

Lecture 17: *C. elegans*

Some facts about *C. elegans*

3 days life cycle

Invariant cell lineage

959 cells in hermaphrodite

1031 cells in male

Small genome 97 MB

19,000 genes (1 gene per 5 kb)

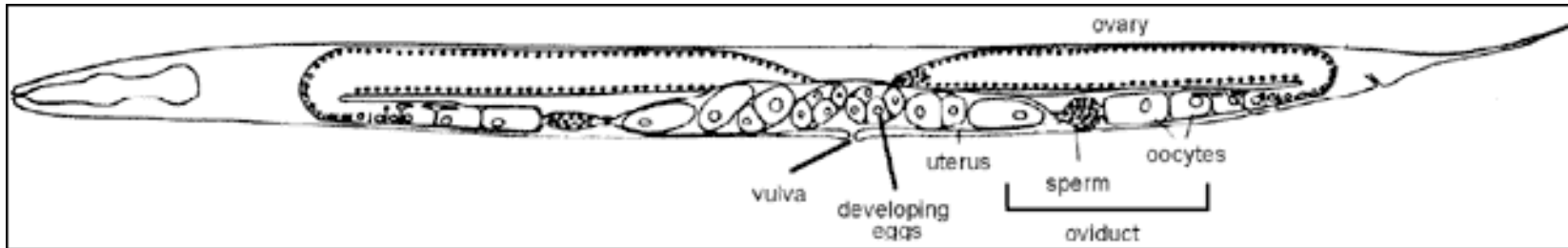
Two sexes: hermaphrodite and male

Six pairs of chromosomes



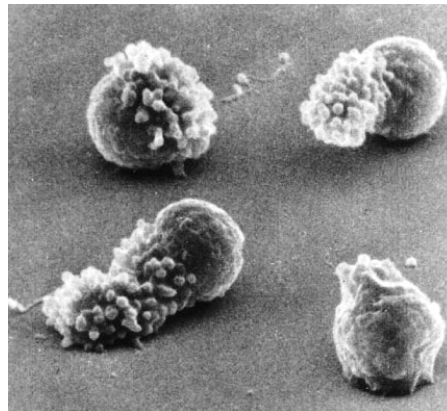
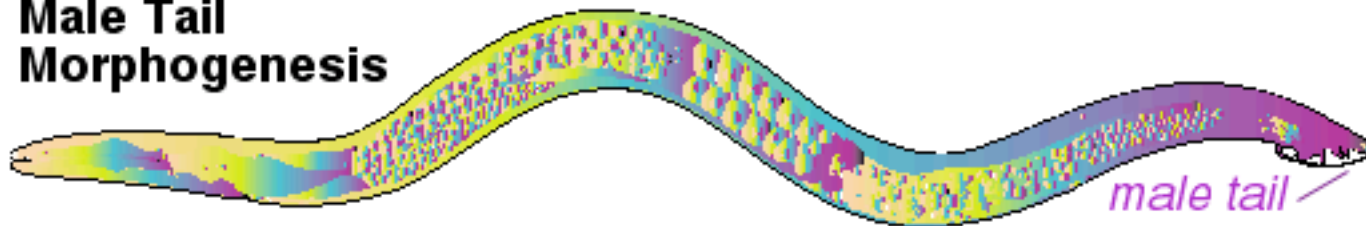
Fig. C.1

