Experimental animals: Past, Present and Future

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Near East University
Faculty of Medicine, Department of Medical Biology

"Our story is pretty typical. We met in the lab."

Model organisms

vs

Experimental organisms

Why do we need animal models (or model animals)?

- to explore normal biological mechanisms
- to identify the genetic, physiological or biochemical basis of both normal and pathological cellular mechanisms
- to provide ‘models’ of human disease to explore possible treatments
- to test the toxicity of possible treatments

"Trust me, I saw a book on human anatomy and this in not the worst thing that could be growing on my back."

Which model (experimental) organism?

- Biological suitability
- Ability to be tamed and used as standardized research material
- What is the question at hand?
- Availability of techniques and practices to be used to answer the question
- MONEY!

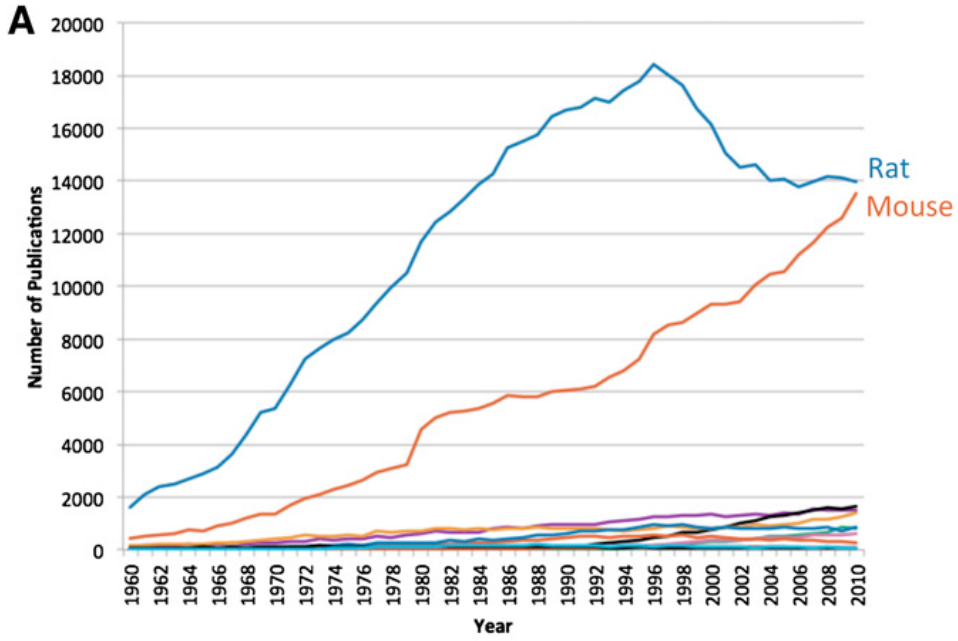
Organisms to study various processes

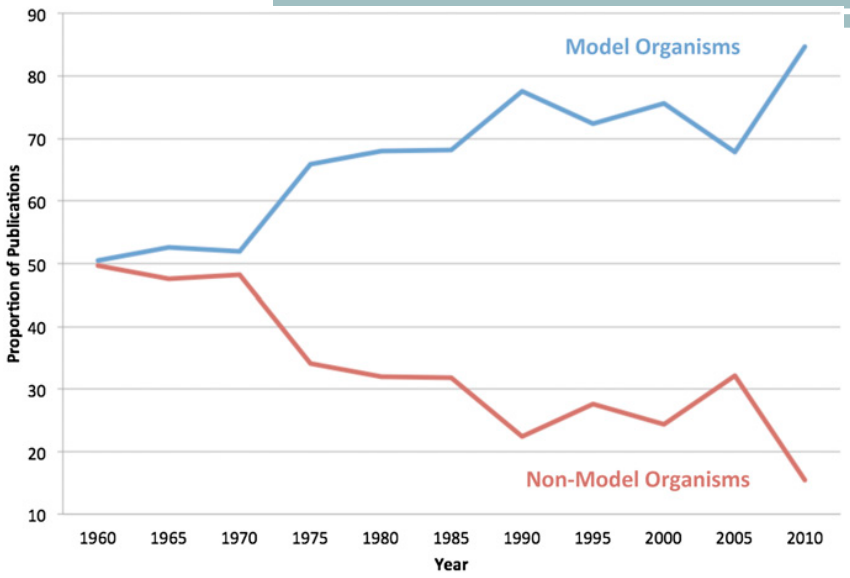
- In 1999, the NIH produced a list of model organisms
- Overall, there are over 80 organisms but these are the most common ones:
  - *Drosophila melanogaster* (the fruit fly)
  - *Caenorhabditis elegans* (the worm)
  - *Mus musculus* (The mouse)
  - Rattus norvegicus (the brown rat)
  - *Danio rerio* (the zebrafish)
  - *Xenopus laevis* (the frog)
  - *Gallus gallus* (The chicken)
  - *Arabidopsis thaliana* (the plant ☺ - a weed from the mustard family)
  - *Saccharomyces cerevisiae* (The budding yeast)
  - *Schizosaccharomyces bombe* (the fission yeast)
  - Daphnia magna (the water flea)
  - *Neurospora (the fungi)*
  - *Slimemolds*

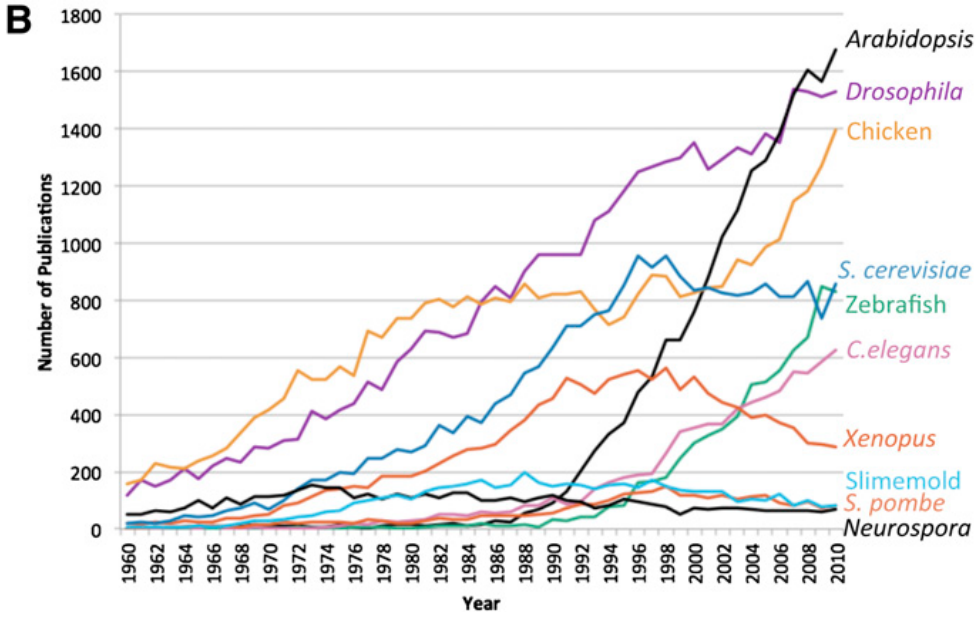
A snapshot of the landscape of genomic engineering in multicellular organisms.

Ying Peng et al. Development 2014;141:4042-4054


Your Plate.
GO VEGAN.
PETA
Try to Relate to Who's on Your Plate.







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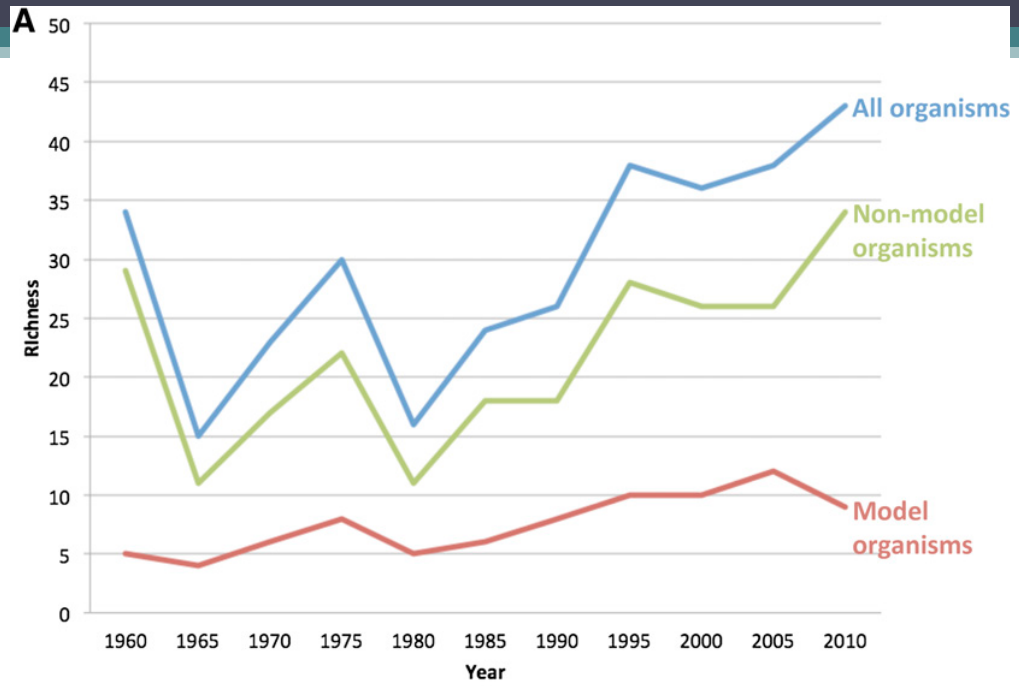

