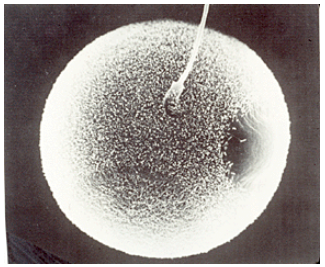
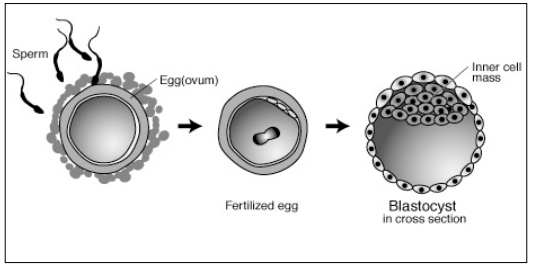
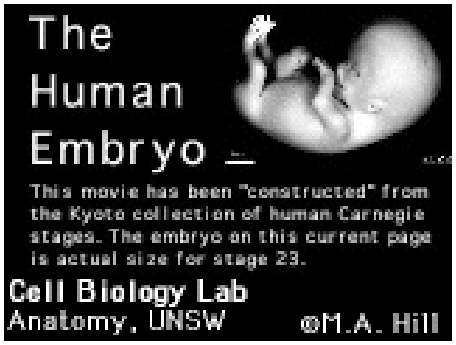
Genetics of Behavior and Development I

