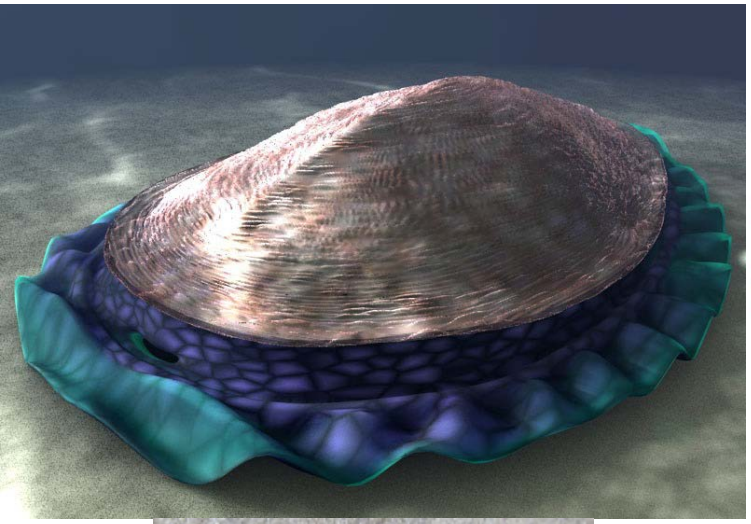
Model organism

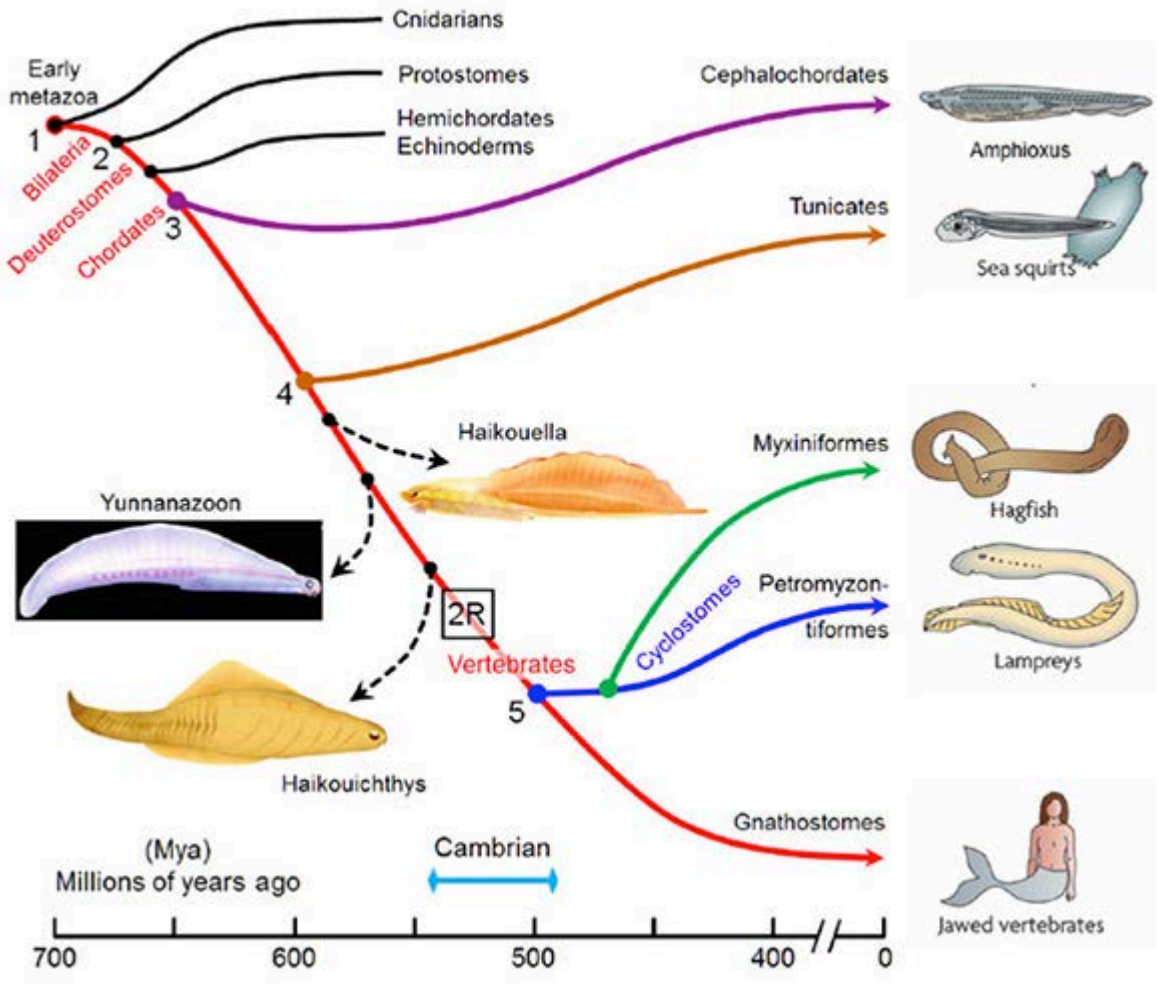
PG

2017

Ancestry to bilateral symmetry



Kimberella



The beginning

- A common core of genetic pathways guiding development and have made it possible to reconstruct many features of the most recent common ancestor of all bilateral animals, which most likely lived 600–800 million years ago.
- This ancestor can be imagined as an advanced worm-like or primitive shrimp-like creature which had a few distinct body specializations along the nose-to-tail axis and was subdivided into three distinct germ layers (ectoderm, mesoderm, and endoderm).

Commonality

It also had evolved an inductive signalling system to partition the ectoderm into neural versus non-neural components and is likely to have possessed appendages or outgrowths from its body wall with defined anterior–posterior, dorsal– ventral, and proximo–distal axes, as well as light-sensitive organs, a sensory system for detecting vibrations, a rudimentary heart, a