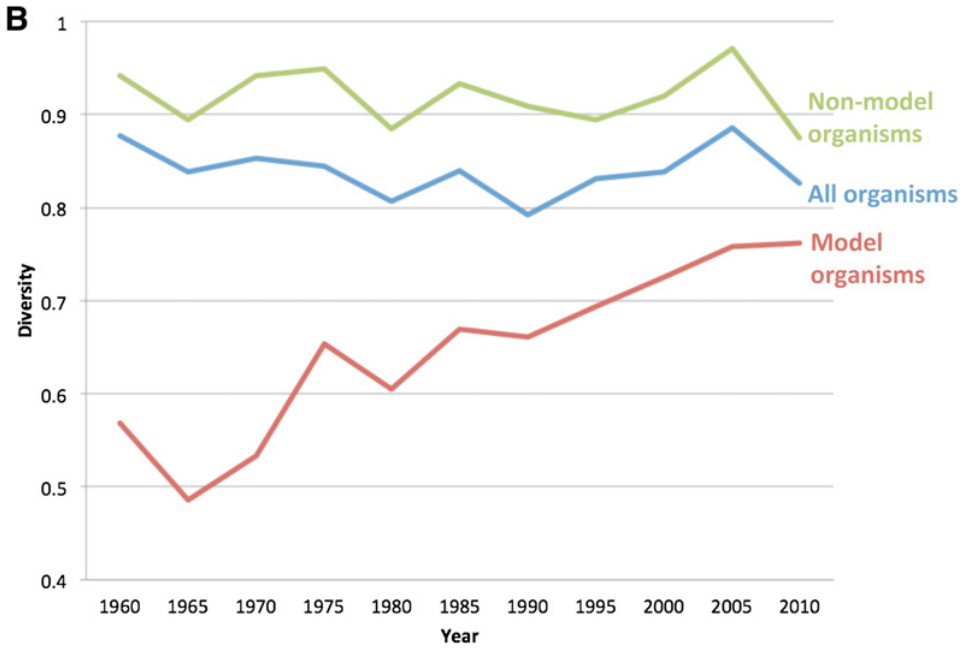

Publication trends in model organism research.
Dietrich MR, Ankeny RA, Chen PM.
Genetics. 2014 Nov;198(3):787-94. doi:
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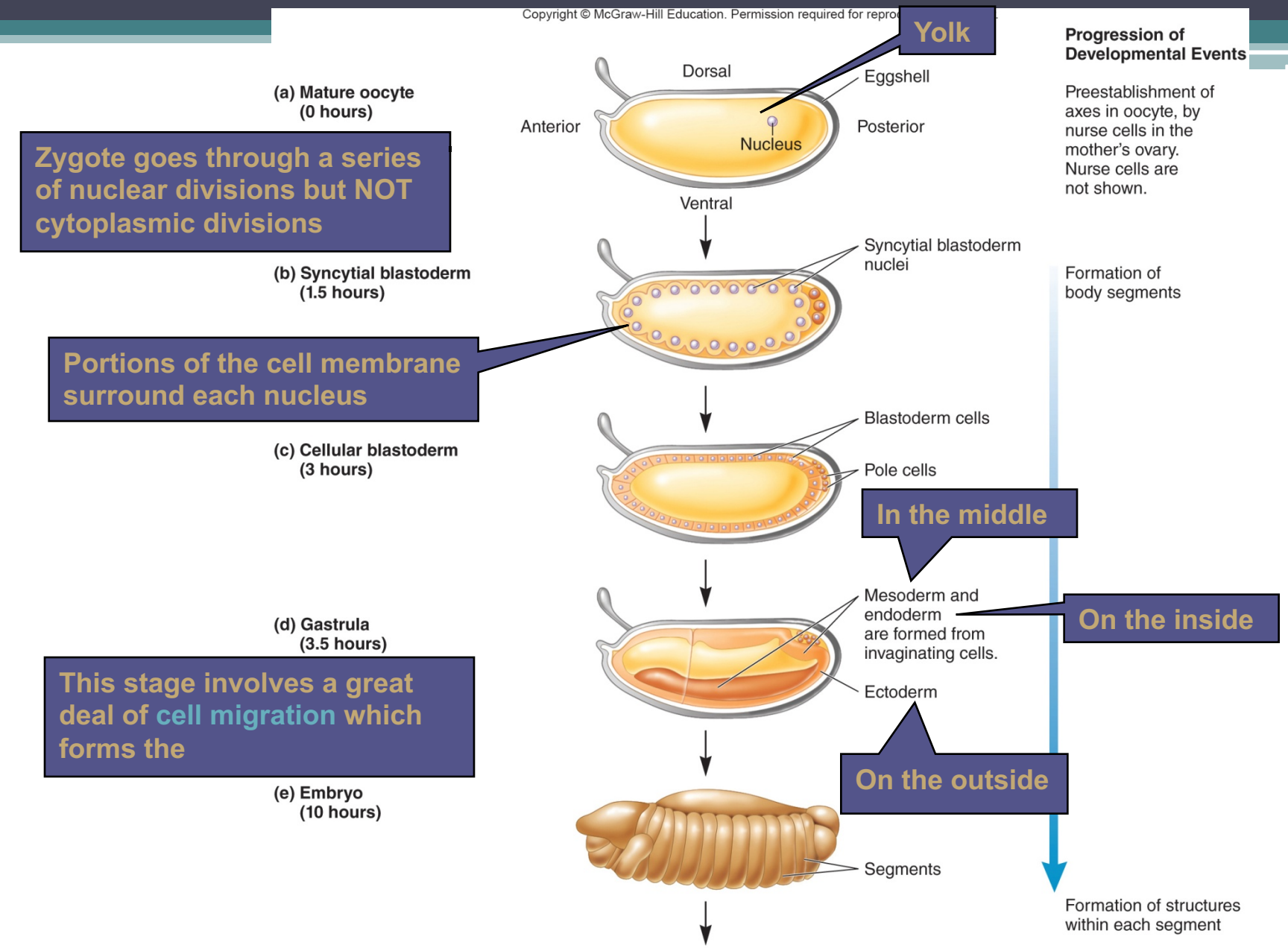
Drosophila melanogaster (The fruit fly)

- Why *use Drosophila melanogaster as a model organism?*
  - The organism is small and easily grown in the laboratory.
  - Generation time is only 2 weeks
  - Embryos develop outside the mother's body
  - Large scale mutational screen to look for genes involved in specific functions.
    - It has many mutant strains with altered developmental pathways
  - Genome has been sequenced (13,600 genes)
  - It is large enough to conduct transplantation experiments
    - Yet small enough to determine the various sites of gene expression



(e) Embryo
(10 hours)

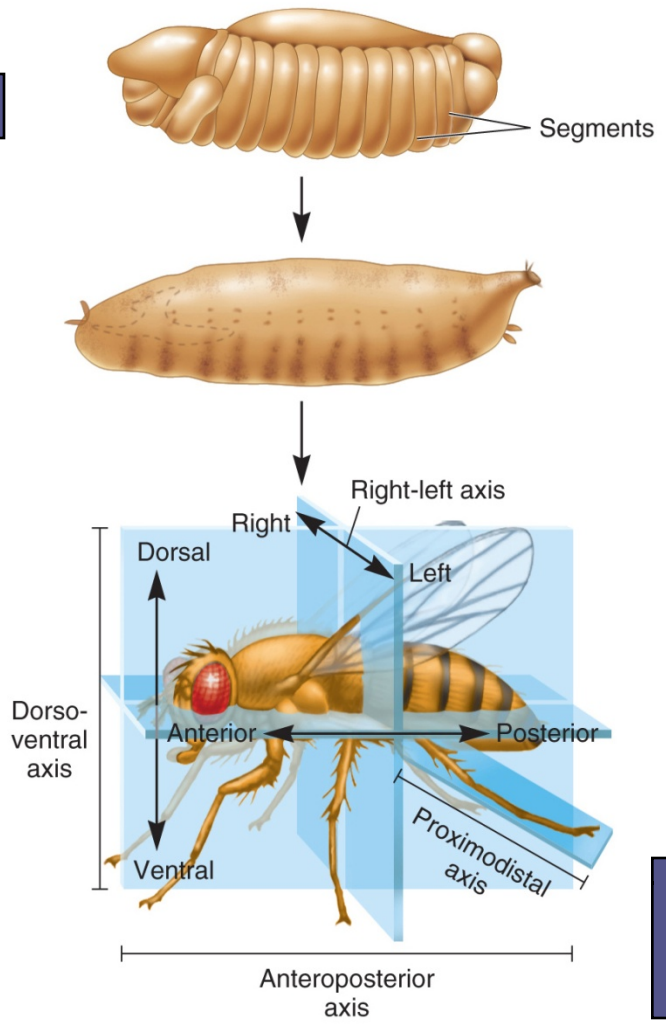
At the end of embryogenesis

(f) Newly hatched larva
(22 hours)

- In *Drosophila*, there are three larval stages separated by molts
  - During molting, the larva sheds its cuticle

(g) Adult
(10–14 days)

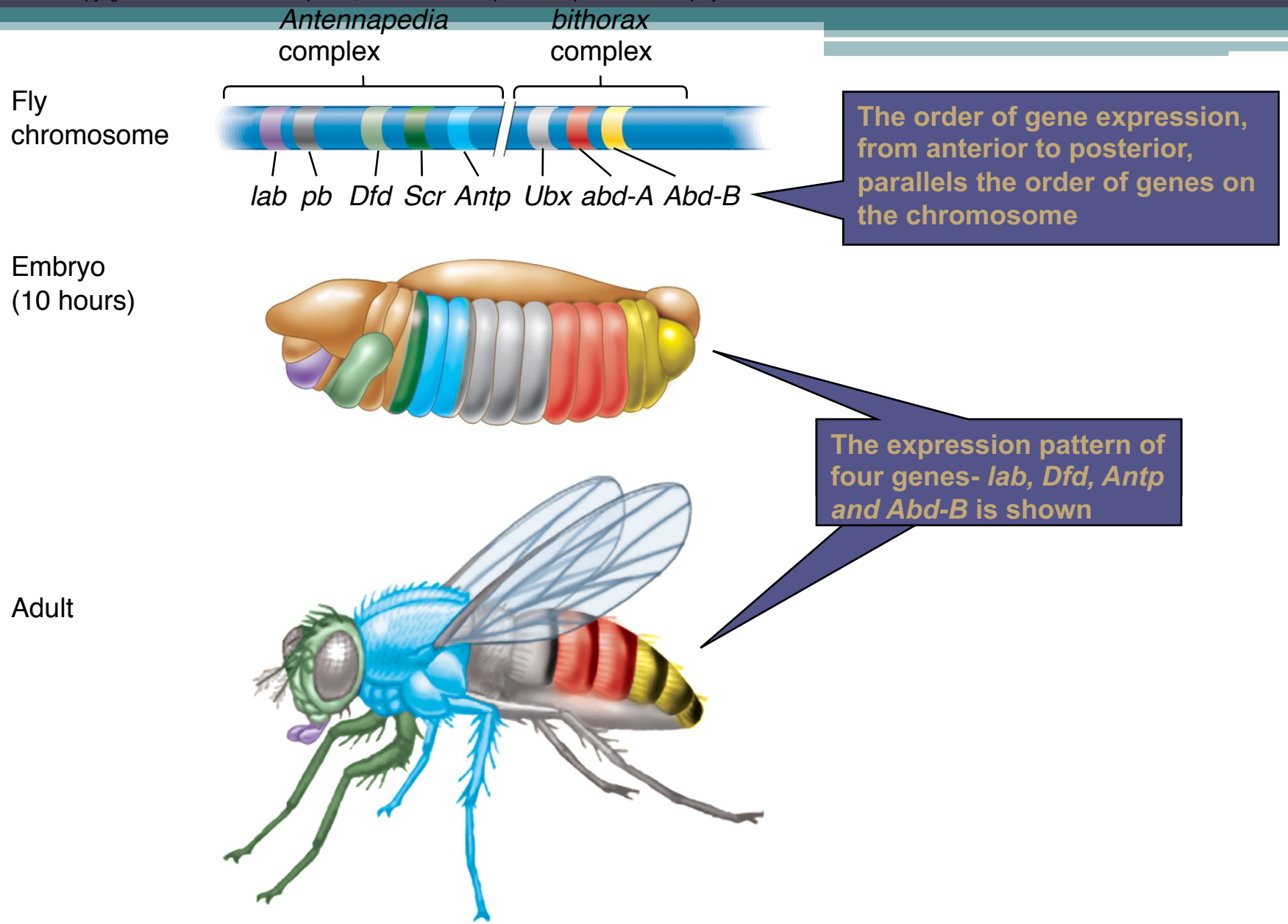
- After the third larval stage, *Drosophila* proceeds through a process termed metamorphosis
  - Groups of cells called imaginal disks were produced earlier in development
  - These imaginal disks grow and differentiate into the structures found in the adult fly
- The fly then emerges from its pupal case



Formation of structures within each segment

In metazoa, the final result of development is an adult body organized along three axes

Even before hatching, the embryo develops the basic body plan that will be found in the adult organism



Expression pattern of homeotic genes in *Drosophila*

Courtesy of E. B. Lewis., California Institute of Technology.