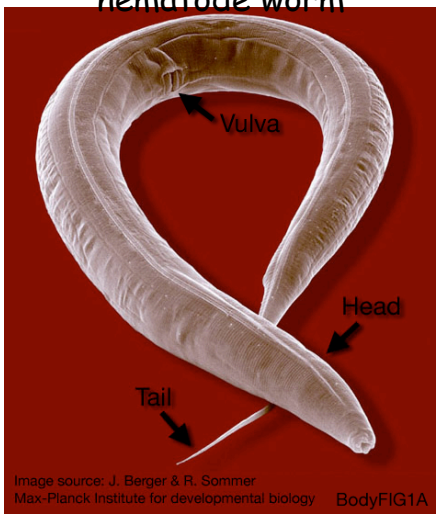
Lecture 34







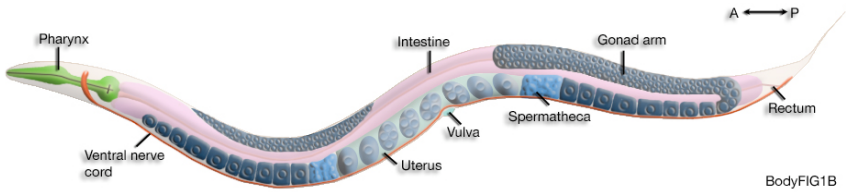
Adult *C .elegans* nematode worm

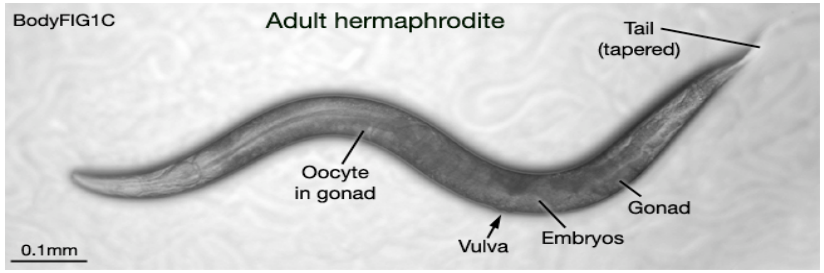


With embryos

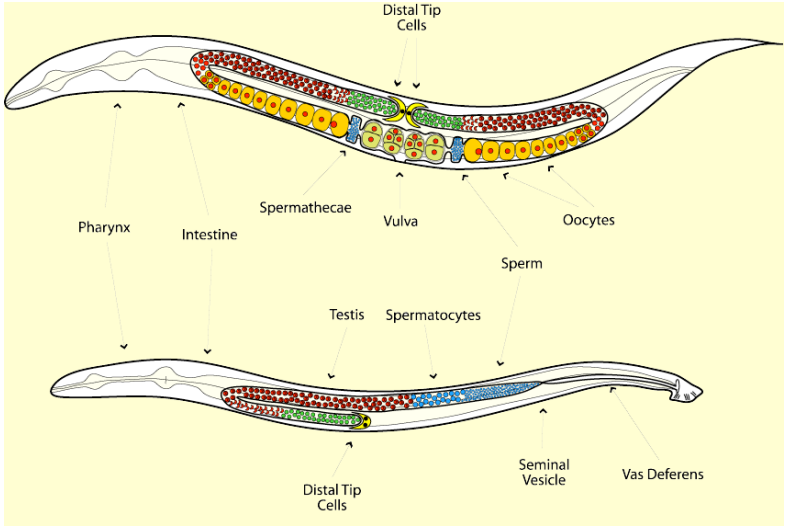
With larvae

The Adult Nematode worm *Caenorhabditis elegans*





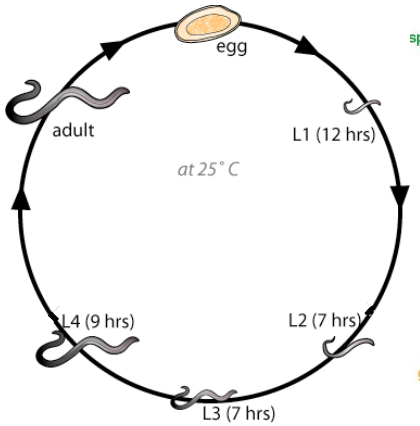
Hermaphrodite

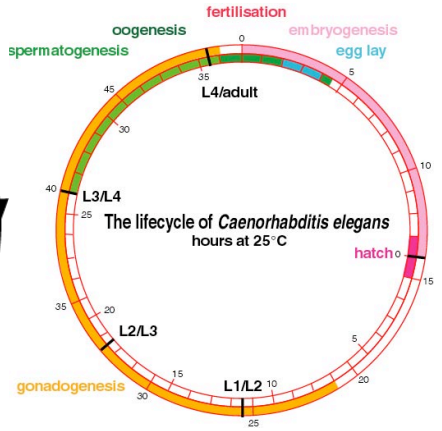


MALE

After egg fertilization the embryo is laid at ~ 6h and it hatches at ~ 12h to enter the first larval stage (L1)

The *C. elegans* Life Cycle – only 50 h





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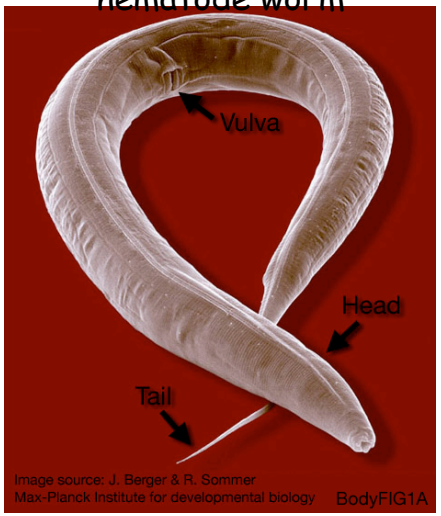
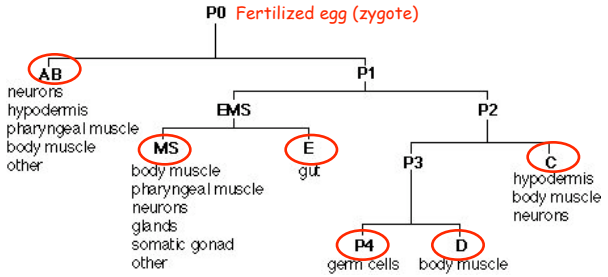
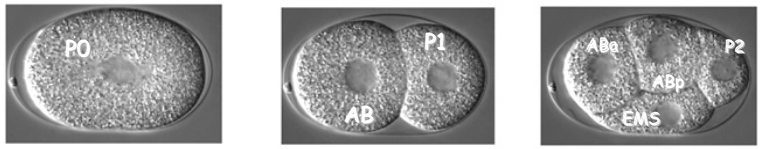


