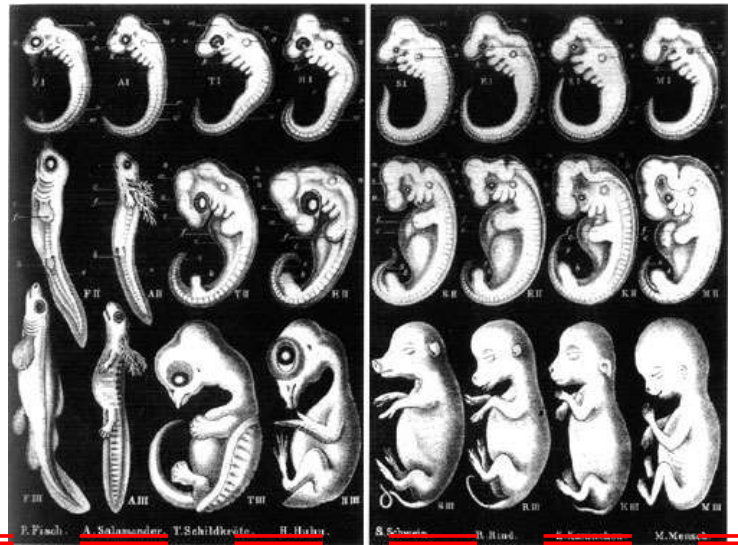
Methods in developmental biology

We generally do not study development in humans.
Why?

- Observation is difficult inside the uterus.
- Morally and ethically we would not want to perform experiments on human embryos.
- We wouldn't want to (nor could we) breed humans to look at effects of gene mutations on embryos.

Researchers study development in model organisms to identify general principles

Developmental processes are so fundamental that there are striking similarities in the development of very varied organisms.



Dr. Nandor Nagy

Developmental model organisms

Often used model organisms in developmental biology include the following:

Vertebrates

- Zebrafish *Danio rario*
- Medakafish *Oryzias latipes*
- Fugu (pufferfish) *Takifugu rubripes*
- Frog *Xenopus laevis*, *Xenopus tropicalis*
- Chicken *Gallus gallus*
- Mouse *Mus musculus* (Mammalian embryogenesis)

Invertebrates

- Lancelet *Branchiostoma lanceolatum*
- Ascidian *Ciona intestinalis*
- Sea urchin *Strongylocentrotus purpuratus*
- Roundworm *Caenorhabditis elegans*
- Fruit fly *Drosophila melanogaster* (Drosophila embryogenesis)

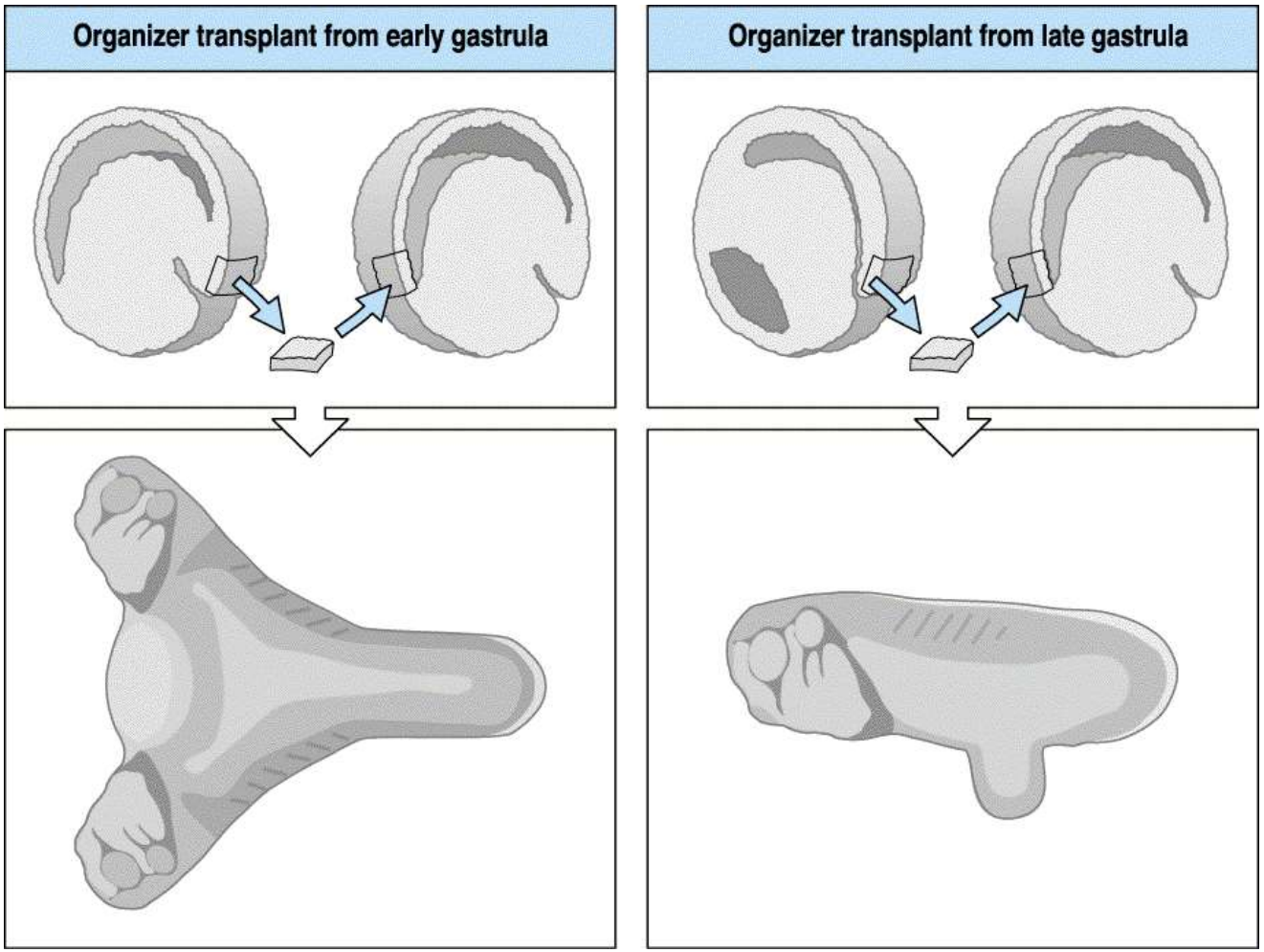
Plants (Plant embryogenesis)