The bithorax mutation in *Drosophila*

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(a) Normal fly

F. R. Turner, Indiana University/Visuals Unlimited

(b) *Antennapedia* mutant

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Article

Identification and In Vivo Characterisation of Cardioactive Peptides in *Drosophila melanogaster*

Ronja Schiemann, Kay Lammers, Maren Janz, Jana Lohmann, Achim Paululat and Heiko Meyer *

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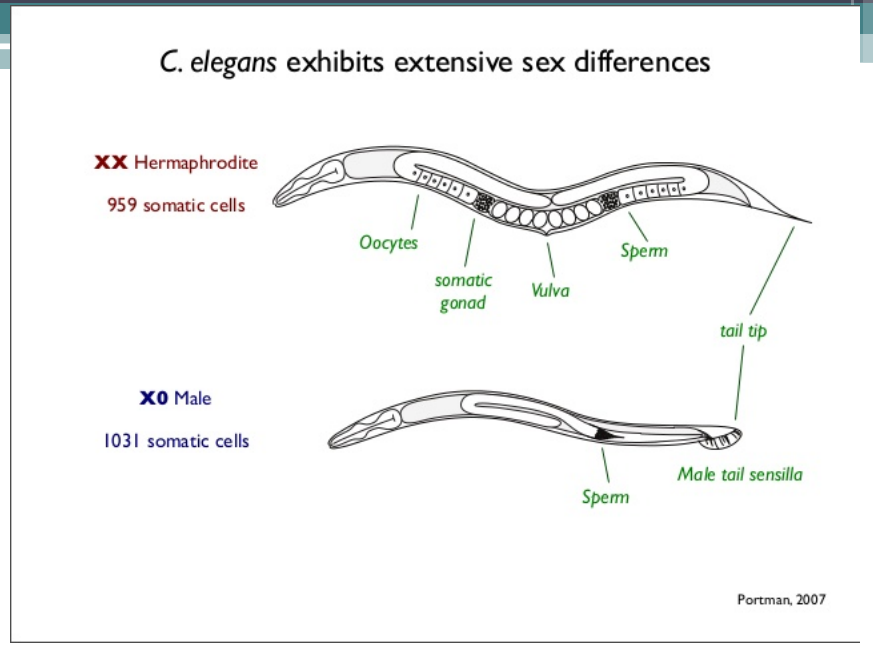
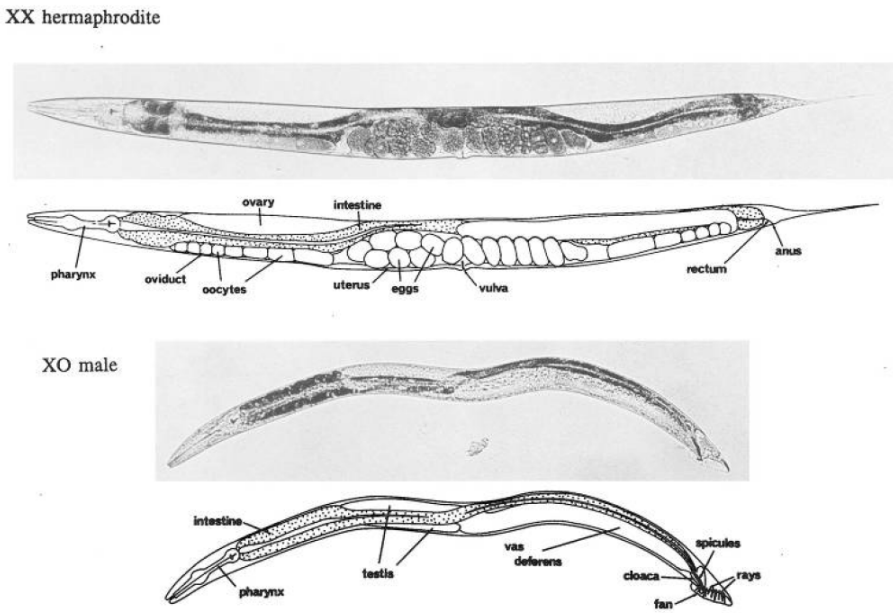
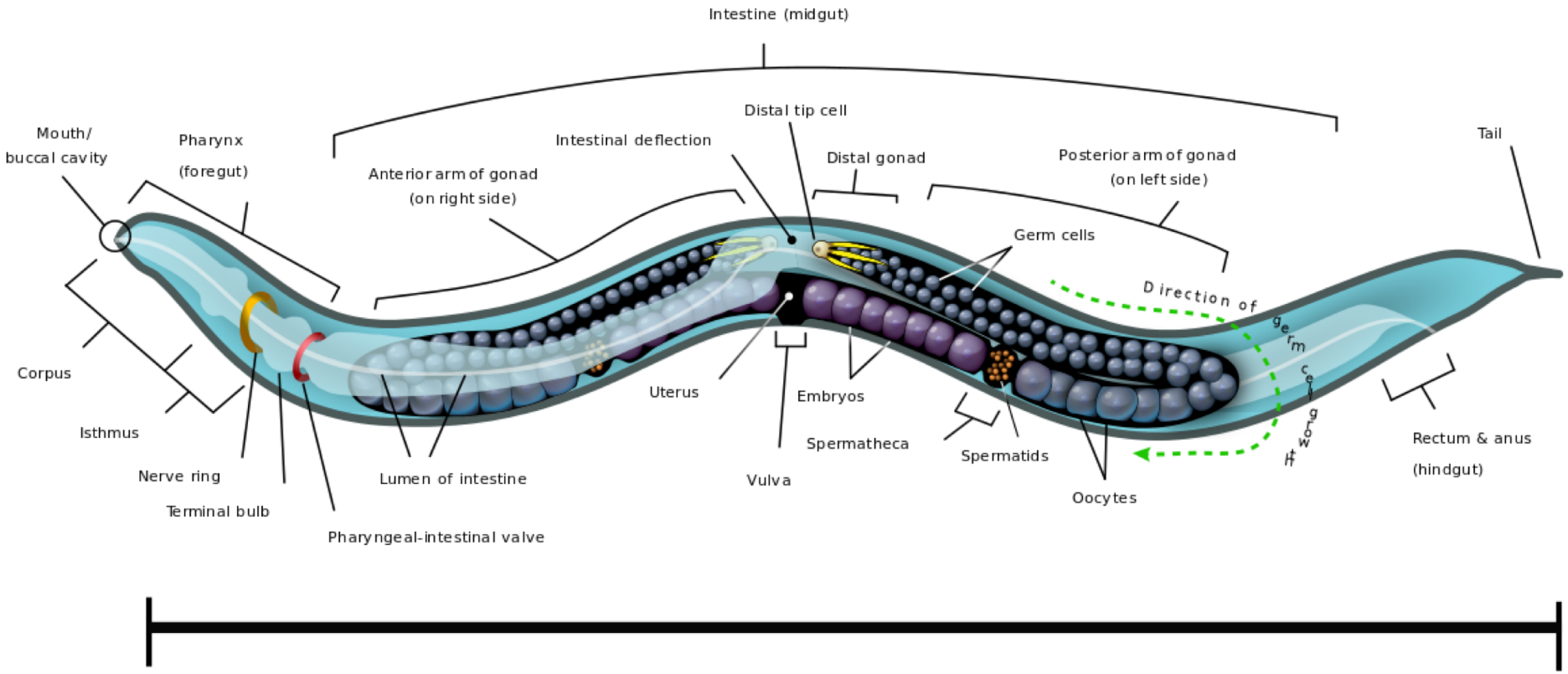
Abstract: Neuropeptides and peptide hormones serve as critical regulators of numerous biological processes, including development, growth, reproduction, physiology, and behaviour. In mammals, peptidergic regulatory systems are complex and often involve multiple peptides that act at different levels and relay to different receptors. To improve the mechanistic understanding of such complex systems, invertebrate models in which evolutionarily conserved peptides and receptors regulate similar biological processes but in a less complex manner have emerged as highly valuable. *Drosophila melanogaster* represents a favoured model for the characterisation of novel peptidergic signalling events and for evaluating the relevance of those events *in vivo*. In the present study, we analysed a set of neuropeptides and peptide hormones for their ability to modulate cardiac function in semi-intact larval *Drosophila melanogaster*. We identified numerous peptides that significantly affected

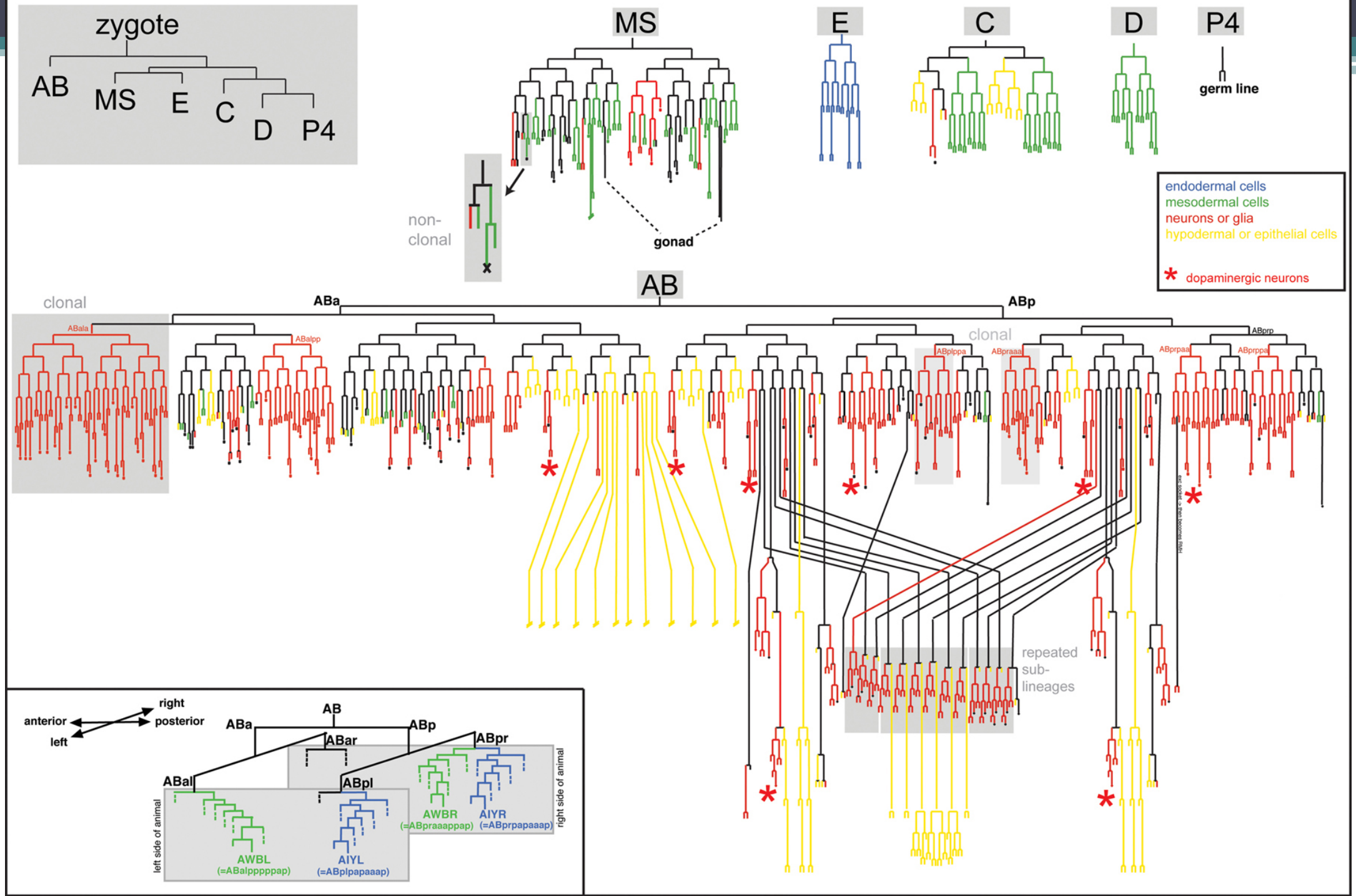
Caenorhabditis elegans (the worm)