With embryos

With larvae

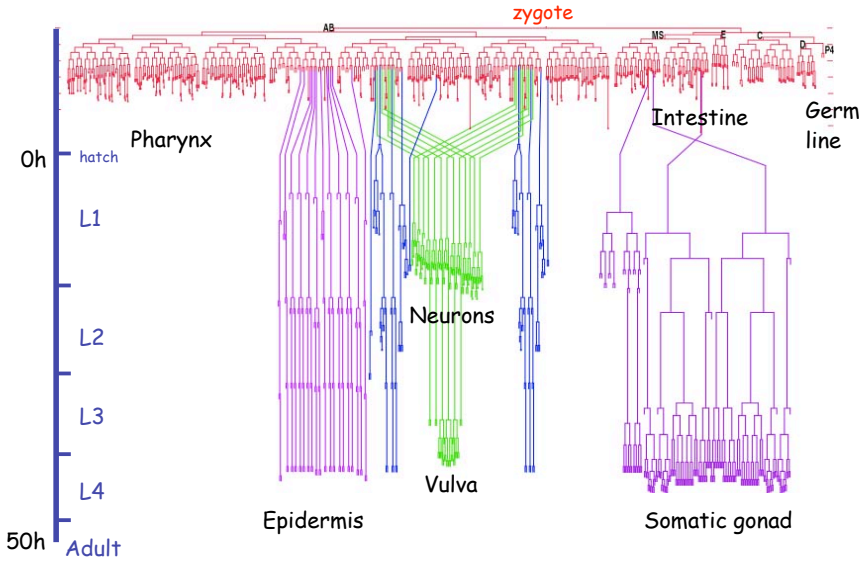
Pattern of early cell divisions from the *C. elegans* zygote to form six Founder Cells





Fertilized egg (zygote) | First cell division | Subsequent divisions

Full lineage of the entire *C. elegans* body



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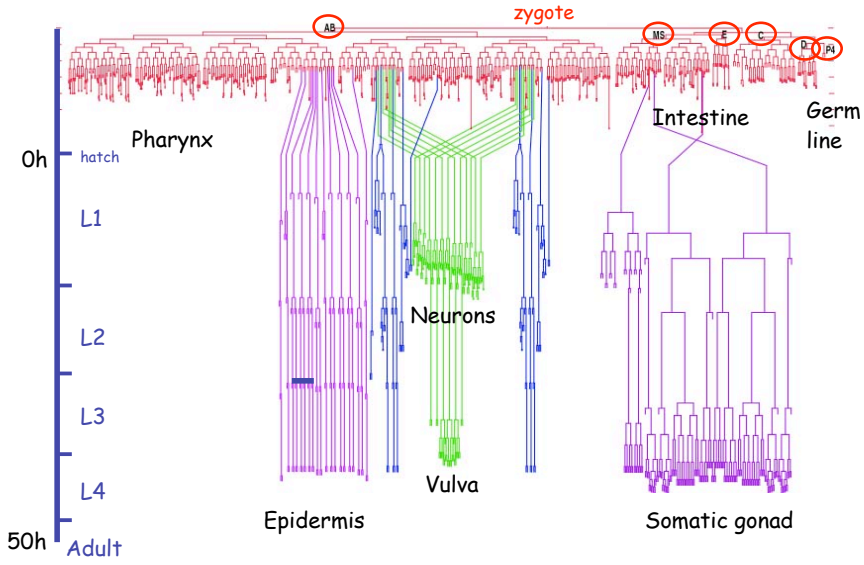
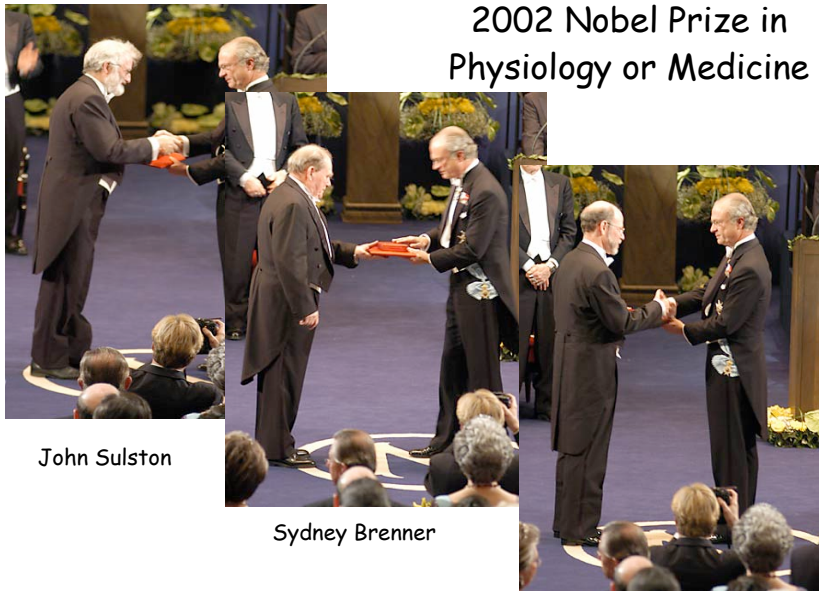