XX: hermaphrodite



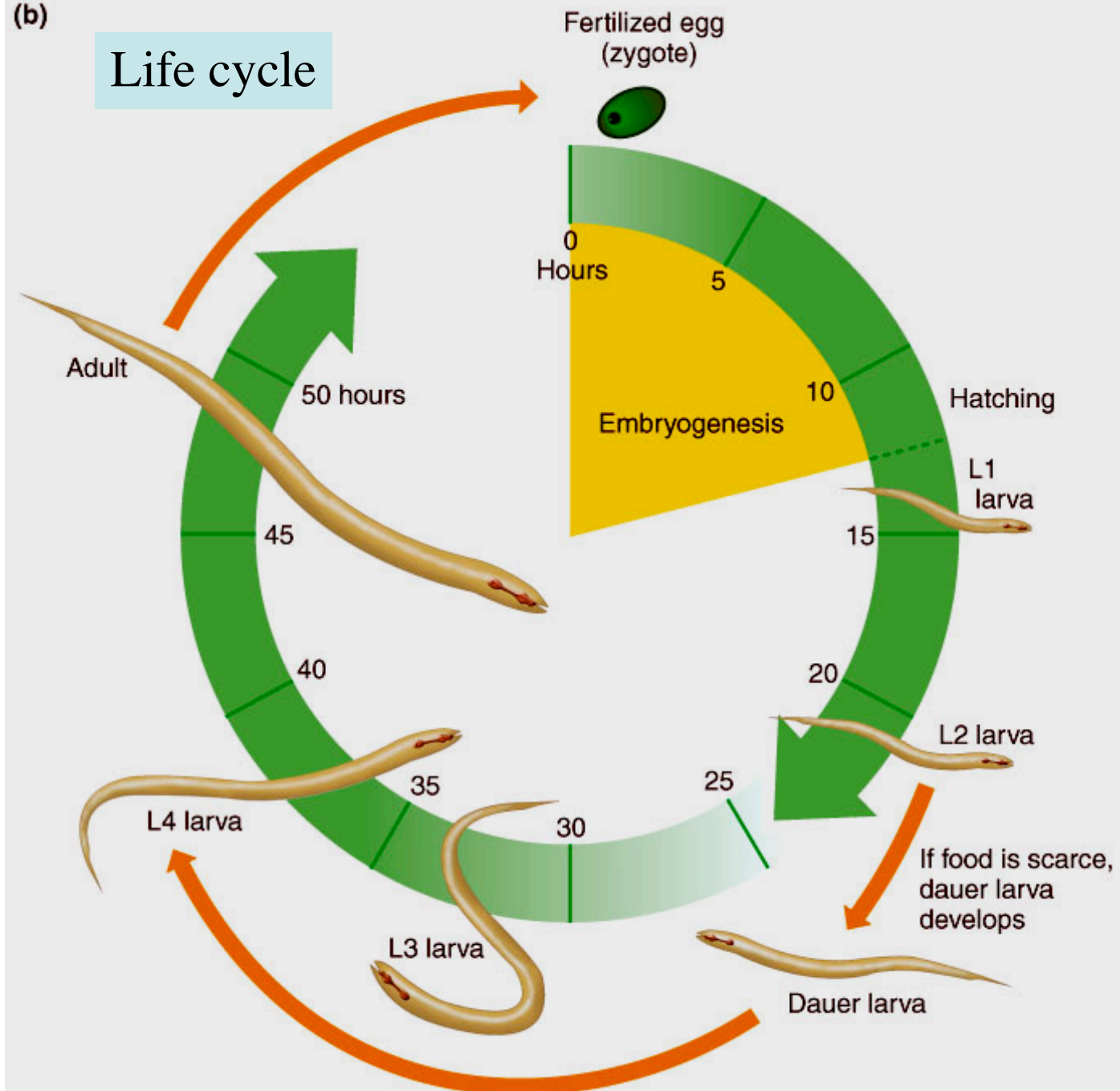
XO: male

**Male Tail
Morphogenesis**

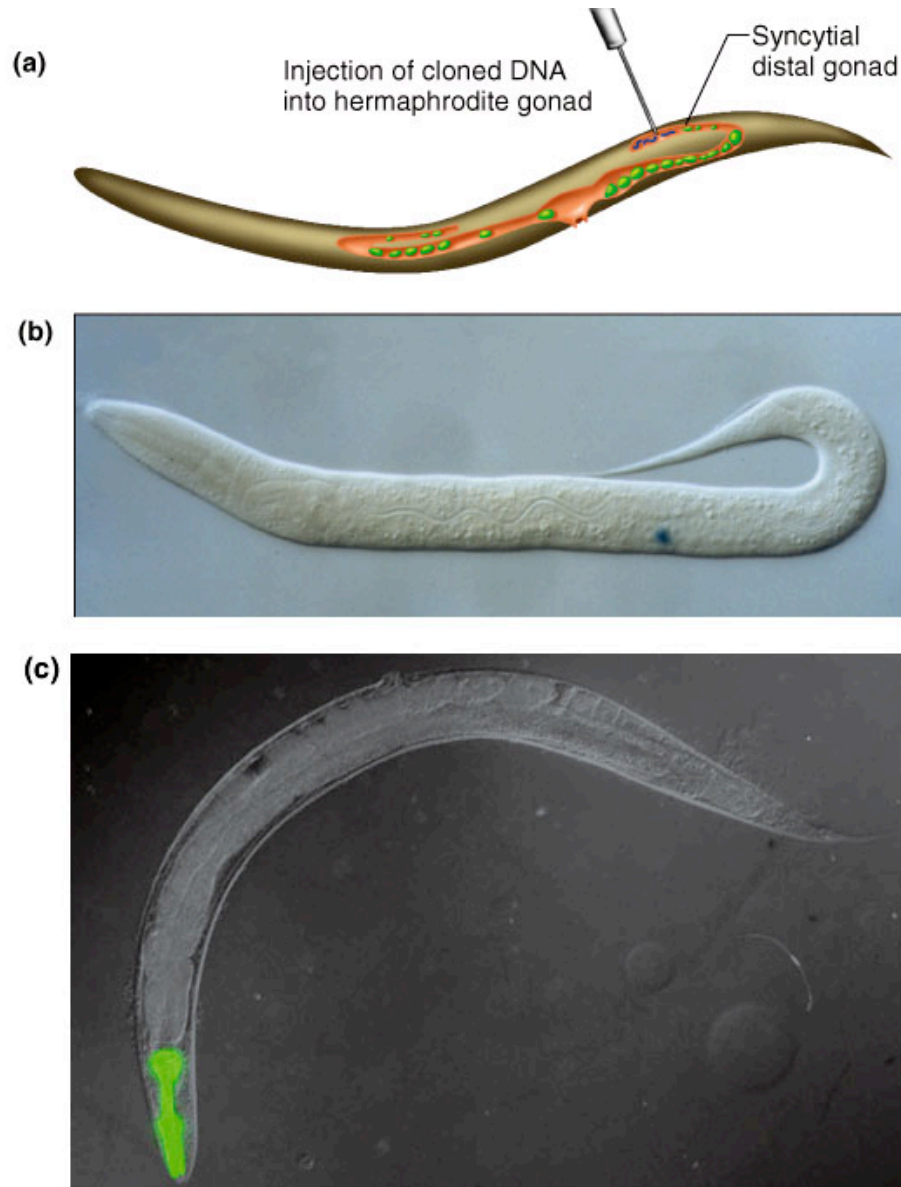


(b)

Life cycle



DNA transformation



- Inject DNA into distal syncytial gonad of hermaphrodites
- Irradiation promotes integration of transgenes into genome
- Reporter constructs show transgenes