molecular guidance system for initiating axon outgrowth to the midline of the nervous system, ion channels for conducting electrical impulses, synaptic machinery required for neural transmission, trachea, germ cells, and an innate immune system.

The rationale

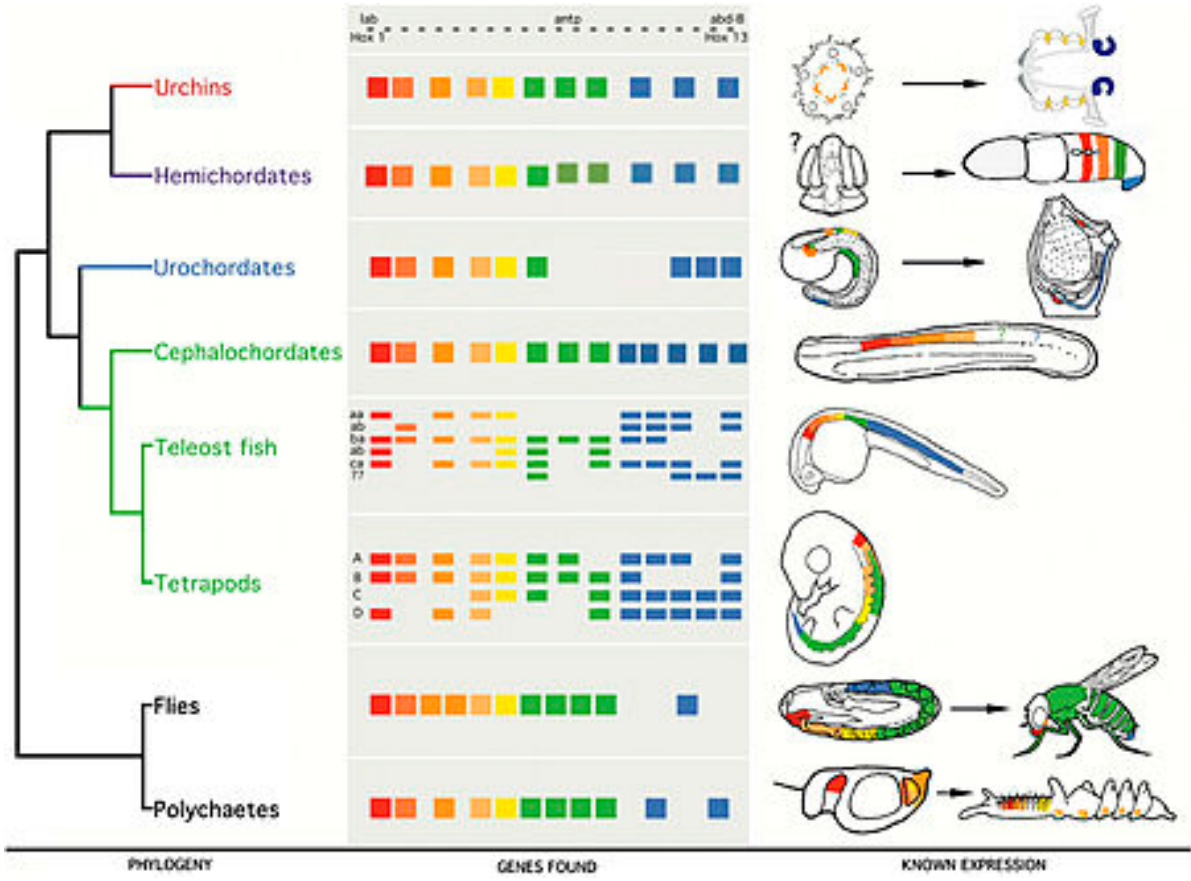
The fact that the ancestor of vertebrate and invertebrate model organisms was a highly evolved creature which had already invented complex interacting systems controlling development, physiology, and behavior has profound implications for medical genetics. The central points that we explore in this chapter can be broadly put into two categories: *(1) the great advantages of model organisms for identifying* and understanding genes that are altered in heritable human diseases and *(2) the functions of many of those genes and the evidence that* they were present in the ancestral bilateral organisms and have remained largely intact in both vertebrate and invertebrate lineages during the ensuing course of evolution.