2002 Nobel Prize in Physiology or Medicine



John Sulston

Sydney Brenner

Bob Horvitz (MIT)

Important features of the *C. elegans* cell lineage

- It is the best documented example of a highly reproducible pattern of cell division for any organism
- The pattern of cell divisions starting from a wild type *C. elegans* fertilized egg is nearly always the same
- About 10 rounds of cell division create the adult worm that has many of the same tissues that we do!
- Any one particular cell undergoes relatively few divisions
- One hemaphrodite worm can produce 500,000 progeny in a week on a petri dish

How would you identify the regulatory mechanisms that control the development of cell lineages?

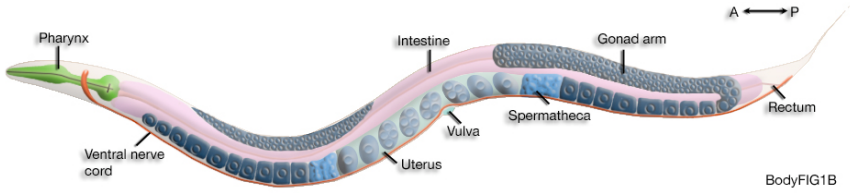
Look for mutants that display aberrant lineages and characterize the genes, of course!

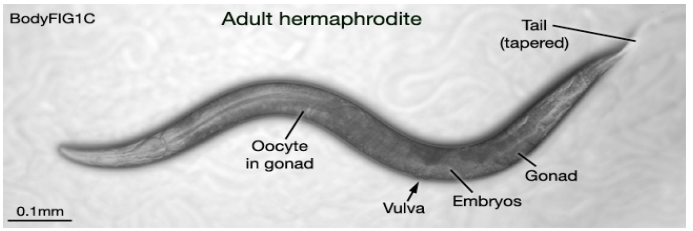
Sydney Brenner (and subsequently others) mutagenized *C. elegans* and screened for "funny looking worms"

What does "funny" mean – altered body shapes, e.g., dumpy, small, long; uncoordinated or otherwise behaving strangely.

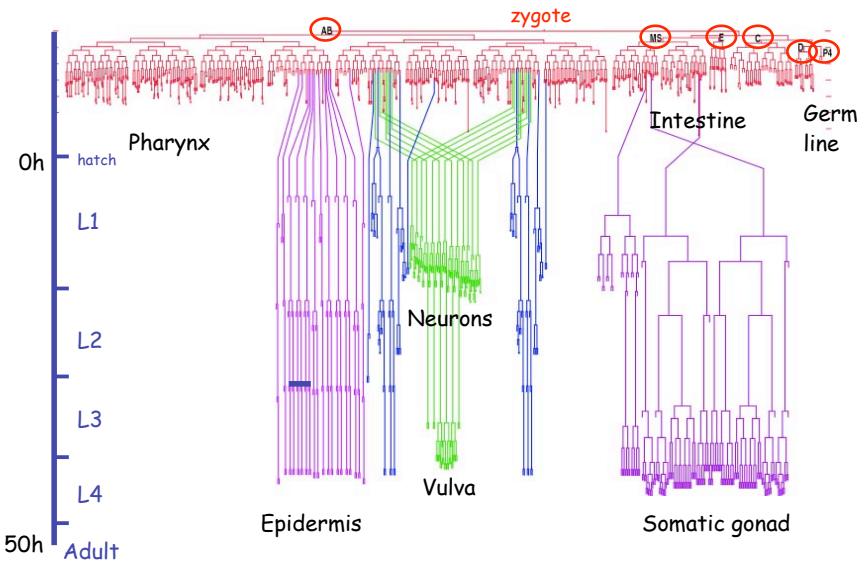
One class of mutants turned out to be lacking a body part…namely the vulva through which the embryos are laid…these animals are unable to lay eggs.