Fig. C.8

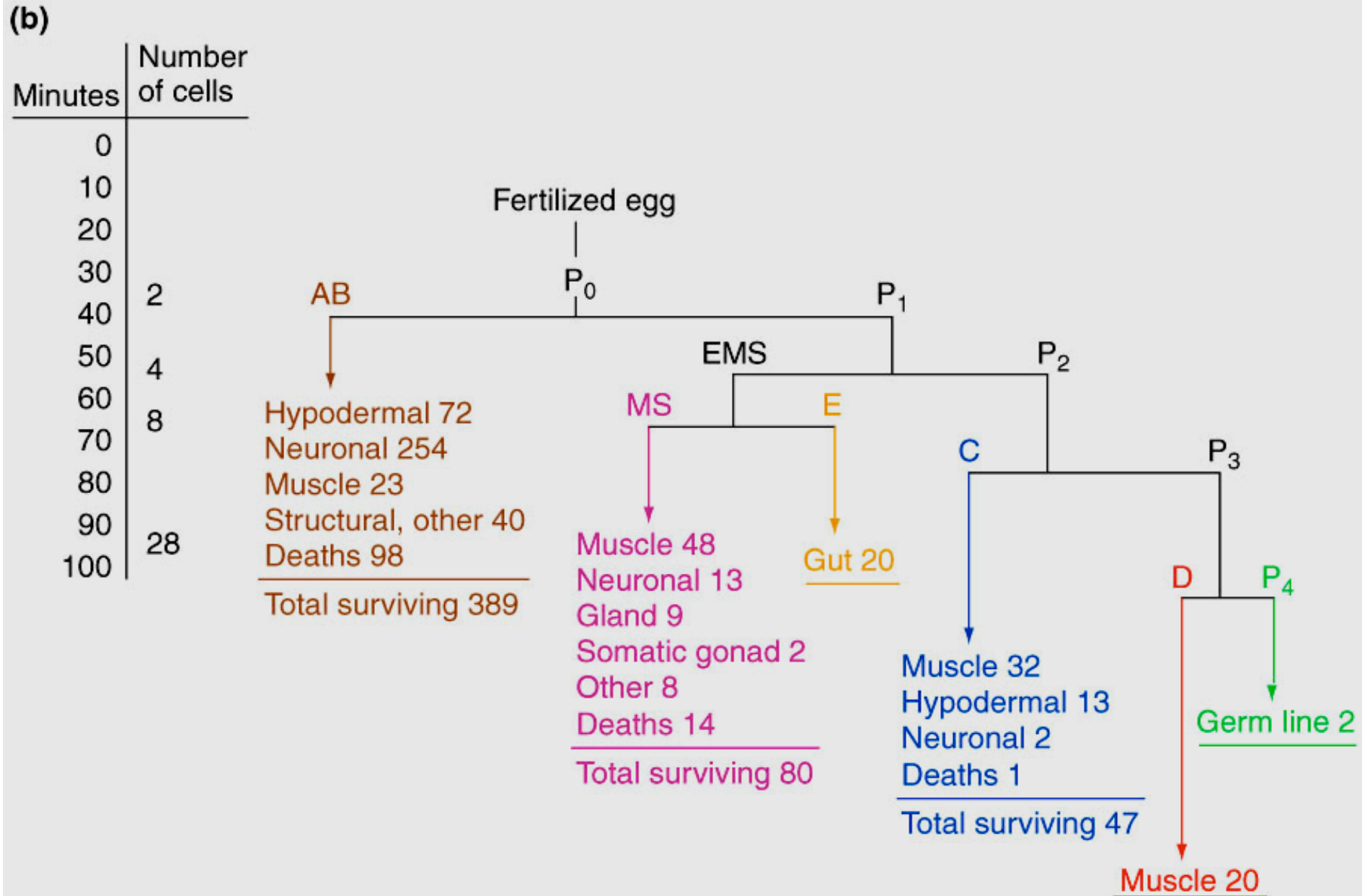


Fig. C.7b

(a)