The systematic view

Disease

Human disease gene homologs in *Drosophila supports this view since 75% of human disease genes are* structurally related to genes present in *Drosophila and more than a* third of these human genes are highly related to their fruit fly counterparts

Development



Caveat

•TGN1412 was withdrawn from development after a catastrophic trial in the UK left six men fighting for their lives in March 2006. The drug was a monoclonal antibody designed to trigger the production of T cells by binding to the T-cell receptor CD28. The crucial part, however, was the supposed accompanying expression of anti-inflammatory cytokines, which, it was hoped, would alleviate rheumatoid arthritis and perhaps other autoimmune conditions. The drug passed various animal trials that yielded *in vivo and in vitro* evidence that although the drug stimulated T-cell production as a whole, it led to the preferential production of regulatory T cells and a down-regulation of active T cells.

Strengths and limitations 1

Species	Experimental Advantages	Experimental Limitations
Yeast	Excellent genetics Very powerful second site screening Powerful molecular techniques Genes can be easily cloned Genome sequence complete Possess all basic eukaryotic cell organelles Cell cycle control similar to animals	No distinct tissues
Slime mold	Excellent genetics Very powerful second site screening Powerful molecular techniques Genes can be easily cloned Genome sequence nearing completion Simple cellular behaviors similar to animals Motility Chemotaxis	Limited cellular diversity
Nematode	Excellent genetics Hermaphrodites, self-fertilization Fast generation time Second site suppressor/enhancer screens Powerful molecular techniques Genes can be easily cloned Transposon tagging SNP mapping Rapid cosmid rescue Deletion collections span genome RNAi effective Genome sequence complete Few cells: 959 cells, 302 neurons Morphology fully characterized Serial EM reconstruction All cell lineages known Time lapse microscopy of development Laser ablation of single identified cells	Limited external morphology Less similar to human than flies (61% of *Drosophila* genes have human counterparts vs. 43% of *C. elegans* genes) Detailed direct analysis of gene expression patterns can be difficult Some embryological manipulations difficult