- Normally found in the soil but we can grow it on the petri dish
- Simple transparent body. 1mm long.
- Takes 3.5 days from zygote to adult.
- Able to self fertilize. (Think about the heterozygote hermaphrodite!!!)
- The exact cell number of adults is known.
- Complete cell lineage has been mapped.






Intestine (midgut)
Mouth/
buccal cavity
Pharynx
(foregut)
Intestinal deflection
Distal tip cell
Distal gonad
Anterior arm of gonad
(on right side)
Posterior arm of gonad
(on left side)
Tail
Germ cells
Direction of germ cell growth
Corpus
Isthmus
Nerve ring
Terminal bulb
Pharyngeal-intestinal valve
Lumen of intestine
Uterus
Vulva
Embryos
Spermatheca
Spermatids
Oocytes
Rectum & anus
(hindgut)
~1 mm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AIYR
(=ABprpapaaap)
AWBL
(=ABalpppppap)
AIYL
(=ABplpapaaap)
left side of animal
right side of animal

Advantages of the worm

- **Short generation time:** between 3 days-1 week depending on temperature.
- **Stocks can be frozen:** the eggs survive the freezing process so stocks don't have to be continuously propagated.
- **Very cheap to maintain:** essentially all you need for C. elegans research is a microscope and an incubator, no expensive animal house costs.
- **Temperature sensitive:** the worms grow at different speeds depending on the temperature.
- **Present no biohazard:** not much paperwork and no IRB necessary. Agar plates do not require special disposal.
- **The first complex organism to have its genome sequenced**
- **The fate of all cells are known:** mostly all cells have been traced through development, making *C. elegans* a great developmental model.
- **Simple organisms with complex structures:** such as a nervous system, digestive system, and extensive germline.
- **Very easy to do forward genetic screens**
- **Plentiful morphological markers**
- **RNAi was discovered in C. elegans** and can be incorporated by feeding. The Arliger lab has created an extensive library of RNAi constructs in bacteria. These can be grown up and fed to the worms.
- **Embryos and adults are translucent**. Easy to GFP labelled structures and other phenotypes.
- **Hermaphroditic,** self mating allows for efficient generation of recessive mutants
- **Large brood size:** for easy screening and large N value. Single Hermaphrodite has about 300 progeny.
- **They are not cute and fuzzy**. One does not feel remorse for harming a worm as one might when working with more complex organisms. They do not make noise and they do not bite.

Disadvantages of working with the worm

- **No site directed mutagenesis**, due to only one crossover per chromosome. There are a couple ways around this. Forward genetics screens are very easy. Also transgenic constructs can be either injected or bombarded into worms. (New technology new horizons)
- **Researchers have to argue for funding**. It is sometimes difficult to argue for the applicability of research human drug and disease.
- **Plates can become contaminated** by fungus, other bacteria, or mites. Low levels of contamination can be countered by chunking of good regions. Massive contamination can be eliminated by successive rounds of bleaching.

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CRISPR/Cas9 Methodology for the Generation of Knockout Deletions in *Caenorhabditis elegans*.

Au V[1], Li-Leger E[1], Raymant G[1], Flibotte S[1], Chen G[1], Martin K[1], Fernando L[1], Doell C[1], Rosell FI[2], Wang S[1], Edgley ML[1], Rougvie AE[3], Hutter H[4], Moerman DG[5].

Author information

Abstract

The *Caenorhabditis elegans* Gene Knockout Consortium is tasked with obtaining null mutations in each of the more than 20,000 open reading frames (ORFs) of this organism. To date, approximately 15,000 ORFs have associated putative null alleles. As there has been substantial success in using CRISPR/Cas9 in *C. elegans*, this appears to be the most promising technique to complete the task. To enhance the efficiency of using CRISPR/Cas9 to generate gene deletions in *C. elegans* we provide a web-based interface to access our database of guide RNAs (http://genome.sfu.ca/crispr). When coupled with previously developed selection vectors, optimization for homology arm length, and the use of purified Cas9 protein, we demonstrate a robust and effective protocol for generating deletions for this large-scale project. Debate and speculation in the larger scientific community concerning off-target effects due to non-specific Cas9 cutting has prompted us to investigate through whole genome sequencing the occurrence of single nucleotide variants and indels accompanying targeted deletions. We did not detect any off-site variants above the natural spontaneous mutation rate and therefore conclude that this modified protocol does not generate off-target events to any significant degree in *C. elegans* We did, however, observe a number of non-specific alterations at the target site itself following the Cas9-induced double-strand break and offer a protocol for best practice quality control for such events.

KEYWORDS: C. elegans; CRISPR/Cas9; homology dependent repair; mutagenesis

PMID: 30420468 PMCID: PMC6325907 DOI: 10.1534/g3.118.200778

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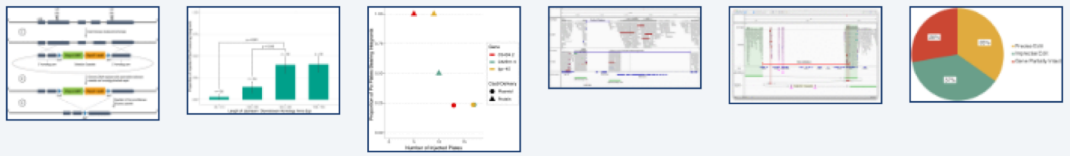

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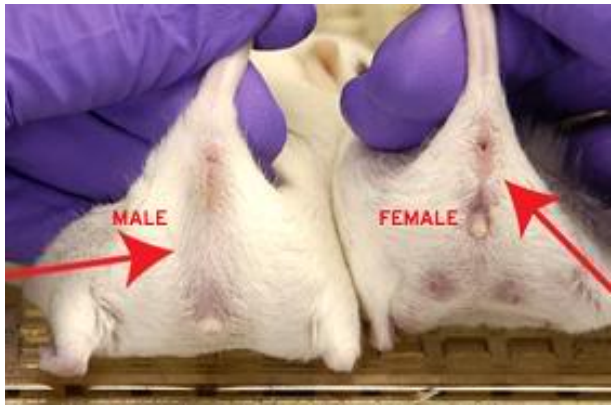
Mus musculus (The mouse)

- Mammalian model of development
- A lot is known regarding its genes and biology
- Very sophisticated techniques exist to manipulate the mouse
  - Transgenic mice
  - Knock-out mice



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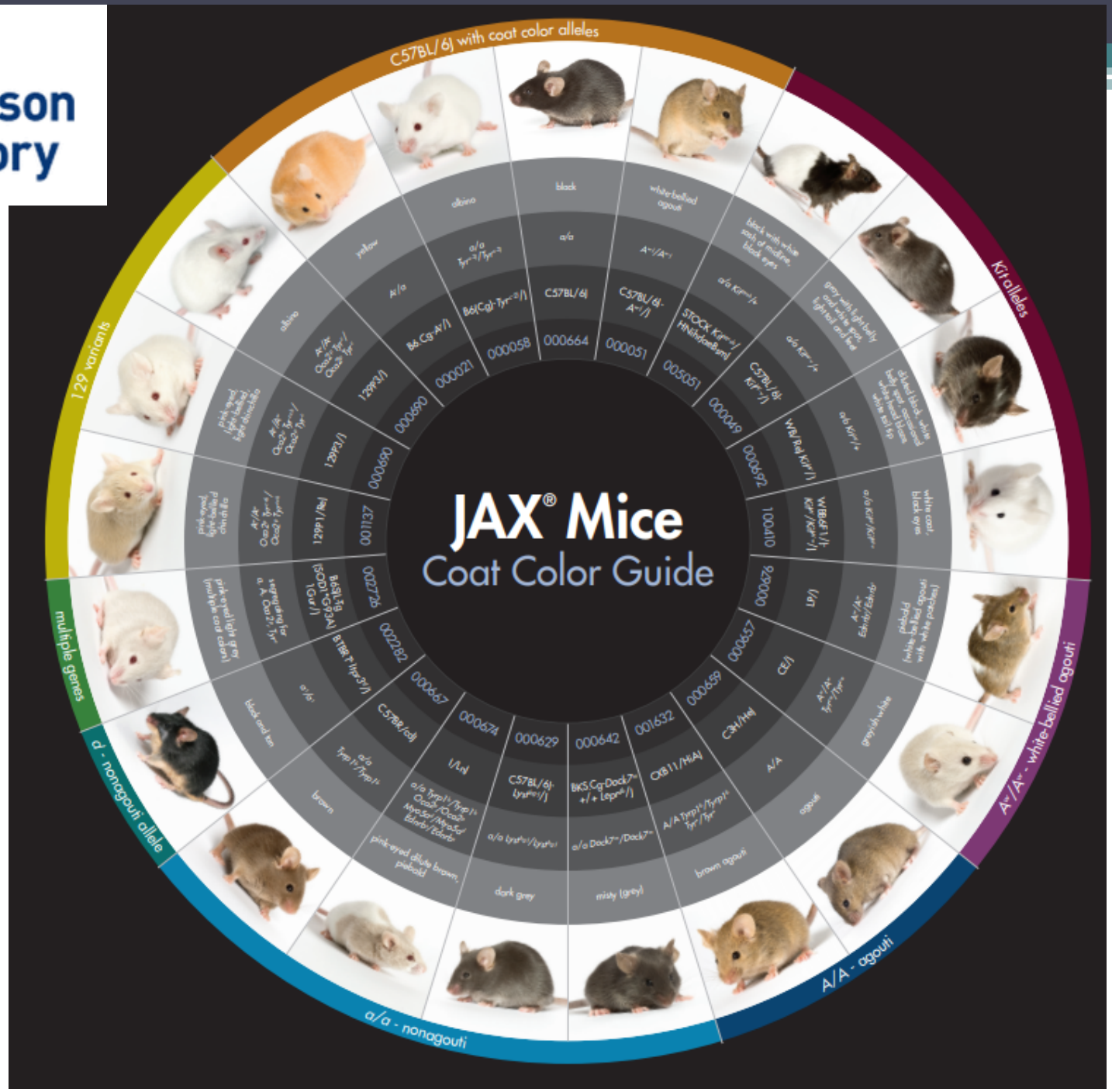
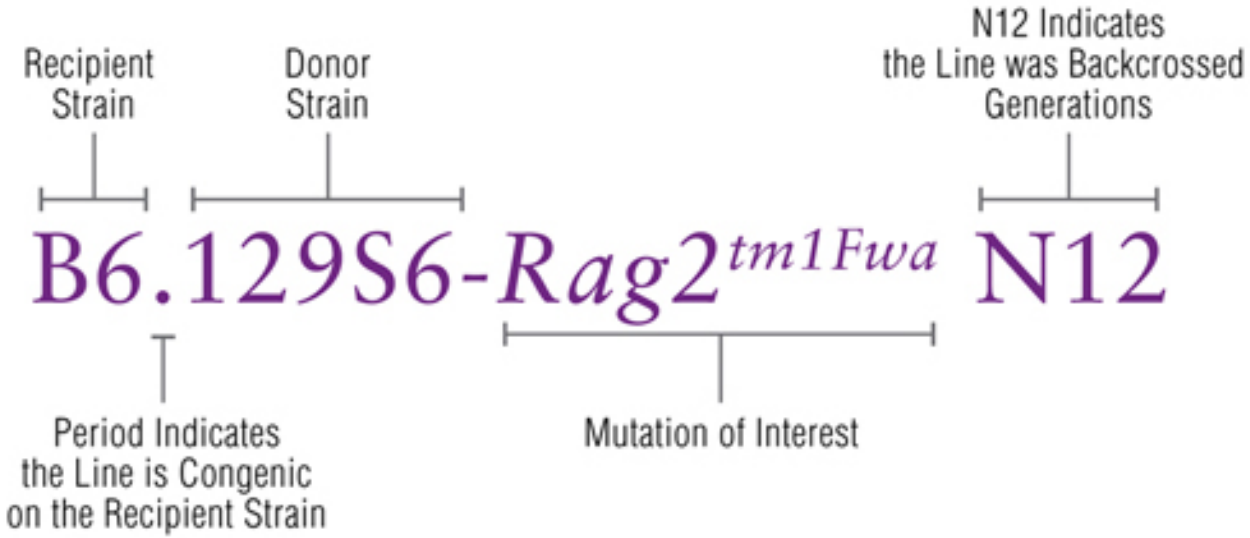