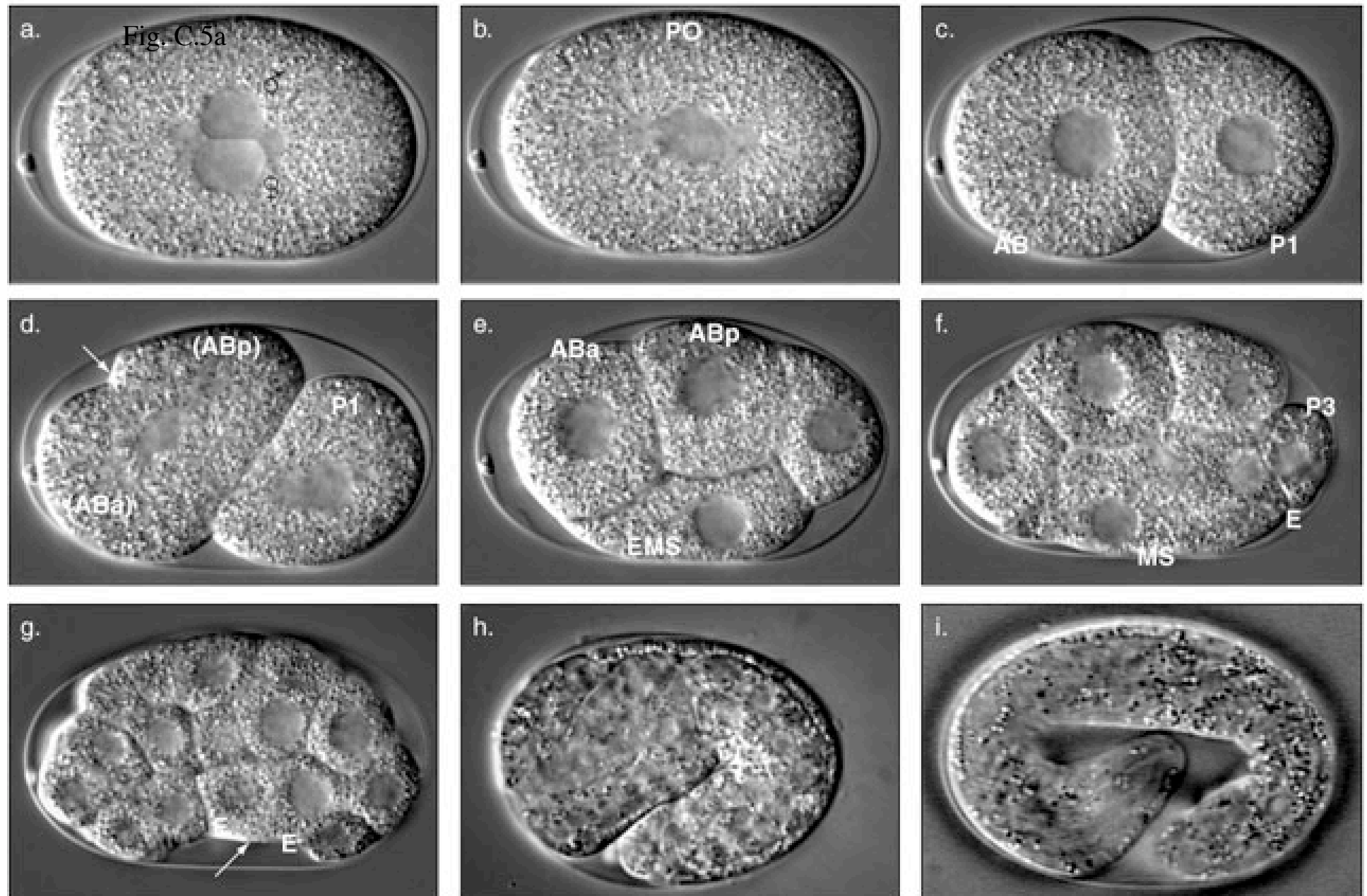
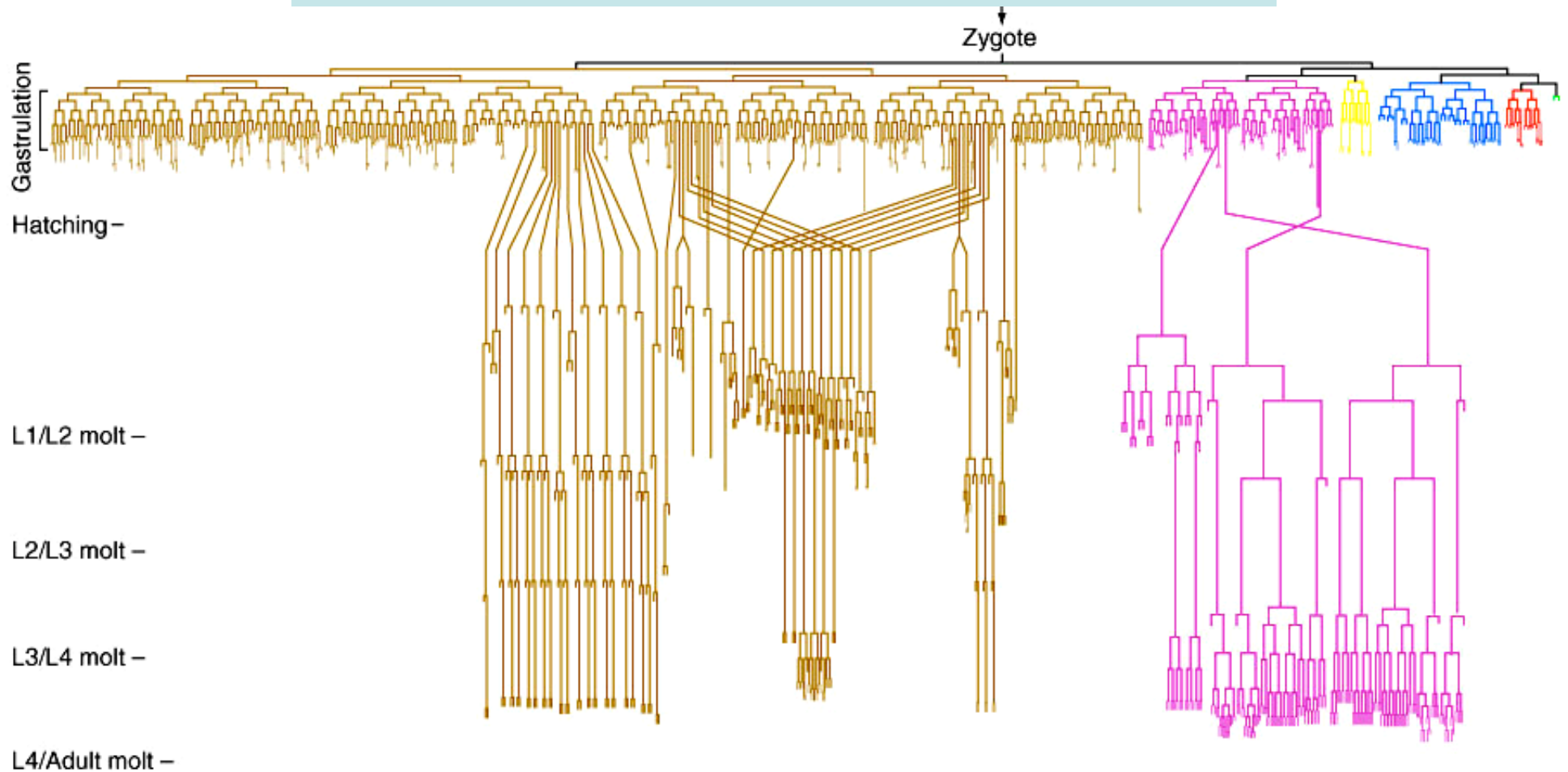


Fig. C.7a

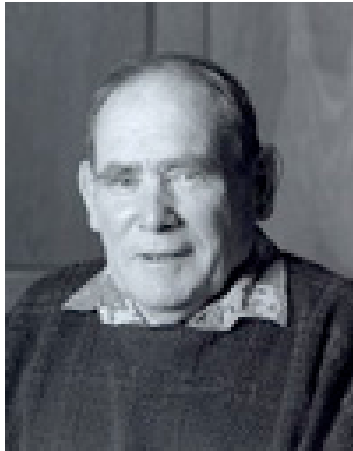
Invariant cell lineages (959 somatic cells in hermaphrodite)

(a)