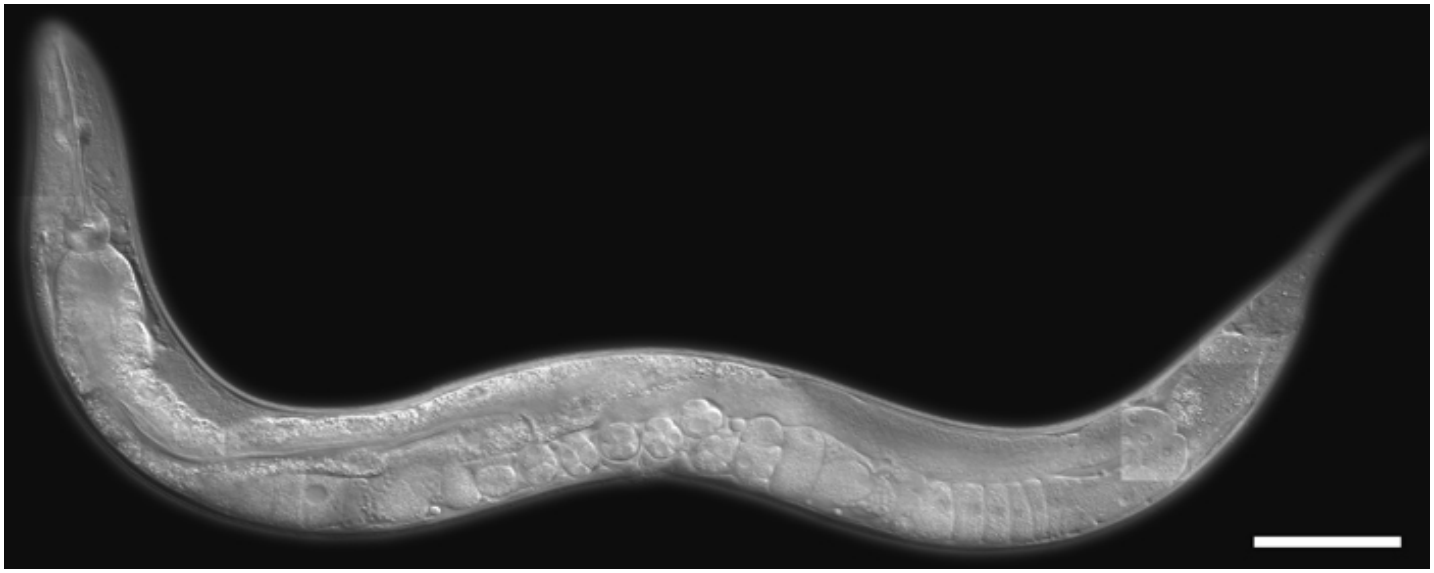
Strengths and limitations 2

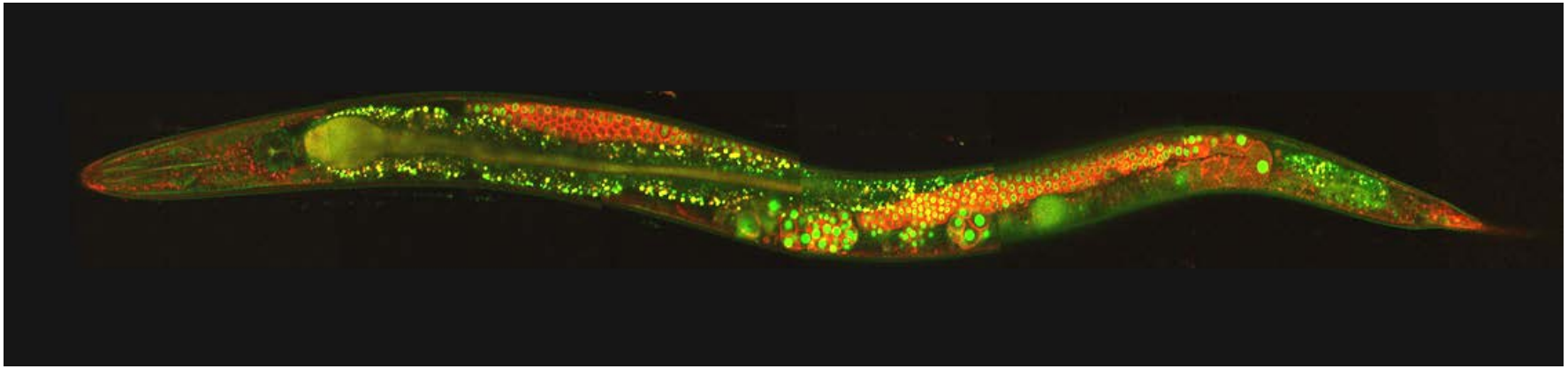
Species	Experimental Advantages	Experimental Limitations
Fruit fly	Excellent genetics Genome sequence complete Targeted gene disruption RNAi effective Fast generation time Second site suppressor/enhancer screens Powerful molecular techniques Genes can be easily cloned Transposon tagging SNP mapping Transgenic animals easily generated Targeted misexpression of genes in space and time Mosaic analysis: determine where gene acts	Embryological manipulations difficult Targeted gene disruption still difficult, although possible
Zebrafish	Simplest vertebrate with good genetics: nearly saturated for zygotic patterning mutants Genome analysis well under way (good SNP and linkage maps) Easy examination of morphological defects (clear embryos) Embryological manipulations possible Organ systems similar to other vertebrates (e.g., eyes, heart, blood, gastrointestinal tract) Rapid vertebrate development	Not yet trivial to clone genes Cannot easily make transgenic animals No targeted gene disruption
Frog	A vertebrate Ectopic gene expression possible in early embryos, although manipulation of levels difficult Accessibility of embryo (pond no shell) Excellent experimental embryology grafting induction preparations (Keller sandwiches/animal caps, etc.) Injection of RNA into identifiable blastomeres	No genetics, although under development Difficult to create transgenic animals