- *Arabidopsis thaliana*
- Maize
- Snapdragon *Antirrhinum majus*

Other

- Slime mold *Dictyostelium discoideum*

Induction



The Nobel Prize in Physiology or Medicine 1935 was awarded to Hans Spemann *"for his discovery of the organizer effect in embryonic development"*.

Model Organisms

Throughout history, and today:
Model organisms

Mouse, chick, *Xenopus*, zebrafish, *drosophila*, *c. elegans*, *arabidopsis*

FRUIT FLY (*Drosophila melanogaster*)

Advantages: *In ovo* (rapid) development, genetic manipulation, history of use, inexpensive
Disadvantages: Invertebrate

Wild type

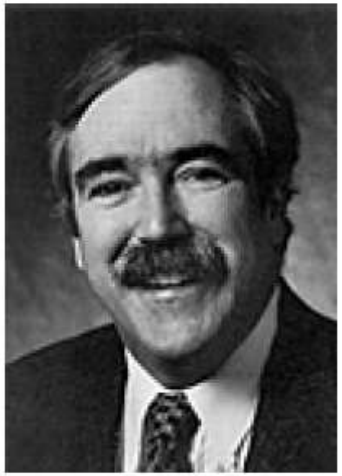
Ubx mutation

1995 Nobel Prize in Physiology and Medicine

"for their discoveries concerning the genetic control of early embryonic development"