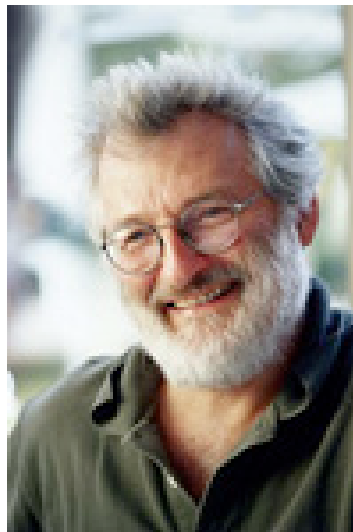
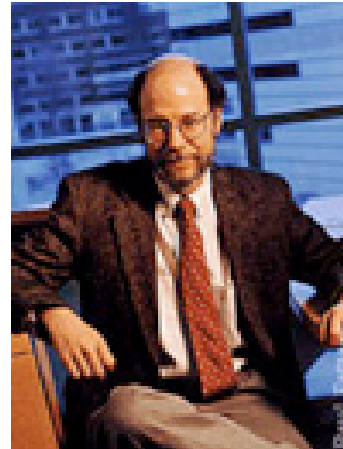


2002 Nobel Prize Winners

Sydney Brenner



Bob Horvits



John Sulston

Apoptosis is important in development

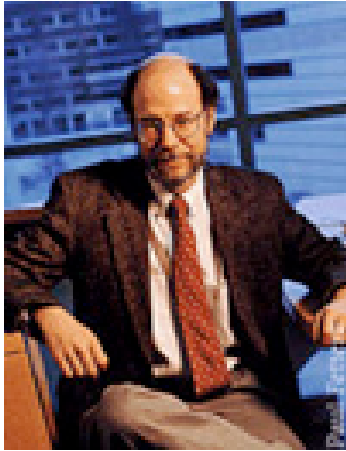
Apoptosis patterns in developing *Xenopus* embryos detected via TUNEL



TUNEL: TdT-mediated dUTP digoxigenin nick end labeling

Genetic pathway	Decision to die							Commitment to die		Execution of death		Engulfment of dead cell							
	Fate-determining genes							egl-1		ced-9		ced-4 → ced-3		ced-1 ced-2					
Cells fated to live								ced-9 ON		ced-4 OFF		ced-3 OFF		Cell LIVES					
Cells fated to die								ced-9 OFF		ced-4 ON		ced-3 ON		Cell DIES		ced-1 ced-2 ON		Dead cell engulfed and digested	

Fig. C.15



Bob Horvitz

Programmed Cell Death Naturally occurring, or programmed, cell death (apoptosis) is common during animal development, and abnormalities in programmed cell death are associated with many human diseases, including certain cancers and neurodegenerative disorders. Our laboratory has defined a molecular genetic pathway for programmed cell death. We have characterized genes that cause cells to die, that protect cells from dying, that function in the engulfment of dying cells by their neighbors, and that are involved in destroying the debris generated by cell corpses. Most of these genes have human counterparts. For example, the killer gene *ced-3* encodes a **caspase (cysteine aspartate protease)**; mammalian caspases similarly cause programmed cell death. The action of *ced-3* is facilitated by *ced-4*, which is similar to human APAF1, identified because it promotes caspase activation in a biochemical system. The function of *ced-4* is blocked by *ced-9*, which protects cells against programmed cell death and is similar to the human proto-oncogene *BCL2*, which also protects against cell death. The activity of *ced-9* is inhibited by the worm killer gene *egl-1*, which is similar to a number of mammalian killer genes. The activity of *egl-1* is controlled in a cell-specific fashion by genes that specify which cells are to live and which are to die