Key to Coat Color Symbols

A ..... agouti	*Dock7*^{m} ..... misty	*Myo5a*^{d} ..... dilute	*Tyrp1*^{b} ..... brown
A^{w} ..... white-bellied agouti	*Ednrb*^{s} ..... piebald	*Oca2*^{p} ..... pink-eyed dilution	+ ..... wild-type
A^{w-J} ..... white-bellied agouti Jackson	*Kit*^{W} ..... dominant spotting	*Tyr*^{c} ..... albino	
A^{y} ..... yellow	*Kit*$^{W-sh}$ ..... sash	*Tyr*$^{c-2J}$ ..... albino 2 Jackson	
a ..... nonagouti	*Kit*$^{W-v}$ ..... viable dominant spotting	*Tyr*$^{c-ch}$ ..... chinchilla	
a^{t} ..... black and tan	*Lyst*$^{bg-J}$ ..... beige Jackson	*Tyr*$^{c-e}$ ..... extreme dilution	



Parents

C57BL/6J=B6

129S1/SvImJ=129S

F1 Hybrid

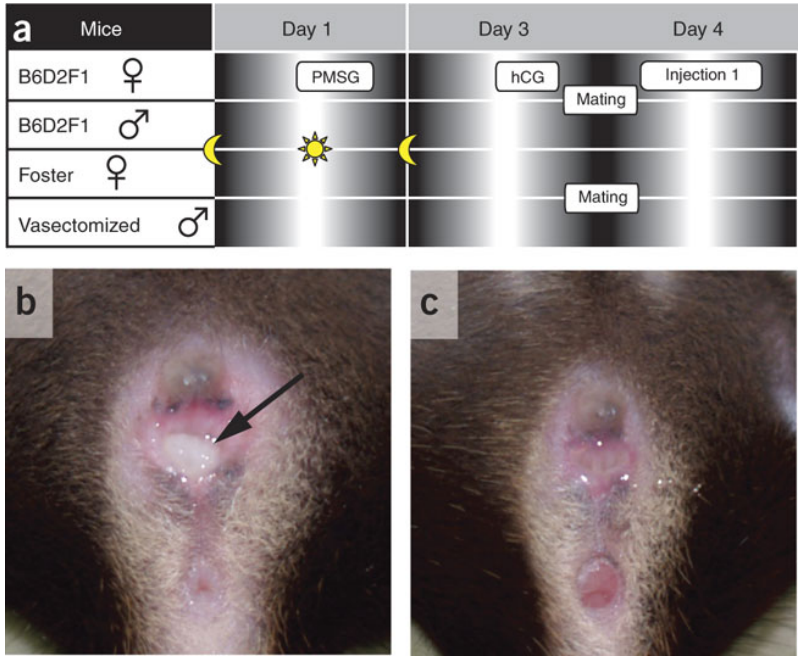
B6129SF1/J

♀ ♂

C57BL/6J-*Apc*^{Min}/J

Background Strain | *Affected Gene* | *Mutant Allele* | Holding Site Lab Code

- They vary in color from white to grey to light brown to black.
- Females have a significantly smaller distance between their anus and genital opening.
- Estrous cycle about four to six days long estrus itself lasting less than a day. If several females are held together under crowded conditions, they will often not have an estrus at all.
- If they are then exposed to male urine, they will come into estrus after 72 hours.
- Following copulation, female mice will normally develop a copulation plug which prevents further copulation. This plug stays in place for some 24 hours. The gestation period is about 19–21 days, and they give birth to a litter of three to 14 young (average six to eight).
- One female can have 5 to 10 litters per year, so the mice population can increase very quickly.
- The newborn are blind and without fur. Fur starts to grow about three days after birth, and the eyes open one to two weeks after birth. Males reach sexual maturity at about eight weeks and females at about six weeks, but both can breed as early as five weeks.



Advantages of using mice

- **Advantages**
  - Short generation time
  - Small
  - many knockout versions available
  - Many molecular tools are available.
  - It would be impossible to develop a fruit fly or bacterial model of heart disease, stroke, obesity, or even learning and memory that would be directly applicable to humans.
- Genetic and physiological similarities to humans allows for the generation of disease and treatment models.
- Entire genome sequenced- allows for the generation of specific mutant lineages and reverse genetics studies.

Disadvantages of working with mice

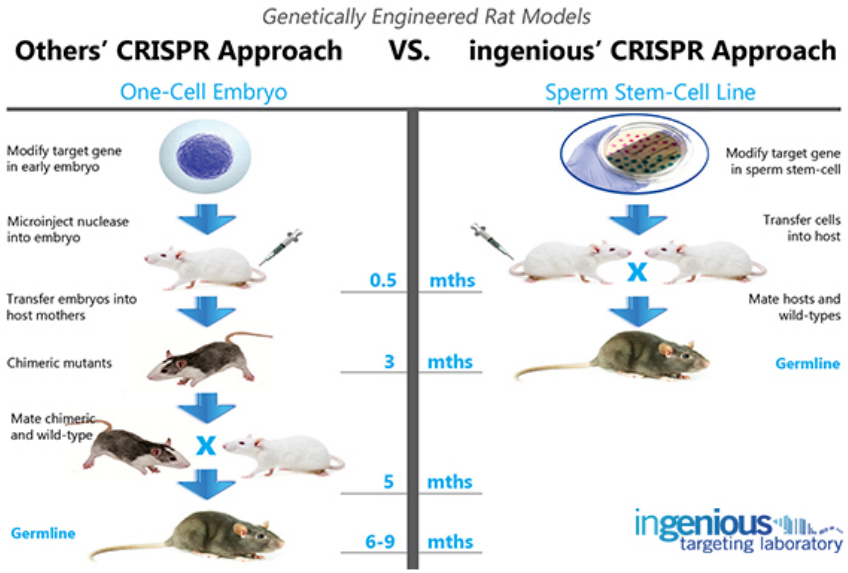
- No animal model is ever perfect and there are still many irreconcilable differences between mice and humans.
- Embryo develops in the uterus away from human eyes.
- Generation interval about 3 months.
- Draws negative attention from animal rights activists (i.e. PETA) and can be considered immoral in some social circles.
- Can be expensive to house and maintain

The advantages of using rat

- Larger animal makes it easier to handle and sample
- More is known about pathways and physiology after many years of research
  - accurately reflects human physiology than other species
  - mimicking human disease more accurately than mice
- Behavioral and cognitive research
- Now, we are better at manipulating rat genome

Press Release: Breakthrough CRISPR/Cas9 Rat Model Technology

October 17, 2017 | ingenious | Newsletters



RONKONKOMA, N.Y., October 17, 2017 (Newswire.com) – ingenious targeting laboratory is excited to announce the addition of custom gene-edited rat models via an exciting breakthrough technology. Our unique CRISPR/Cas9 rat technology utilizing spermatogonial