These egg-laying mutants were picked for study with the idea that there were obvious problems with the execution of at least some cell





Full lineage of the entire *C. elegans* body



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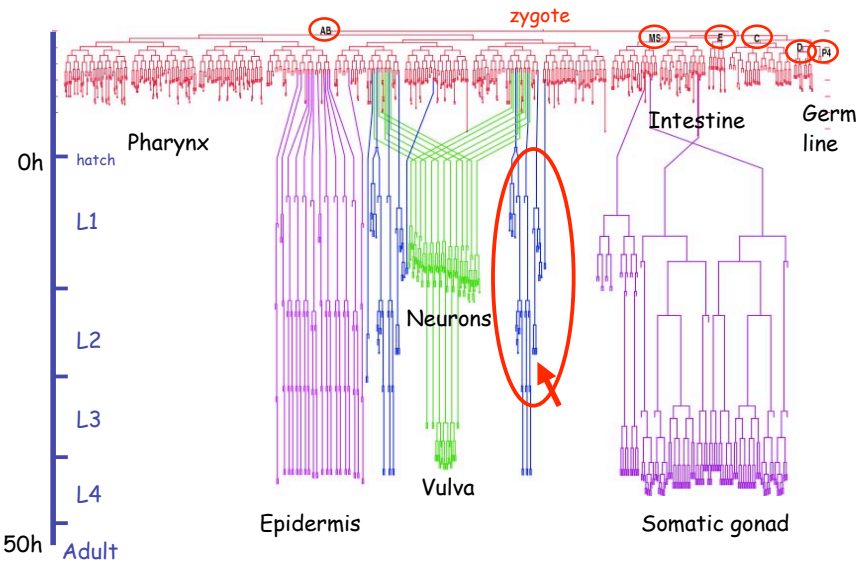
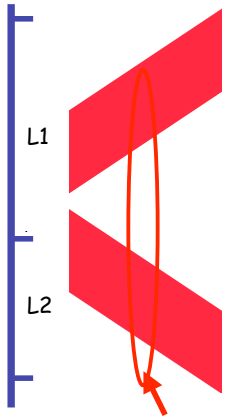
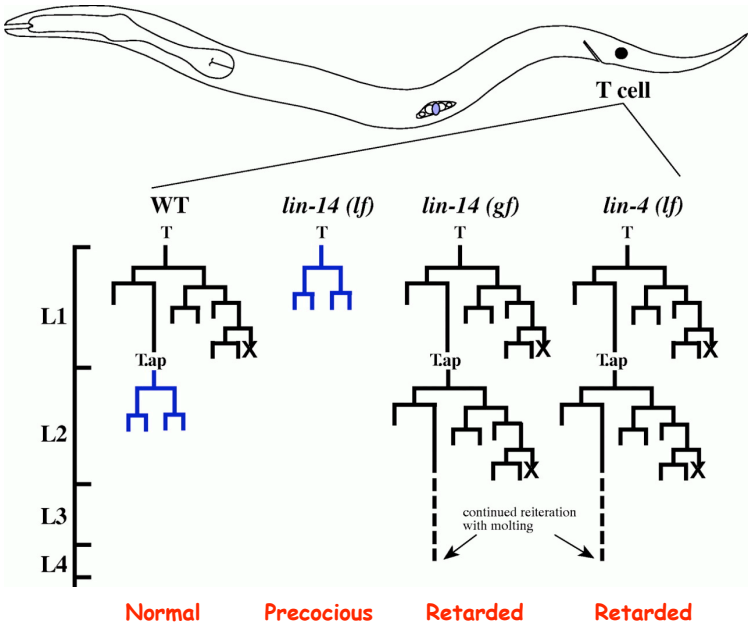
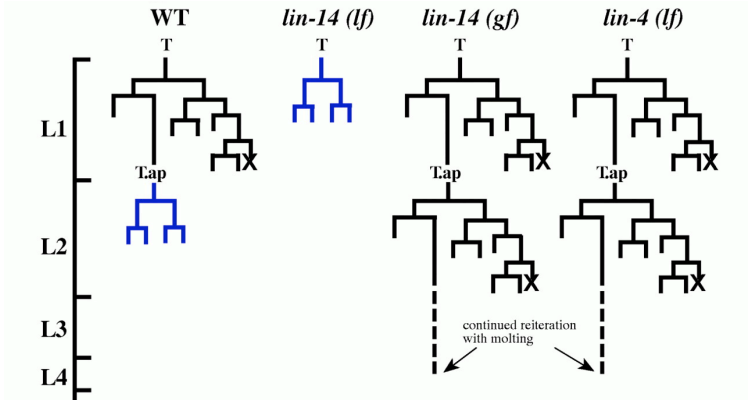