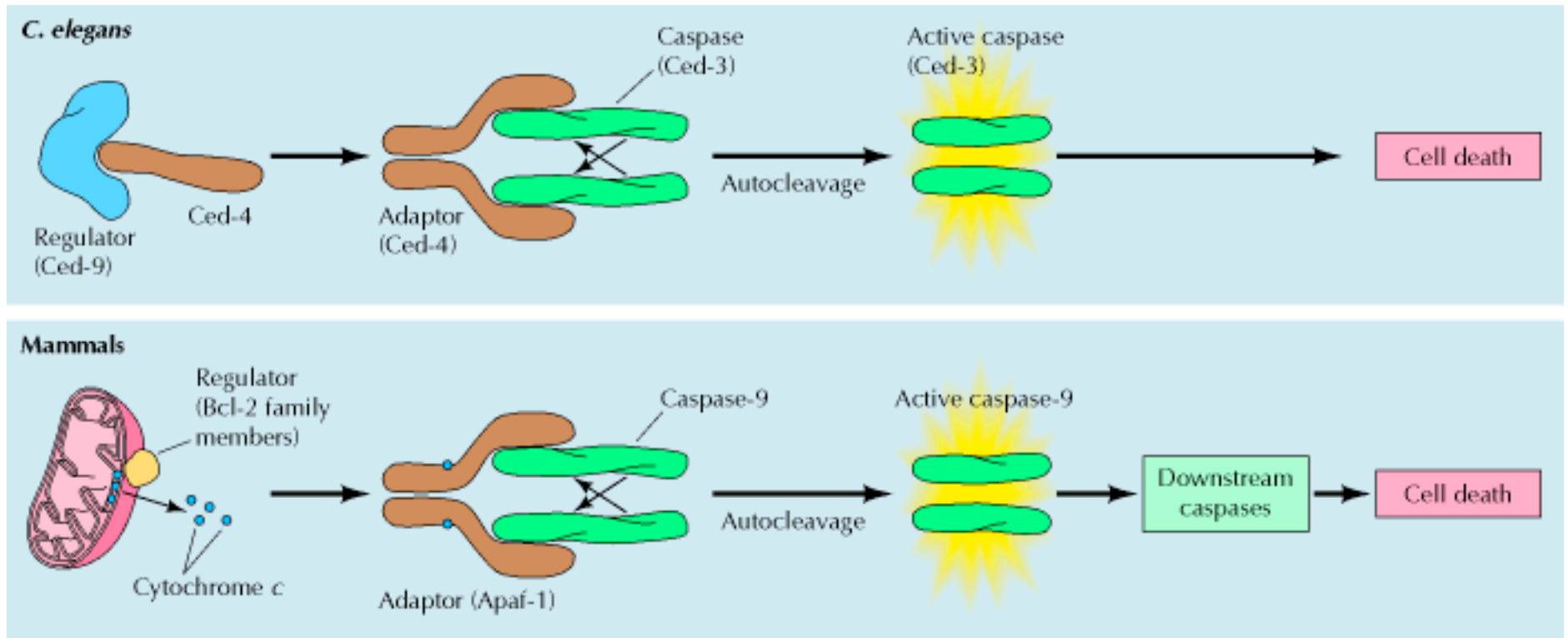


Figure 13.48. Regulators and effectors of apoptosis Many cell death signals induce apoptosis via a conserved pathway of regulators, adaptors, and caspases. In *C. elegans*, the negative regulator Ced-9 inhibits apoptosis by binding to the adaptor Ced-4. In the absence of inhibition by Ced-9, Ced-4 binds two molecules of the caspase Ced-3, resulting in autocleavage and caspase activation. In mammals, regulators of the Bcl-2 family (Ced-9 homologs) act at the mitochondria to control release of cytochrome *c*, which is required for the binding of caspase-9 to the adaptor Apaf-1 (the Ced-4 homolog). Release of cytochrome *c* from mitochondria thus signals the activation of caspase-9, which then activates downstream caspases to induce apoptosis

Programmed cell death in *c. elegans*

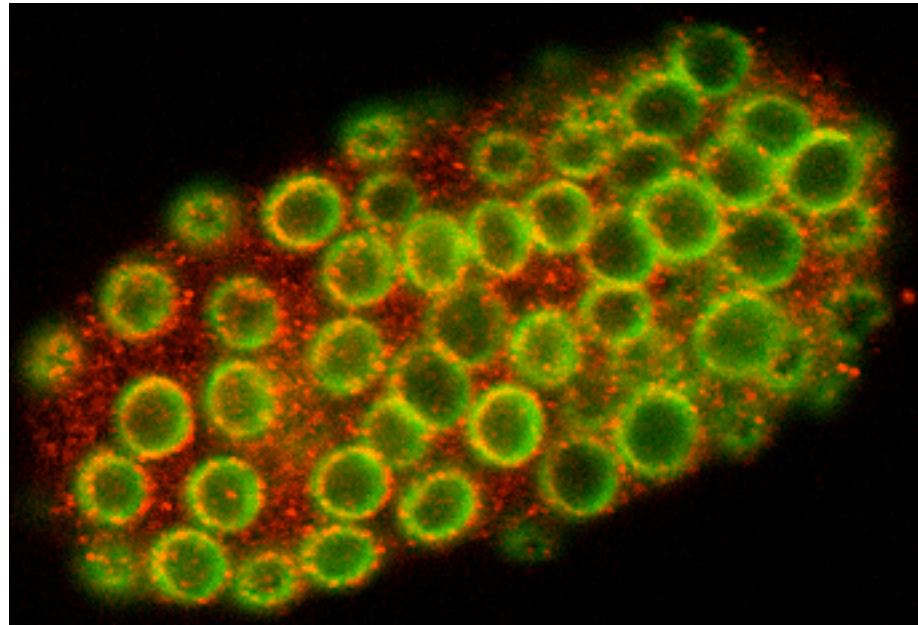


Image using confocal microscopy of a *C. elegans* embryo in which all cells have been caused to initiate programmed cell death (apoptosis). The cell-death killer protein CED-4 (red) and the nuclear envelope protein lamin (green) are both seen at the nuclear envelope (overlap is yellow). By contrast, in normal embryos, CED-4 is instead localized to mitochondria. This experiment helped reveal that CED-4 translocates from mitochondria to the nuclear envelope during programmed cell death.

The *C. elegans* Lin-4 was the first microRNA discovered

In Dr. Victor Ambros' lab



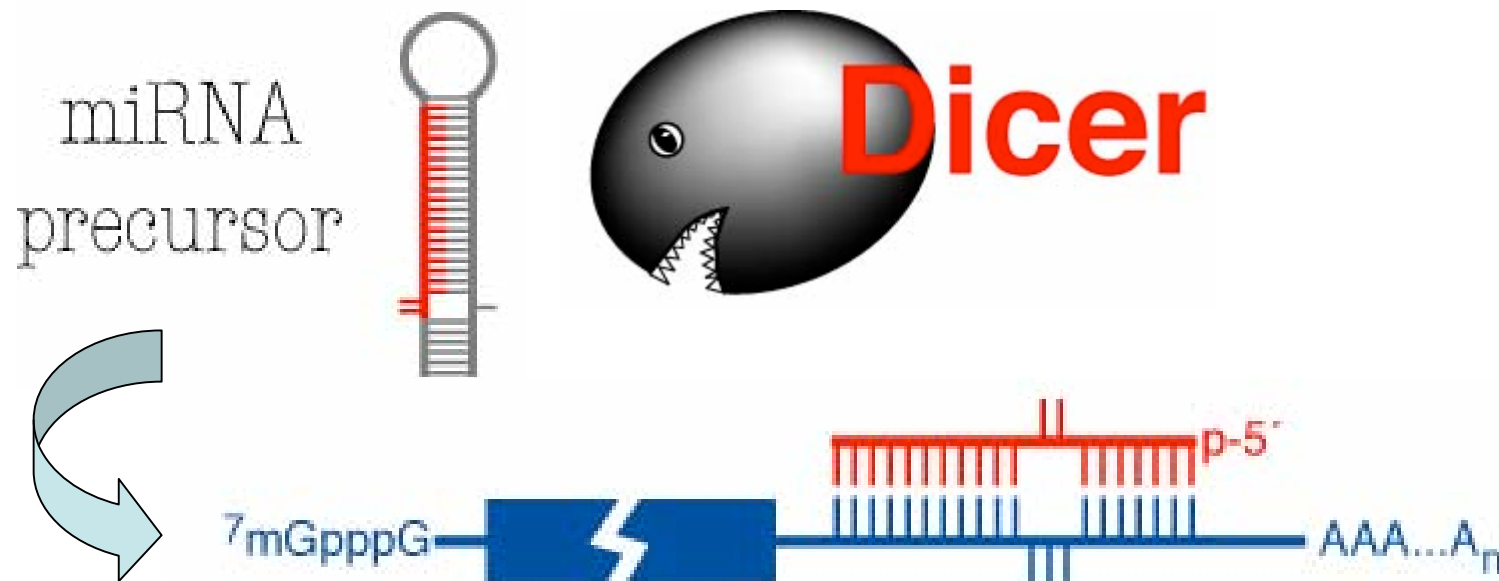
Lee RC, Feinbaum RL, Ambros V. (1993) The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 75(5):843-54.