Strengths and limitations 3

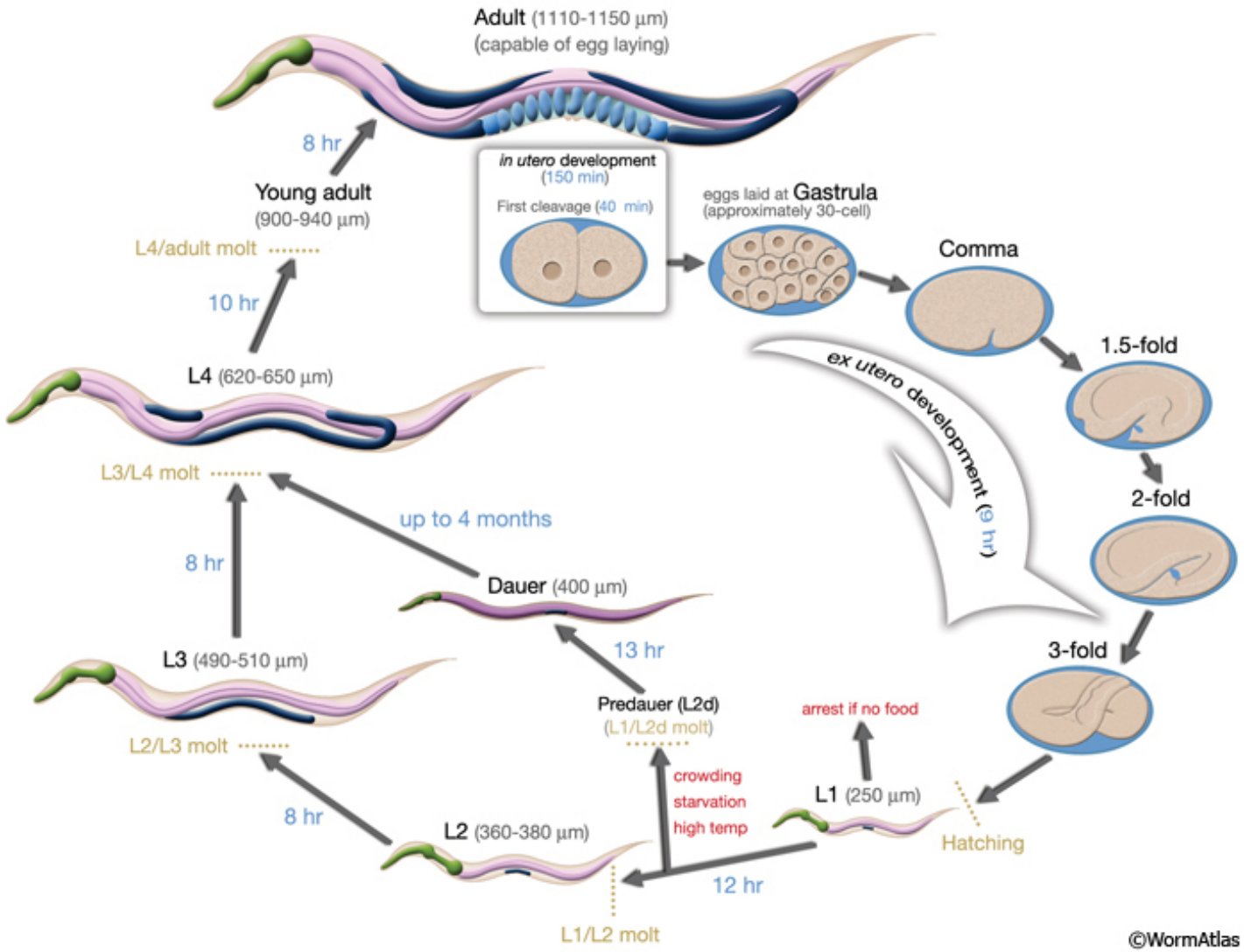
Species	Experimental Advantages	Experimental Limitations
Chicken	Availability, low cost	Limited genetics
	Accessibility, outside of mother	Limited genome data at present
	Well suited for embryological manipulation; transplants of limbs, notocord, neural crest	
	Easily transfected by avian retroviruses	
Mouse	Mammals, brains similar to human, all homologous areas/cell types	Classic "forward" genetics difficult
	"Reverse" genetics: targeted gene knockouts by homologous recombination routine	Early-acting mutant phenotypes difficult to study (resorbed by mother)
	Developmental overview same as for all mammals	Embryonic manipulations difficult (inside mother)
	Large mutant collection	Development and life cycle relatively slow (months)
	Construction of chimeric embryos possible	
	Availability of material at all stages	
	Source of primary cells for culture	
Monkey	Very similar to humans	Fetal experiments difficult
	Developmental connections and physiology, postnatal	No genetics
	Anatomy of learning	High cost, for both animals and facilities
	Responses to injury	
Human	Many diseases, self-reporting mutants (>5000 genetically based diseases)	Fetal material difficult
	Some good family pedigrees	No experimental access
	Genome sequence complete	
	Detailed behavior/ontogeny	