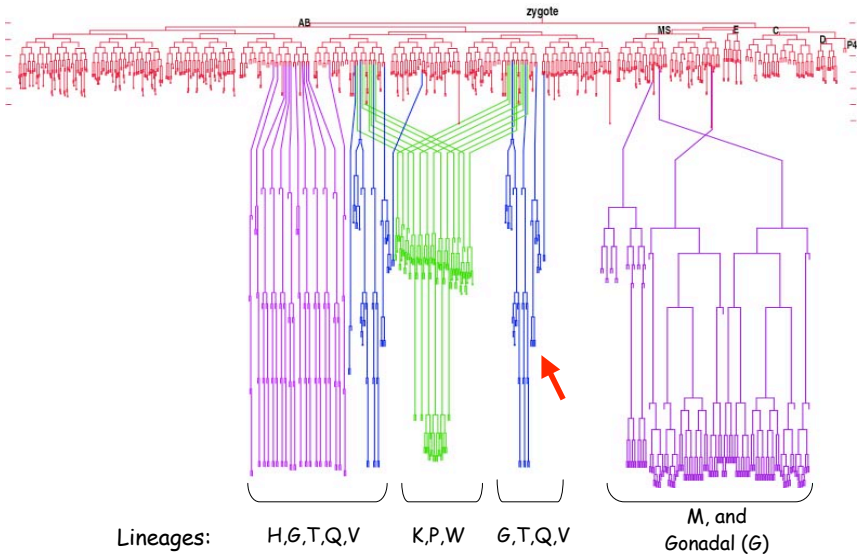
Zoom in on particular cell lineages, in this case the T lineage

Ask whether the development of this lineage is normal in egg-laying mutants





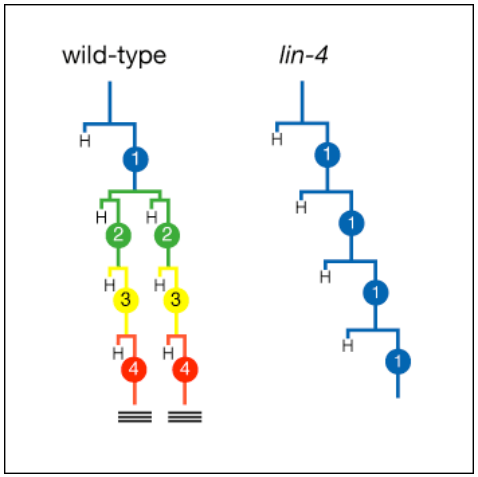
Normal	Precocious	Retarded	Retarded
Distinctive cell division pattern in L1 vs L2	Actually skipped over the L1 cell division	Repeats the L1 cell division pattern over and	Repeats the L1 cell division pattern over and



lin-4 and *lin-14* mutants affect postembryonic lineages H1, H2, M, V1-V6 as well as the T lineage

Heterochronic Mutants

Misregulation of another lineage



These mutants have been called HETEROCHRONIC mutants – they affect the relative timing of major developmental events

The existence of such mutants indicates that there is coordination of the temporal sequence of many cell fates an animal develops

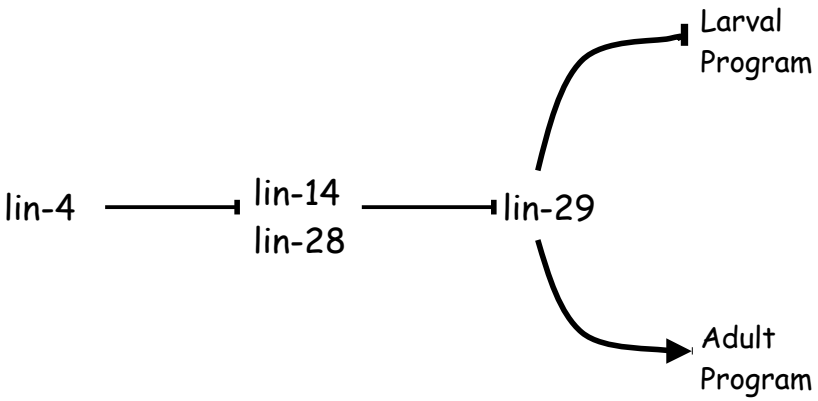
This temporal coordination is genetically regulated