Lee RC, Ambros V. (2001) An extensive class of small RNAs in *Caenorhabditis elegans*. *Science*. 2001 Oct 26;294(5543):862-4.

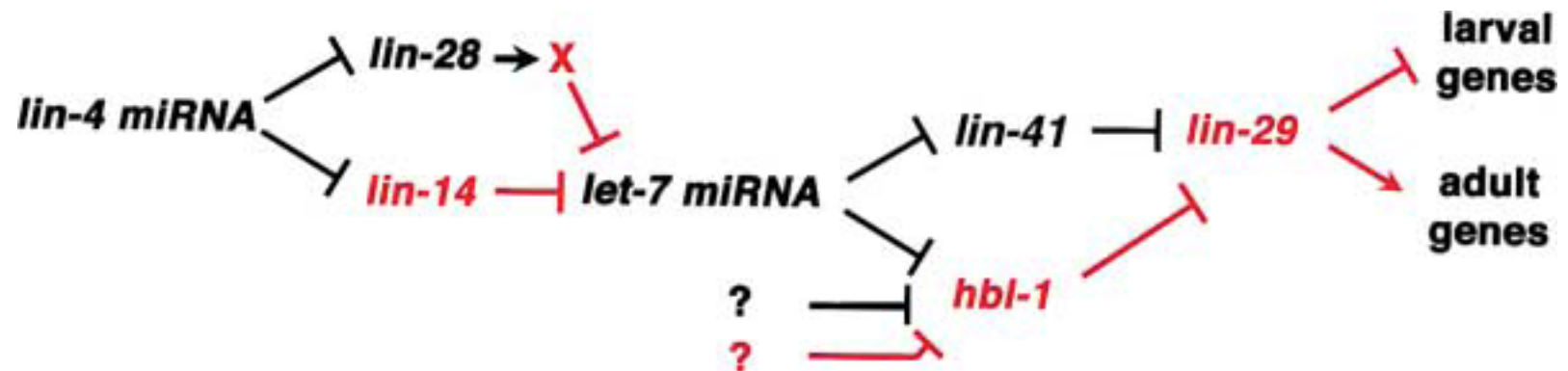
<http://chronic.dartmouth.edu/VRA/ambroslab.html>

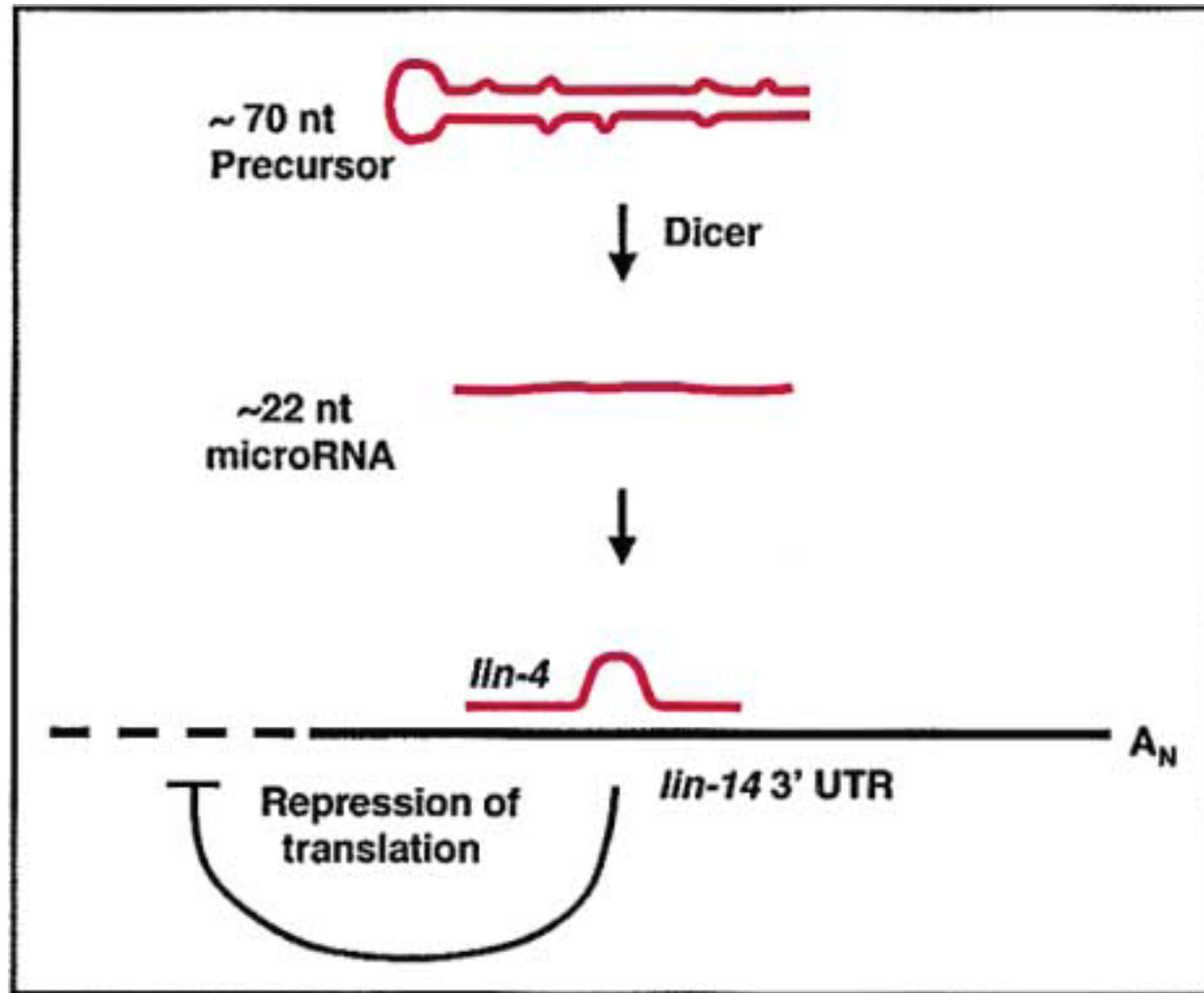
micro RNA (miRNA)