C. elegans





Life Cycle


Adult (1110-1150 µm)
(capable of egg laying)
8 hr
Young adult
(900-940 µm)
L4/adult molt
10 hr
L4 (620-650 µm)
L3/L4 molt
8 hr
L3 (490-510 µm)
L2/L3 molt
8 hr
L2 (360-380 µm)
L1/L2 molt
12 hr
L1 (250 µm)
Hatching
arrest if no food
crowding
starvation
high temp
Predauer (L2d)
(L1/L2d molt)
13 hr
Dauer (400 µm)
up to 4 months
in utero development
(150 min)
First cleavage (40 min)
eggs laid at Gastrula
(approximately 30-cell)
ex utero development (9 hr)
Comma
1.5-fold
2-fold
3-fold
©WormAtlas

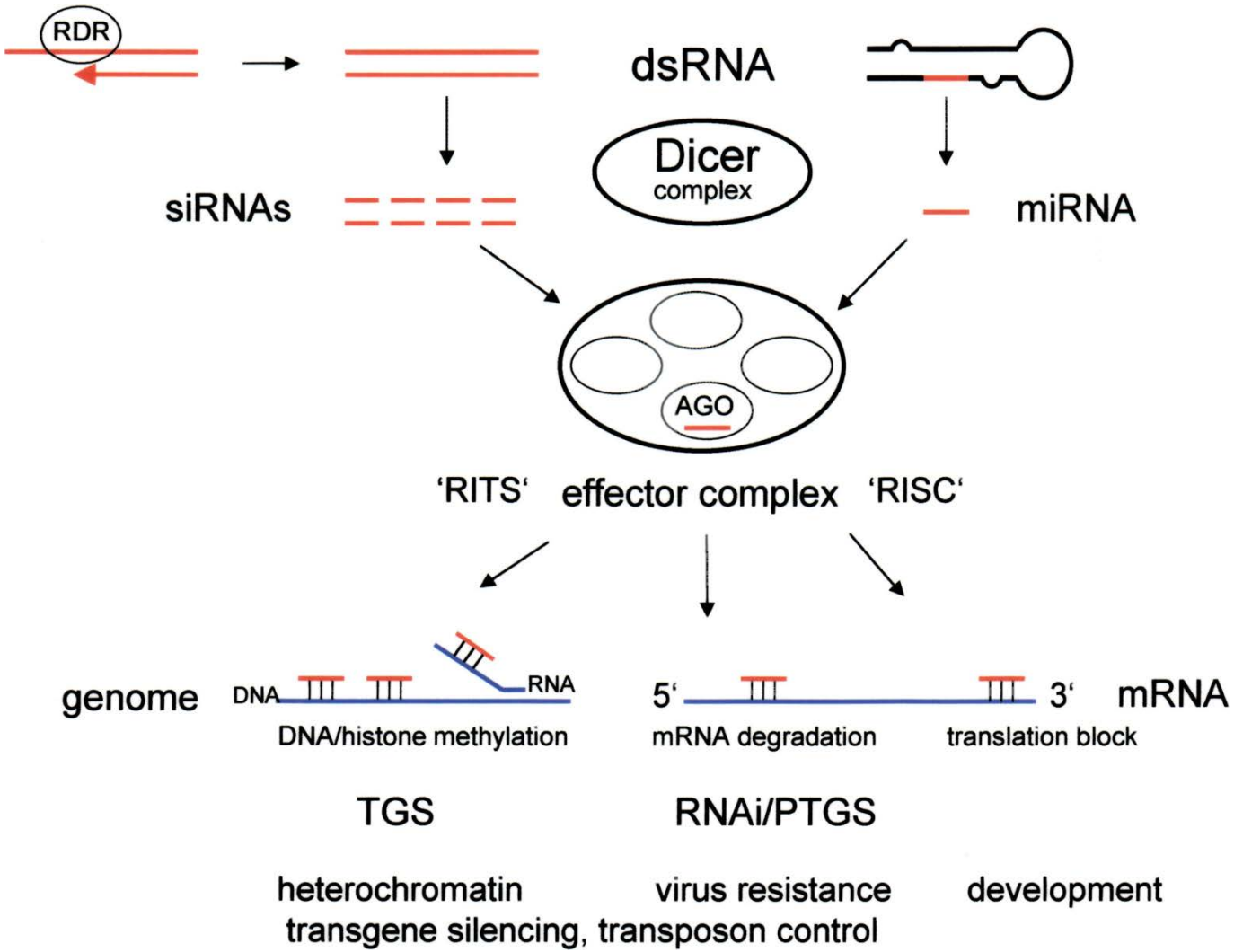
Characters of *C. elegans*

- Small (about 1 mm in length)
- Feeds on bacteria
- Easily to housed and cultivated in large numbers
- Transparent
- Easily to manipulation and observation
- Life cycle is short
- Have 1090 somatic cells at most
- Easily to mutagism
- Can be long-term storage
- Genome is completely sequenced