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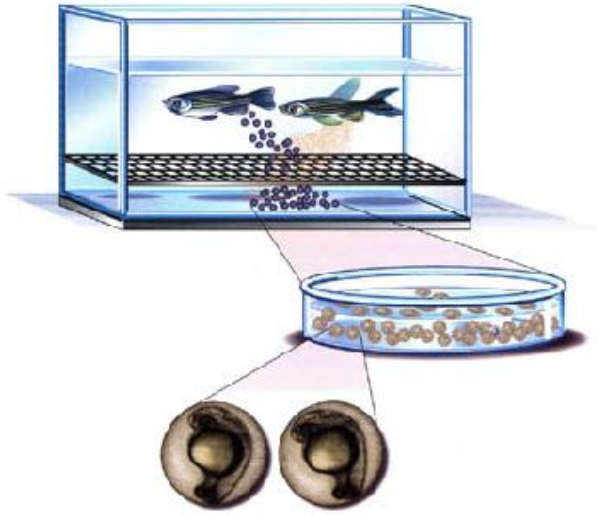
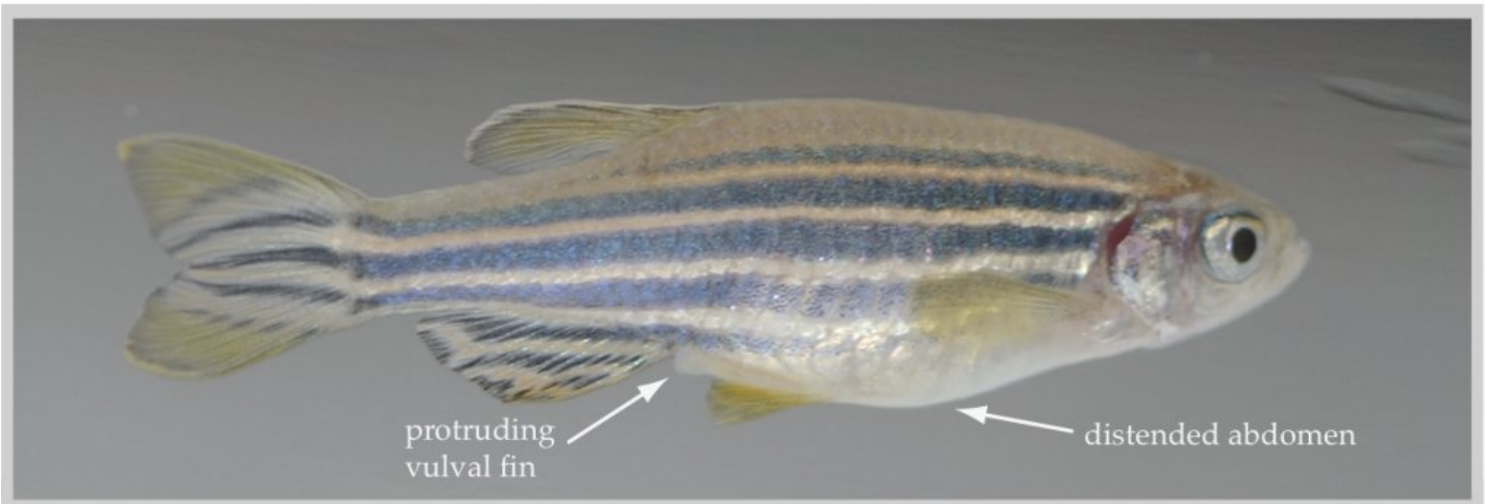
PMID: 31059977

Danio rerio (the zebrafish)

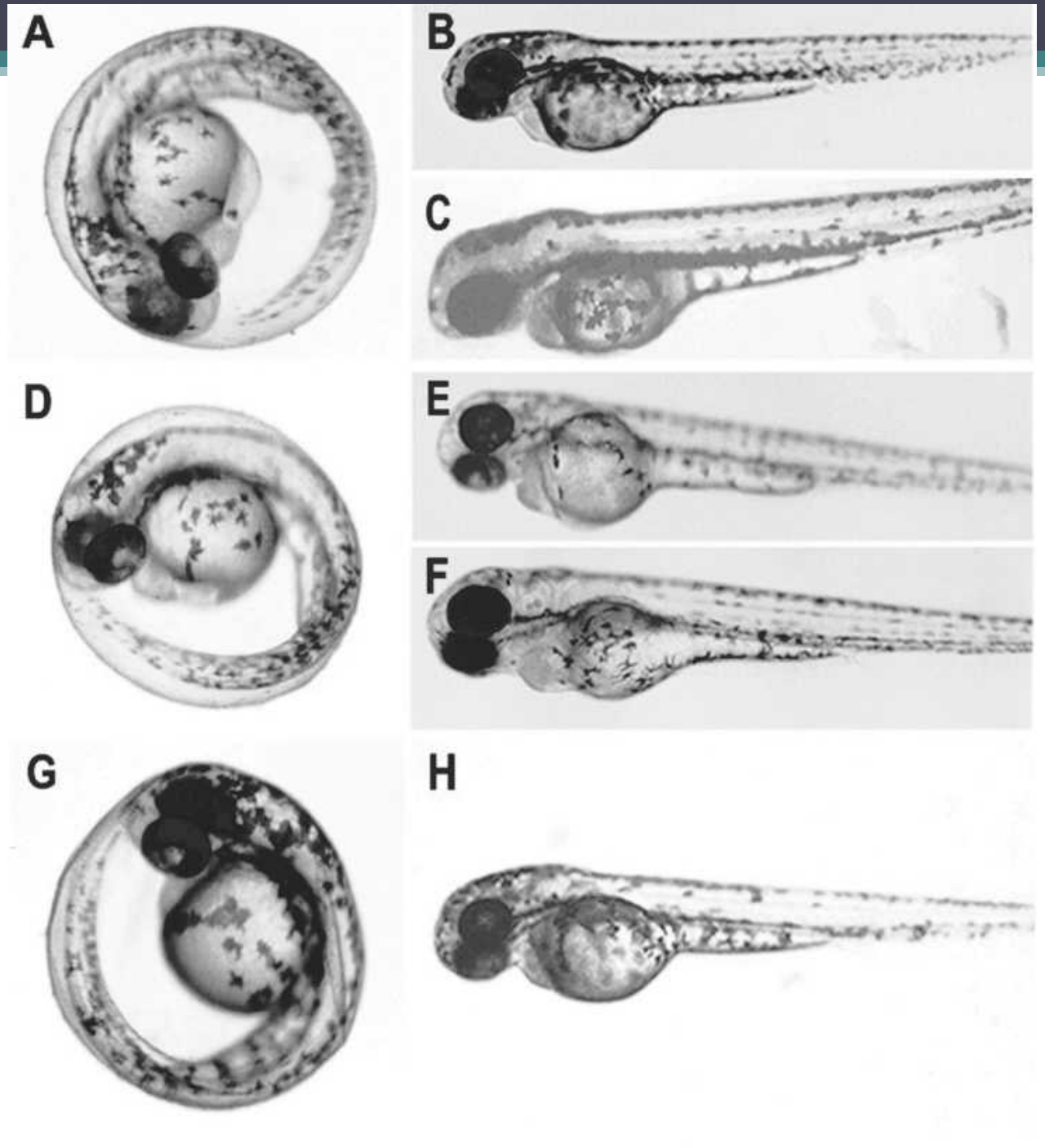


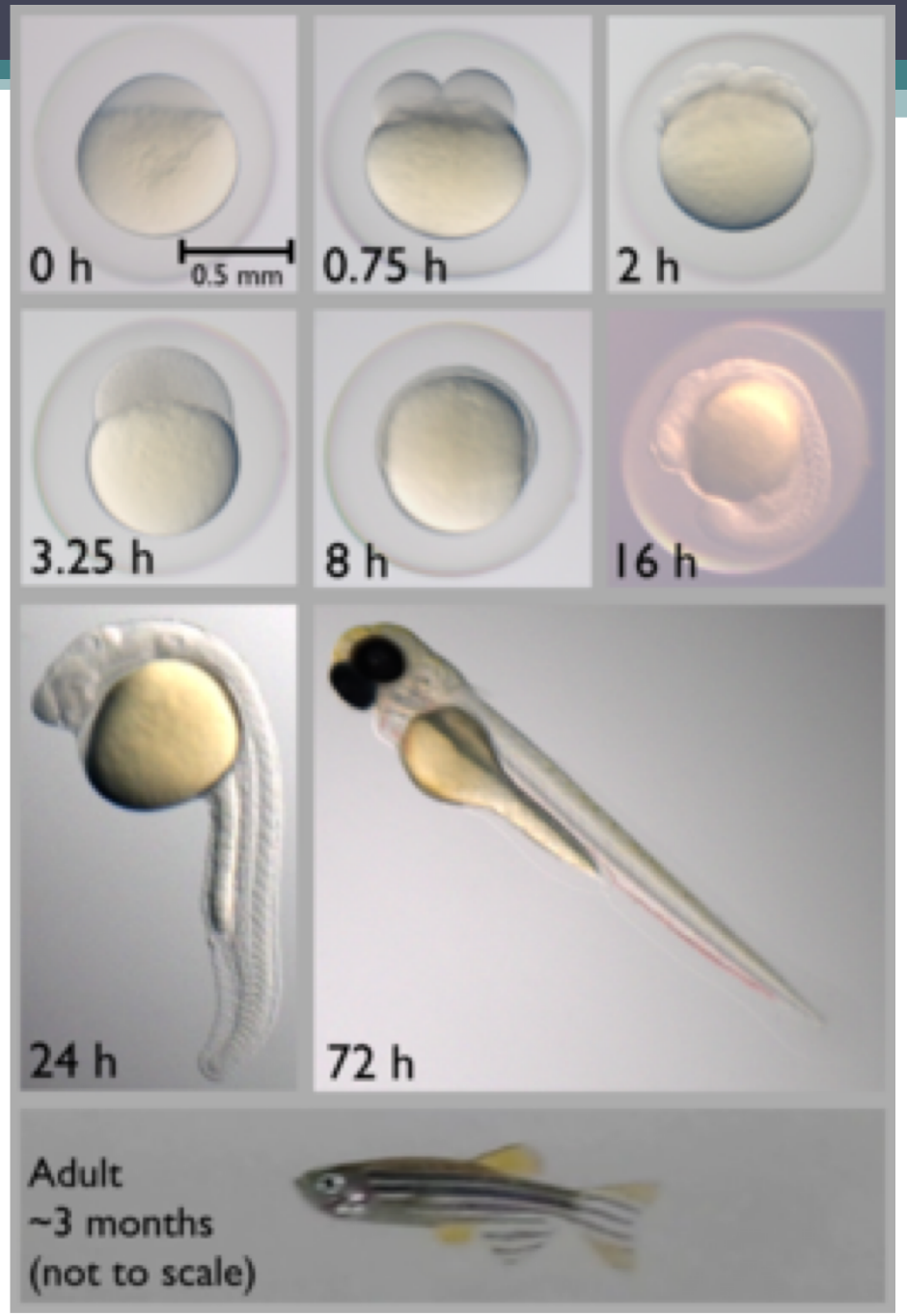
- Another vertebrate model
- 2-4 cm small fish, easy to breed.
- Transparent embryos develop outside the mother.
- The generation time is 2-4 months. But early development is very quick
  - Within 24 hours after fertilization, most tissues and early versions of organs have formed
  - After 2 days the fish hatches out of the egg.
- A lot of molecular techniques have been developed to study genes.

♂ MALE
- faster and more slender in shape
- darker and more red in colour



♀ FEMALE
- more grey/silver in colour
- slower and fatter


A
B
C
D
E
F
G
H


0 h
0.5 mm
0.75 h
2 h
3.25 h
8 h
16 h
24 h
72 h
Adult
~3 months
(not to scale)

RNA. 2019 May 1. pii: rna.069484.118. doi: 10.1261/rna.069484.118. [Epub ahead of print]

Strategies for Genetic Inactivation of Long Noncoding RNAs in Zebrafish.

Lavalou P[1], Eckert H[1], Damy L[1], Constanty F[1], Majello S[1], Bitetti A[1], Graindorge A[1], Shkumatava A[2].

Author information

Abstract

The number of annotated long noncoding RNAs (lncRNAs) continues to grow, however their functional characterization in model organisms has been hampered by the lack of reliable genetic inactivation strategies. While partial or full deletions of lncRNA loci disrupt lncRNA expression, they do not permit the formal association of a phenotype with the encoded transcript. Here, we examined several alternative strategies for generating lncRNA null alleles in zebrafish and found that they often resulted in unpredicted changes to lncRNA expression. Removal of the transcriptional start sites (TSSs) of lncRNA genes resulted in hypomorphic mutants due to the usage of either constitutive or tissue-specific alternative TSSs. Deletions of short, deeply conserved lncRNA regions can also lead to overexpression of truncated transcripts. By contrast, a knock-in of a polyadenylation signal enabled complete inactivation of malat1, the most abundant vertebrate lncRNA. In summary, lncRNA null alleles require extensive in vivo validation and we propose insertion of transcription termination sequences as the most reliable approach to generate lncRNA-deficient zebrafish.