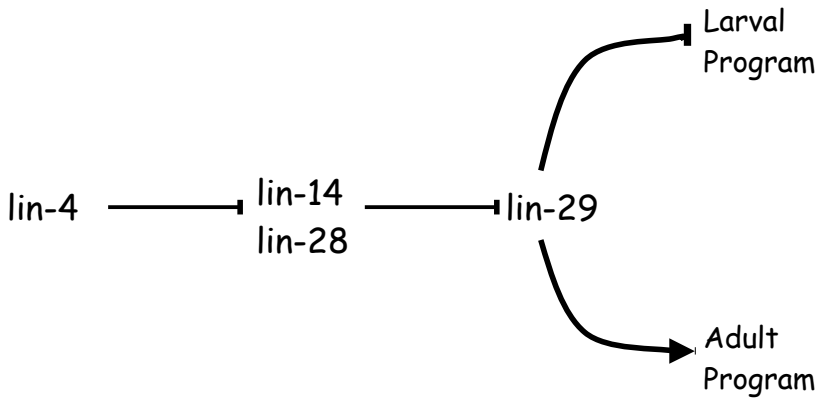
Other Heterochronic mutants also identified

Mutant	Phenotype
lin-4 (lf)	Retarded
lin-14 (lf)	Retarded
lin-14 (gf)	Precocious
lin-28 (lf)	Precocious
lin-29 (lf)	Retarded

How would you go about determining the order in which lin-4, lin-14, lin-28 and lin-29 operate to control the timing of development?

	Single mutants	Double Mutants: *lin-14 (gf)*	*lin-14 (lf)*	*lin-28 (lf)*	*lin-29 (lf)*
lin-4 (lf)	Retarded	Retarded	Precocious	Precocious	Retarded
lin-14 (gf)	Retarded			mixed	Retarded
lin-14 (lf)	Precocious			Precocious	Retarded
lin-28 (lf)	Precocious				Retarded
lin-29 (lf)	Retarded				