Genome

- The genome was completely sequenced in 1998, It is the first multicellular-organism (animal) that has a completely sequenced genome
- The genome size of C. elegans is about a hundred million base pairs
- Five pairs of autosomes and one pair of sex chromosome
- Contains approximately 20,100 protein-coding genes
- Contain more than 16,000 RNA genes

RNAi


RDR
dsRNA
Dicer
complex
siRNAs
miRNA
AGO
'RITS'
effector complex
'RISC'
genome
DNA
RNA
5'
3'
mRNA
DNA/histone methylation
mRNA degradation
translation block
TGS
RNAi/PTGS
heterochromatin
virus resistance
development
transgene silencing, transposon control

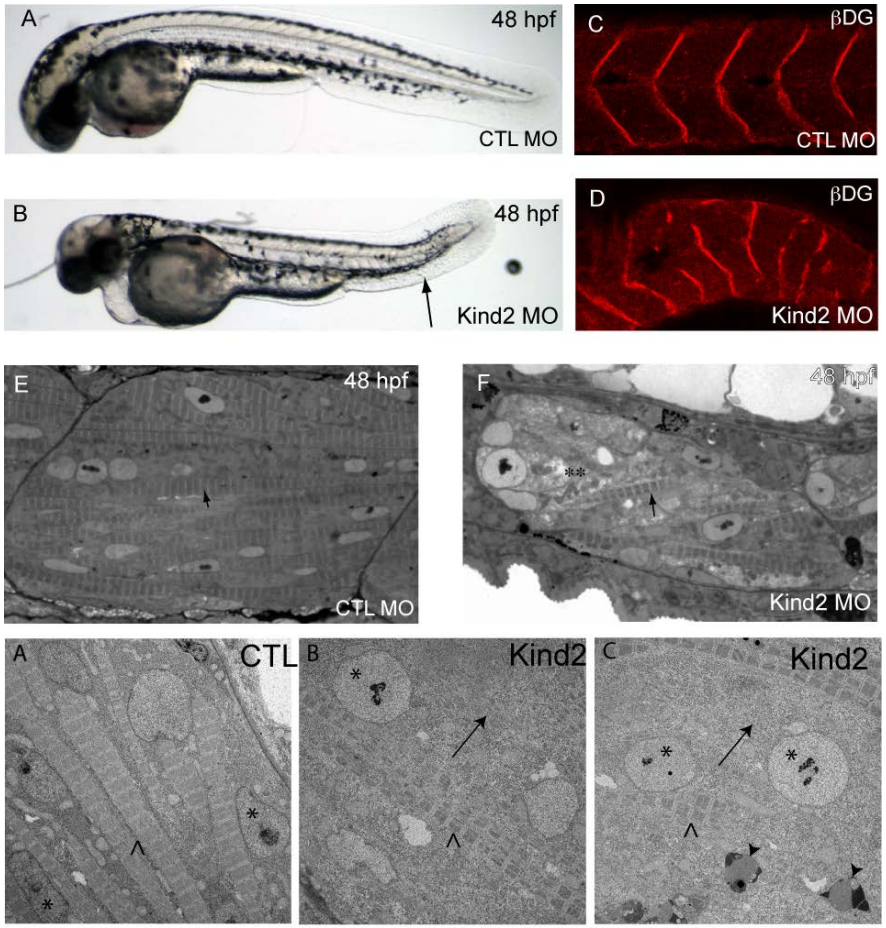
Zebrafish (*Danio rerio)*

- 25 Chromosomes
- 1412 Mb size
- 42,422 genes
- Common aquarium fish
- Transgenic pet fish available

Zebrafish as model system

- Zebrafish are vertebrates. Like humans, they have a backbone.
- Zebrafish have features that make them easy to maintain, manipulate, and observe in the lab.
- The embryos develop outside the mother's body, so you can have easy access to them.
- Zebrafish embryos are transparent. This means you can watch development as it happens in living embryos.
- The embryos develop quickly.
- You can physically manipulate the embryos.
- Great for disease model