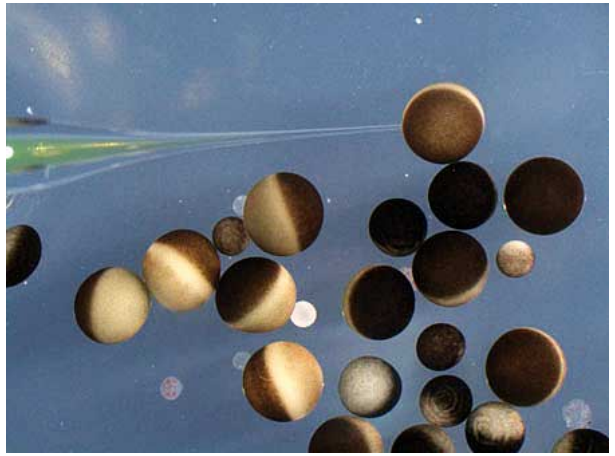
Published by Cold Spring Harbor Laboratory Press for the RNA Society.

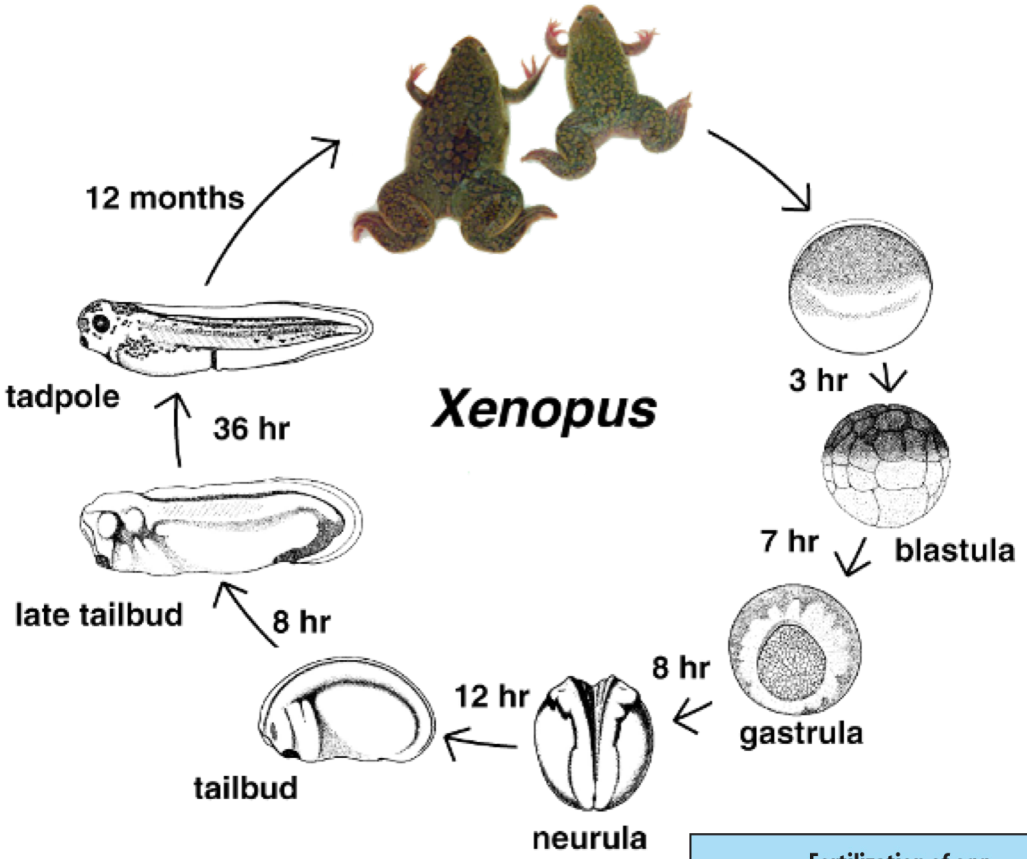
KEYWORDS: CRISPR-Cas9; hypomorph; long noncoding RNAs; polyA signal; zebrafish

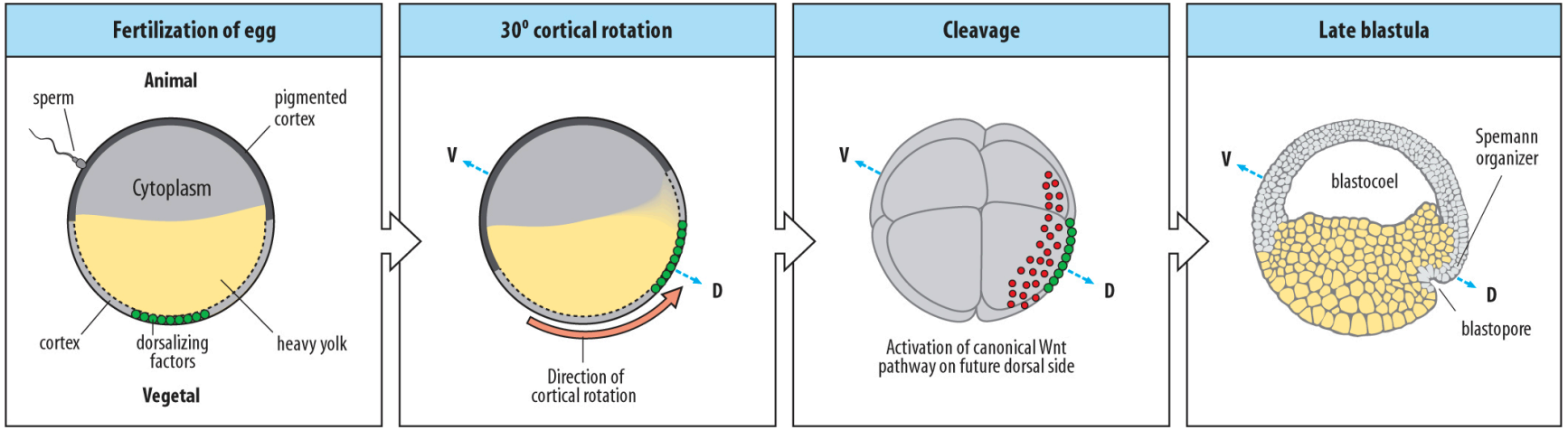
PMID: 31043511 DOI: 10.1261/rna.069484.118

Xenopus laevis (the frog)

- Ease of access and manipulation of embryo
- Robust embryo
- Rapid development; free swimming tadpole in 4 days.
- Very complex genome. Therefore hard to do genetics with.
- Cannot be bred for multiple generations




12 months
tadpole
36 hr
late tailbud
8 hr
tailbud
12 hr
neurula
8 hr
gastrula
7 hr
blastula
3 hr
Xenopus

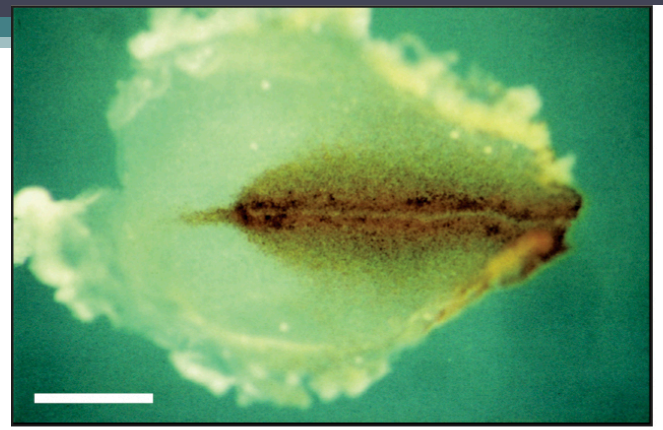

Fertilization of egg
Animal
sperm
pigmented cortex
Cytoplasm
cortex
dorsalizing factors
heavy yolk
Vegetal
30° cortical rotation
V
D
Direction of cortical rotation
Cleavage
V
D
Activation of canonical Wnt pathway on future dorsal side
Late blastula
V
blastocoel
Spemann organizer
D
blastopore

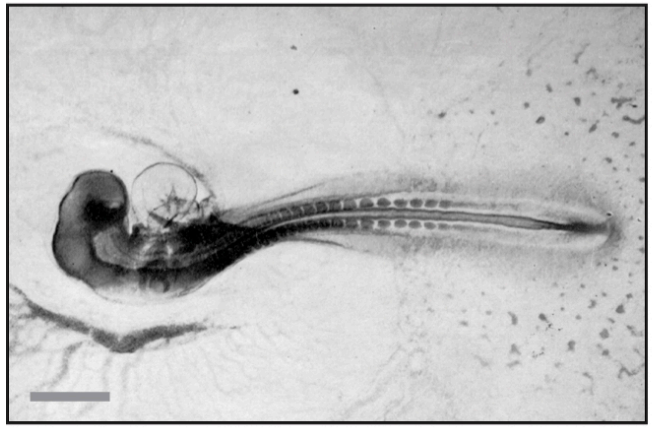
2009 lack of resources for xenopus

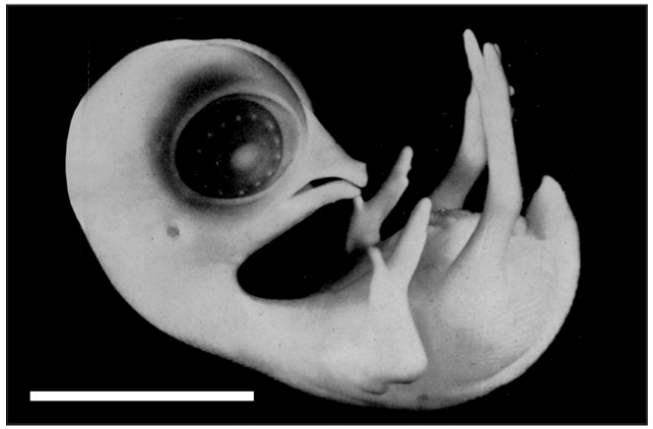
- Complete genome
- Lack of stock and training centers
- Comprehensive database

