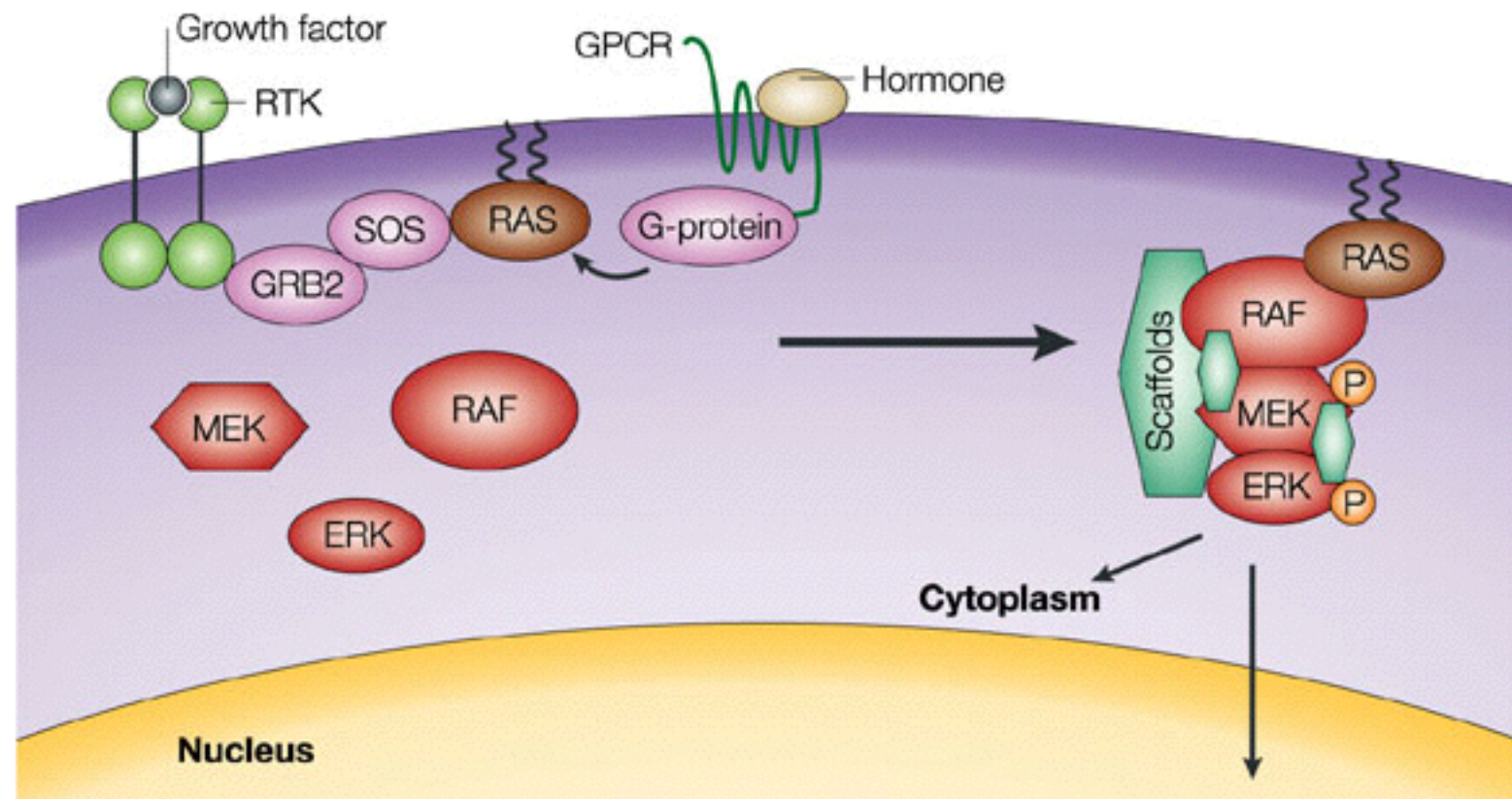


Cell autonomy of synMuv genes



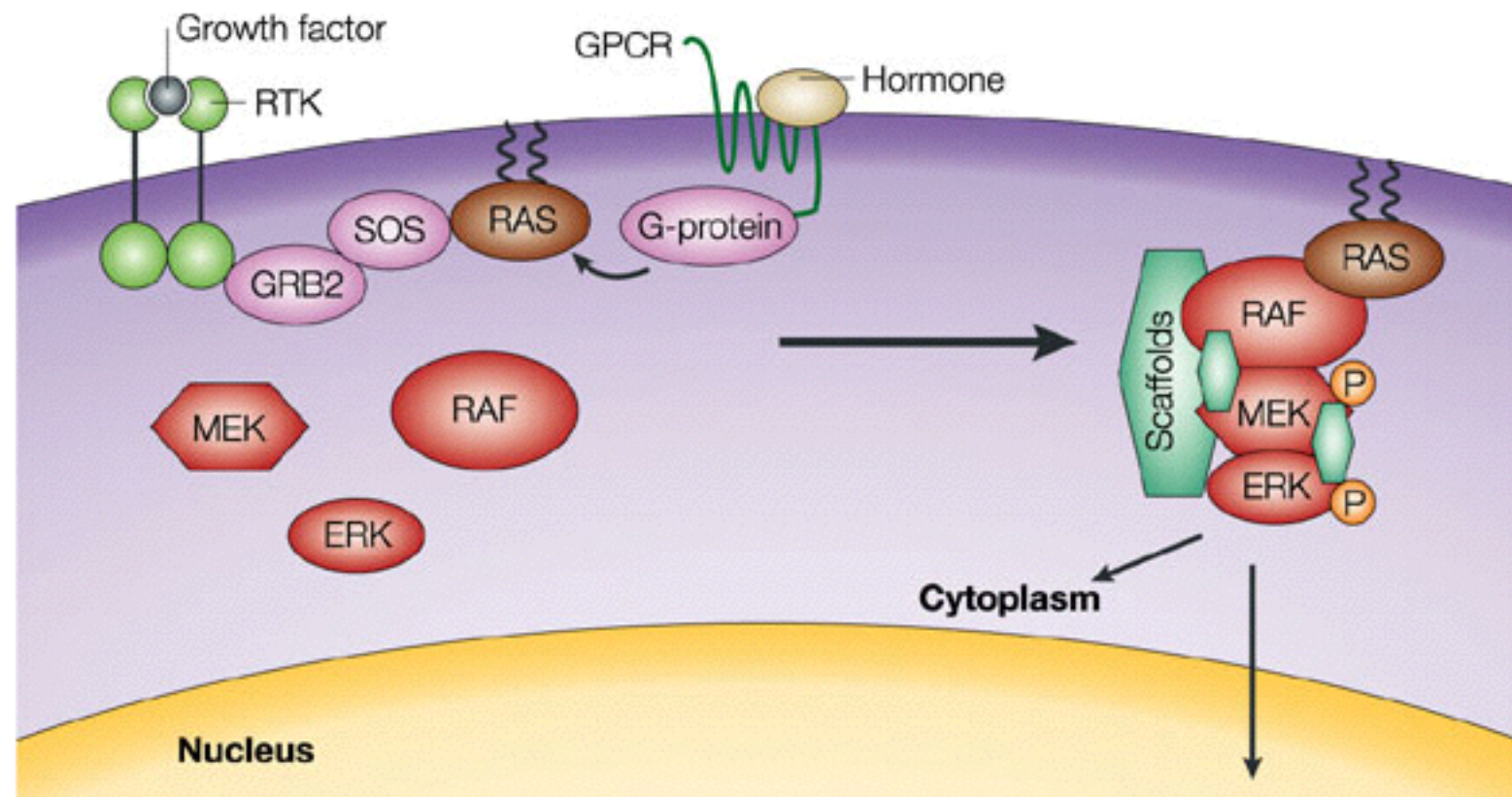
Cell
non-autonomous
action

Two decades of research in *Drosophila* and *C. elegans* led to these pathways



Nature Reviews | [Molecular Cell Biology](#)

Two decades of research in *Drosophila* and *C. elegans* led to these pathways



Nature Reviews | [Molecular Cell Biology](#)

We NEED basic research for this reason!