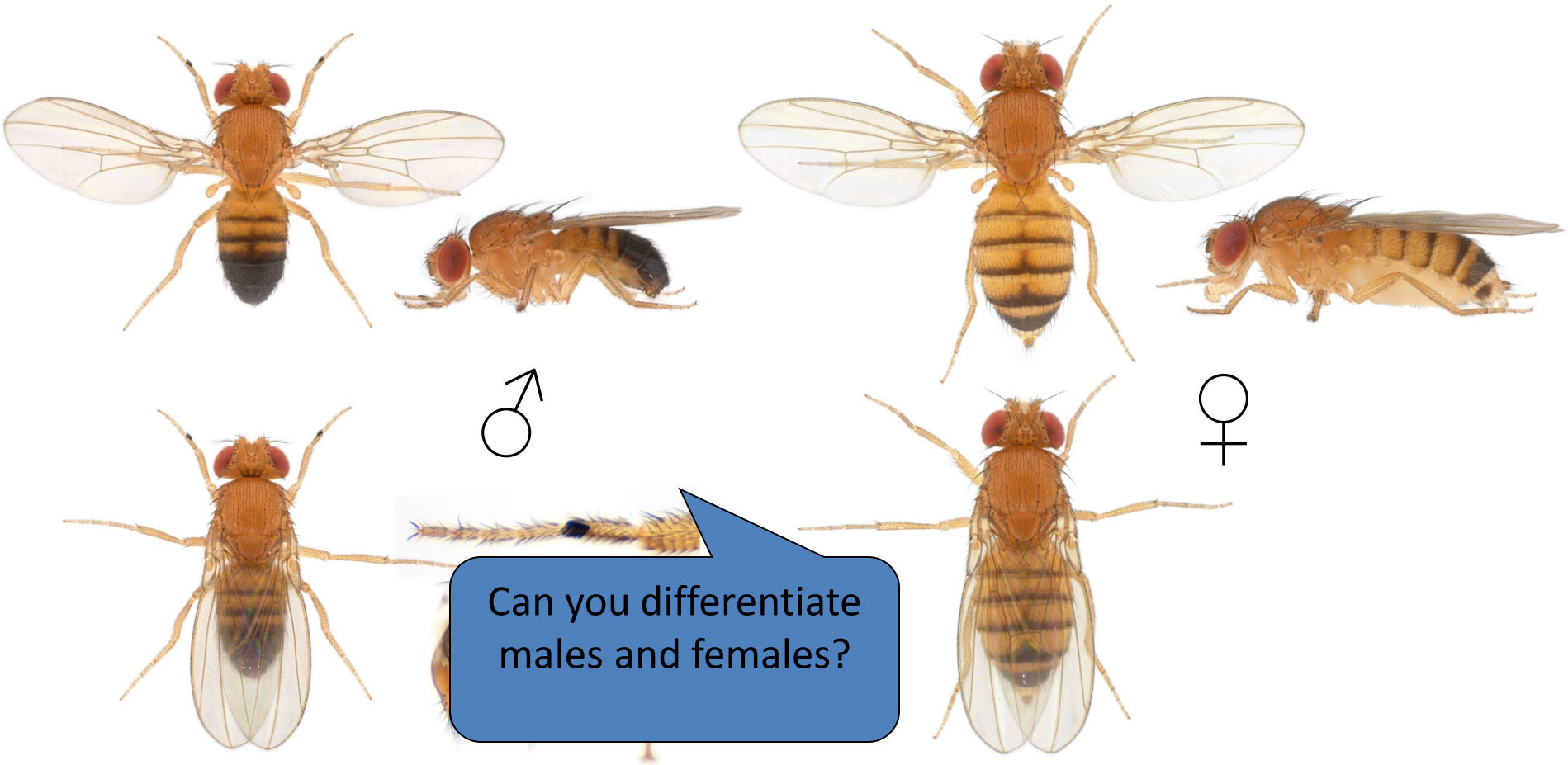
Zebrafish as a model for muscle disease



- Obvious phenotypic consequences from muscle dysfunction
  - Impaired swimming
- Abnormal muscle observable in live fish
  - Can see it with conventional microscopy
- Histopathologic changes that reflect human muscle pathologies
  - (dystrophic pattern in dystrophies, for example)

Drosophila melanogaster

- It is an animal – therefore it can be used to study development, physiology and behavior.
- 90 years of genetics



The Drosophila Genome

- 3 sets of autosomes
  - 2 and 3 - large metacentric chromosome
  - 4 - very small telocentric chromosome
- X/Y sex Chromosomes
  - X is a large telocentric chromosome
- Size: 165 Mb
- 14,000 genes
- 50% have a human homolog
- 61% of human disease genes have a fly counterpart

Unusual Features of Drosophila

- No crossing over in male meiosis
- larval cells (e.g. salivary gland cells) do not grow by mitotic cell division
  - they increase in size and become polyploid
  - the many chromosome strands line up to form the giant polytene chromosomes that give Drosophila it's wonderful cytogenetics.

Polytene Chromosomes

- A consequence of lack of cell division in larval life (2000N).
- DNA strands line up in register
- Giant chromosomes, banding pattern (bands 5 – 200 kb).
- Great cytology – in favorable regions can recognize a 15 kb deletion.
- Uneven Amplification

Need to say more?