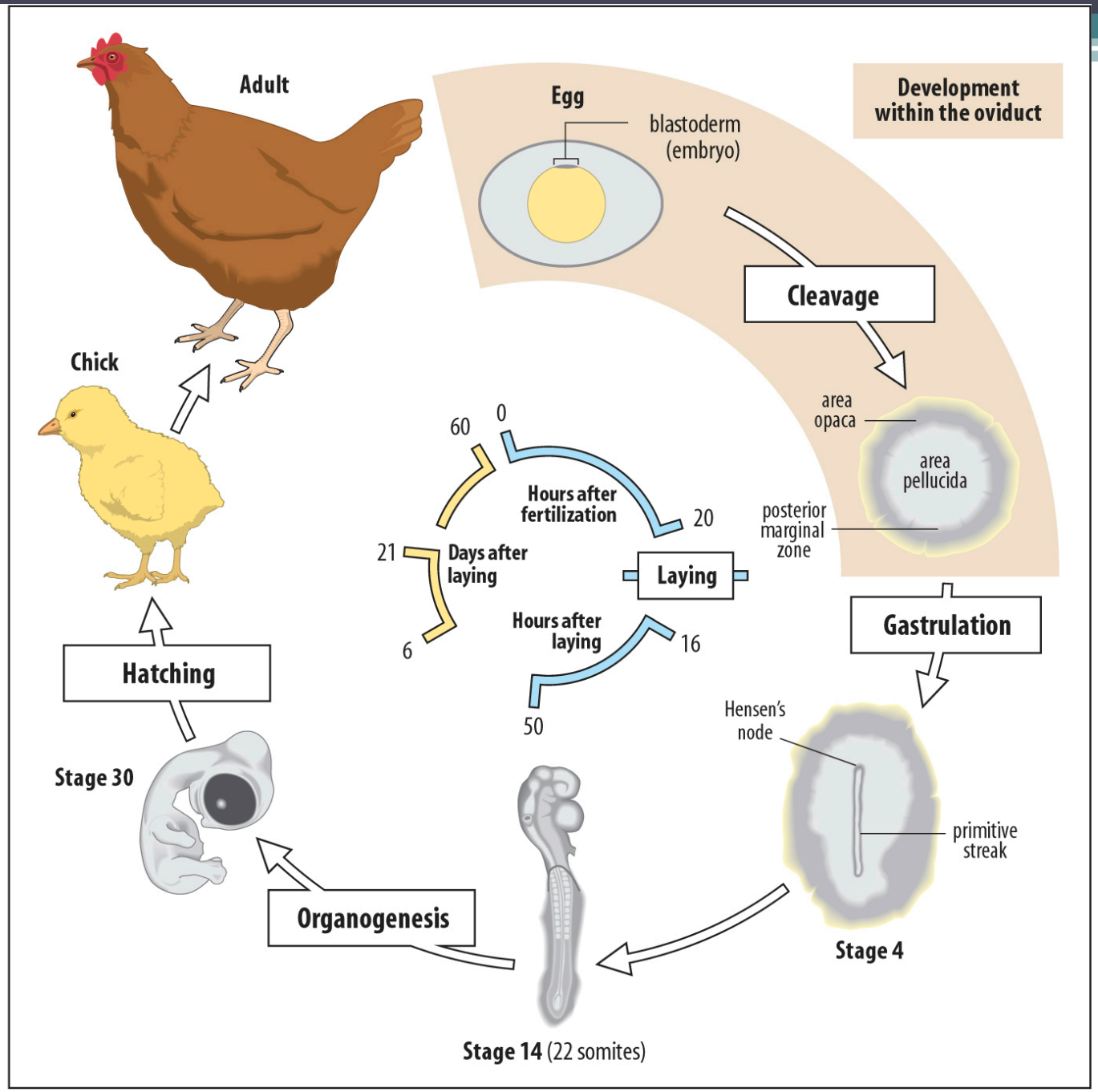
Gallus gallus (The chicken)

- Large easily obtainable eggs
- Development can be observed by cutting a whole in the shell
- The embryos can be manipulated.
- Development similar to mammals
- Not good for classical genetics



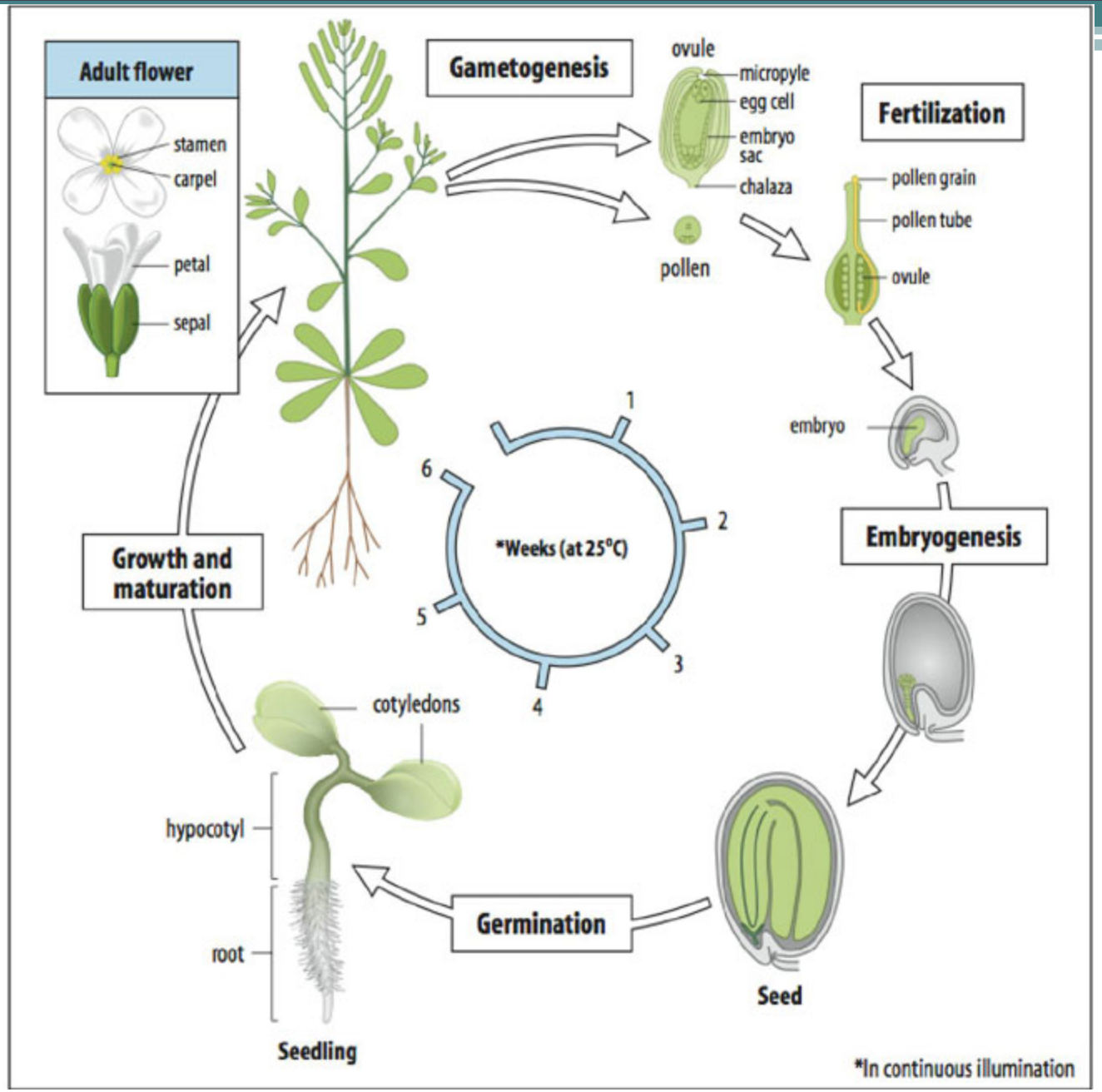





Adult
Egg
blastoderm (embryo)
Development within the oviduct
Cleavage
area opaca
area pellucida
posterior marginal zone
Gastrulation
Hensen's node
primitive streak
Stage 4
Laying
Hours after fertilization
60
0
20
Days after laying
21
6
Hours after laying
16
50
Chick
Hatching
Stage 30
Organogenesis
Stage 14 (22 somites)

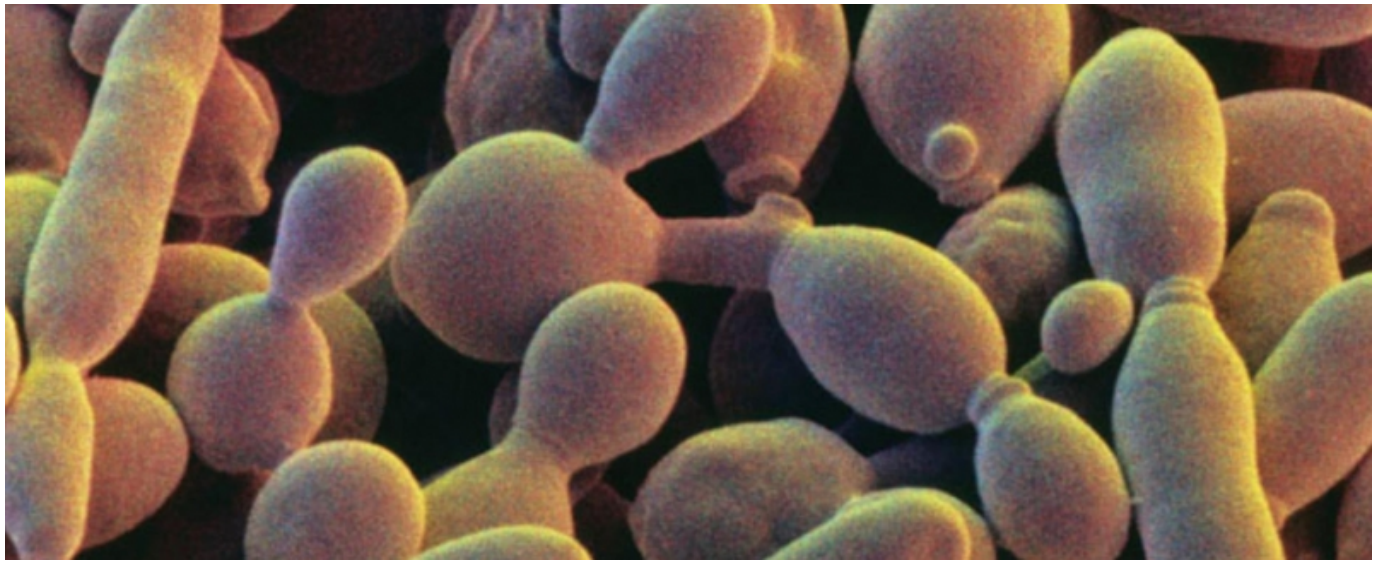
Arabidopsis thaliana

- Model for plant development
- Produce progeny after 8-10 weeks
- Hermaphrodite
- Induce cultured cells to take up DNA
- Small genome


Adult flower
stamen
carpel
petal
sepal
Gametogenesis
ovule
micropyle
egg cell
embryo sac
chalaza
pollen
Fertilization
pollen grain
pollen tube
ovule
embryo
Embryogenesis
Seed
Germination
Seedling
cotyledons
hypocotyl
root
Growth and maturation
1
2
3
4
5
6
*Weeks (at 25°C)
*In continuous illumination

Saccharomyces cerevisiae (The budding yeast)

- The simplest eukaryotic organism
- Grows as haploid and diploid (have sexual and asexual life cycles)
- 50% of human genes have a yeast counterpart
- Fast growth
- Easy to culture



Why do people choose a specific model organisms?

- History of success
- Sequenced genome
- Growing tools and techniques
- Great support community
- Target of interest
- Representational scope
- Already in use or familiarity
- Sometimes the advantages emerge in retrospect
- COST!!!

Thank you