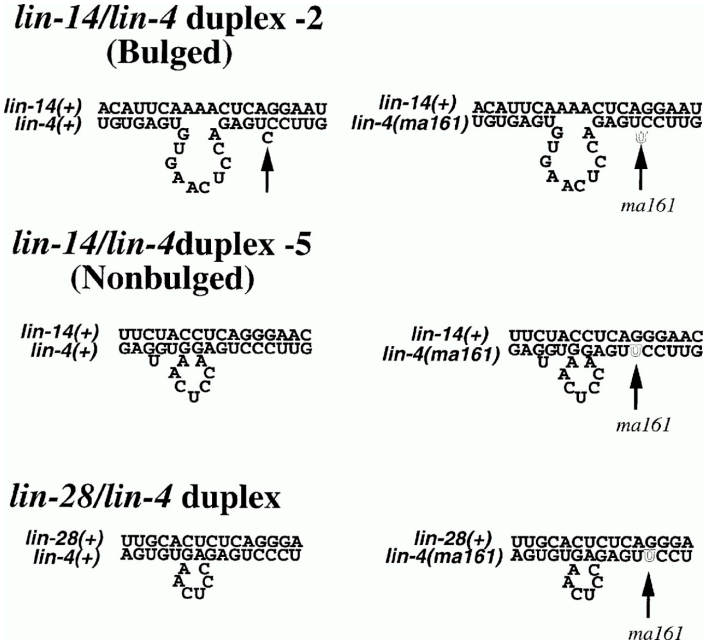


lin-4 encodes small RNAs, 61nt and 21 nt

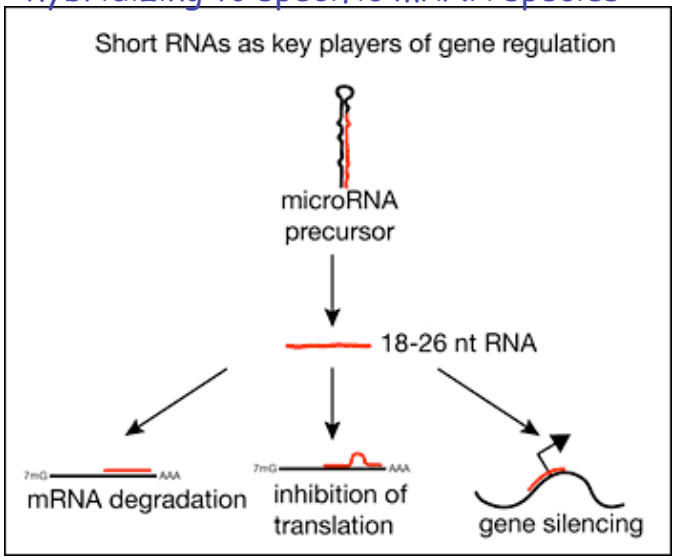
lin-14 encodes a nuclear protein

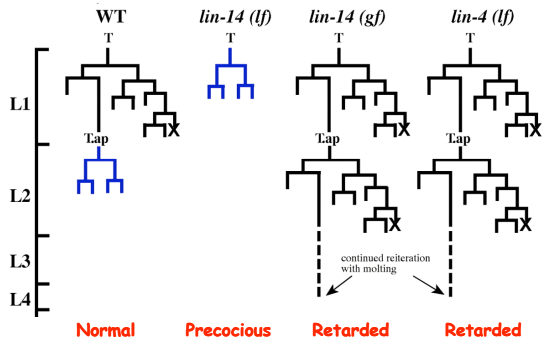
lin-28 encodes another protein

lin-29 encodes a Transcription factor

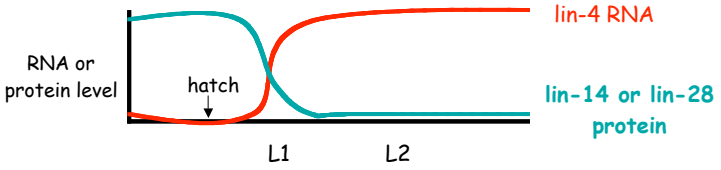


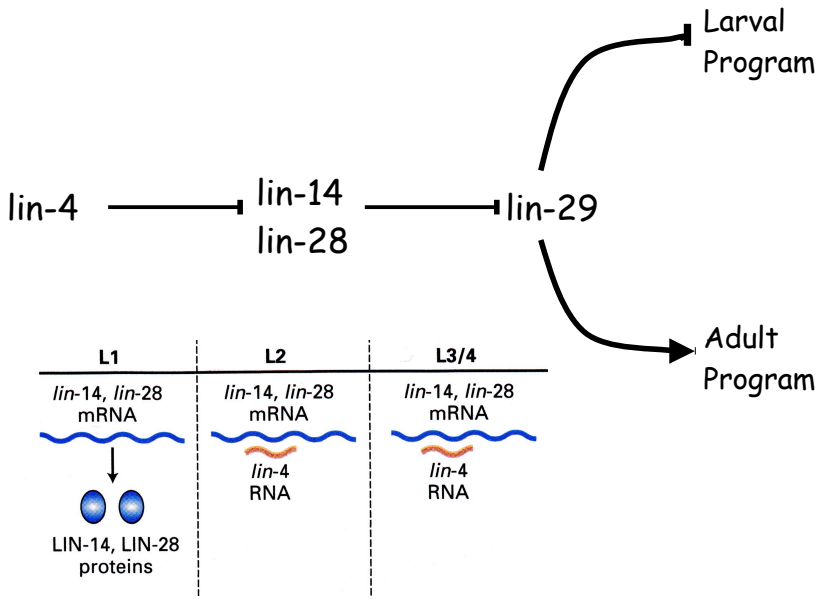
MicroRNAs control gene expression by hybridizing to specific mRNA species

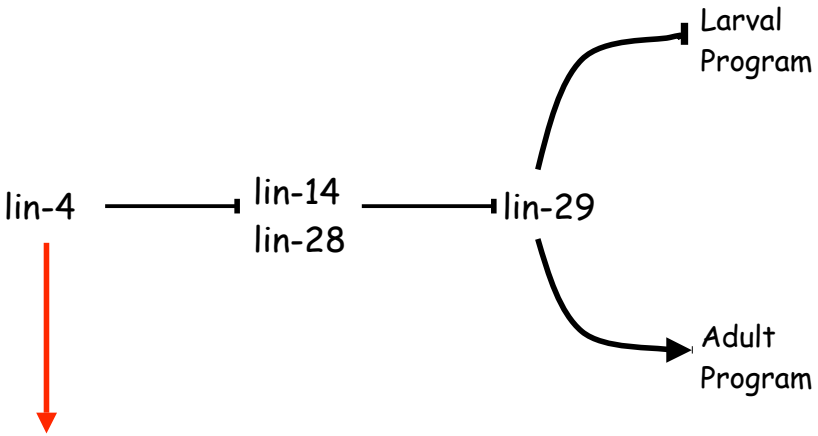




Temporal expression of the *lin-4* RNA is crucial for the orchestration of lineage specific cell division







This was the first microRNA regulatory molecule to be discovered

microRNAs are widespread in nature, including humans, and are very often involved in development and differentiation