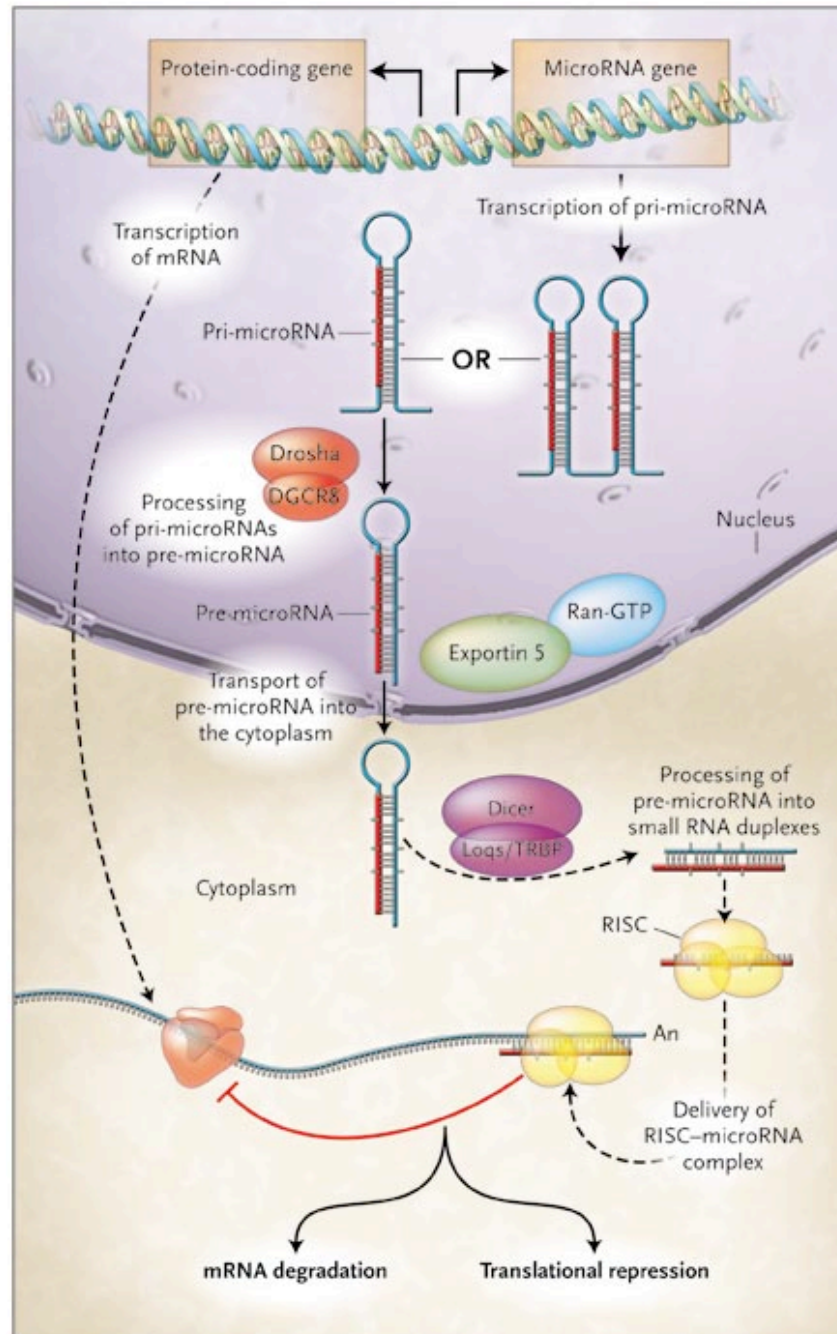
- Gene expression regulation
- Created by similar process to siRNA
- Generally prevents binding of ribosome
- Or degrade target mRNA



Genetic pathway that regulates developmental timing

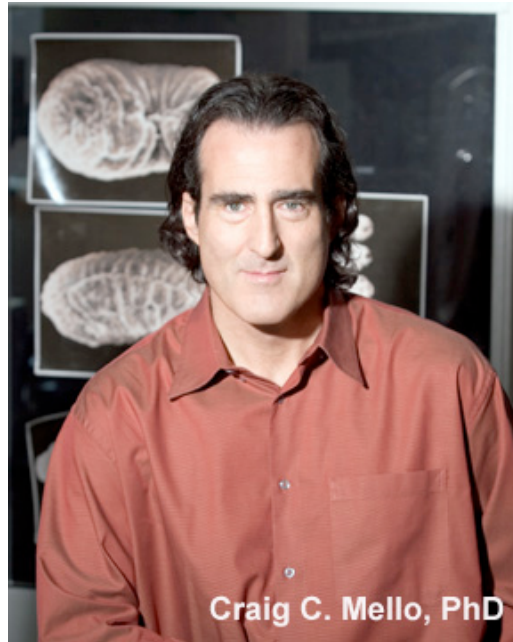






RNAi was first discovered in *C. elegans*

Nobel prize-2006



Fire et al., (1998) Potent and specific genetic interference by double stranded RNA in *C. elegans*. **Nature** vol 391, 806-810

Fig. C.9