Edward B. Lewis

Christiane Nüsslein-Volhard



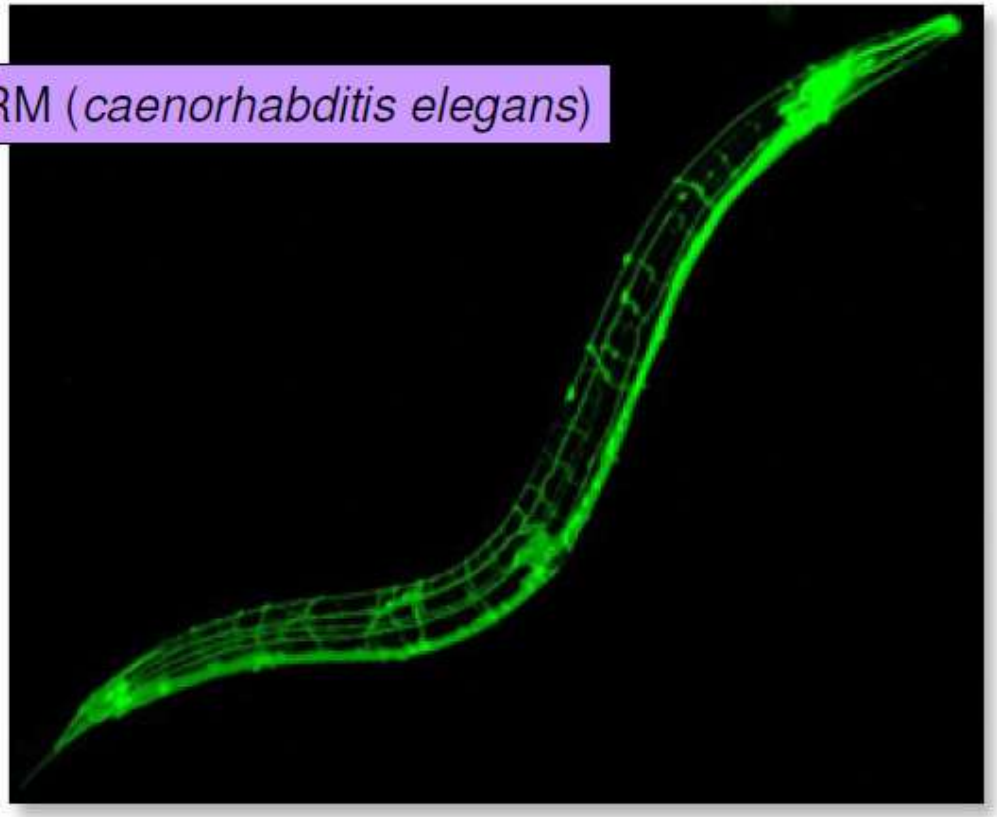
Eric F. Wieschaus

Model Organisms

Throughout history, and today:
Model organisms

Mouse, chick, *Xenopus*, zebrafish, *drosophila*, *c. elegans*, *arabidopsis*

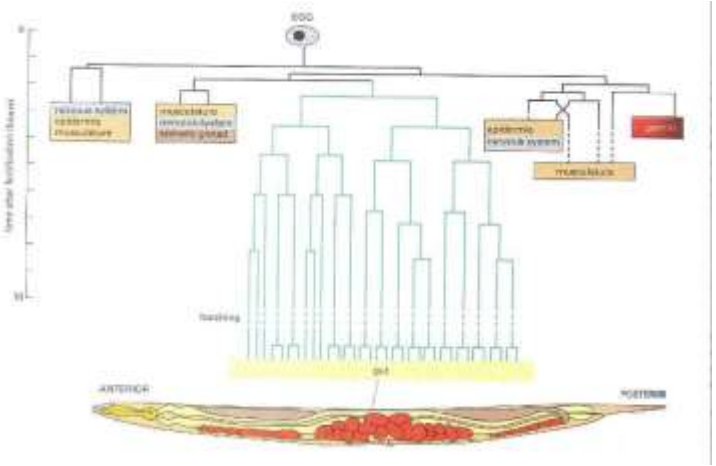
ROUNDWORM (*caenorhabditis elegans*)

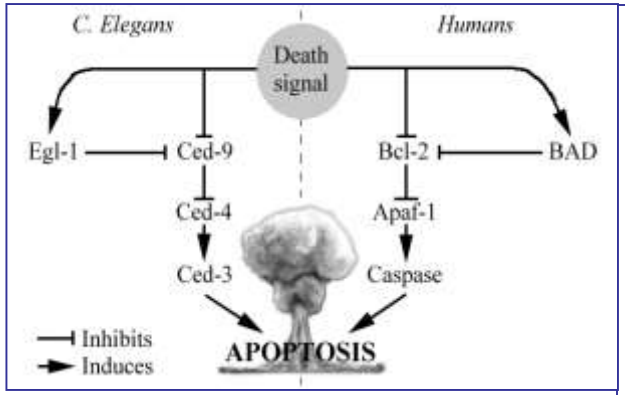


Advantages: *In ovo* development, genetic manipulation, history of use, inexpensive.
Disadvantages: Invertebrate

2002 Nobel prize Psysiology and Medicine:

Sydney Brenner, John E. Sulston, H. Robert Horovitz





By establishing and using the nematode *Caenorhabditis elegans* as an experimental model system, possibilities were opened to follow cell division and differentiation from the fertilized egg to the adult. The Laureates have identified key genes regulating organ development and programmed cell death and have shown that corresponding genes exist in higher species, including man. The discoveries are important for medical research and have shed new light on the pathogenesis of many diseases.

Sydney Brenner

Robert H. Horvitz

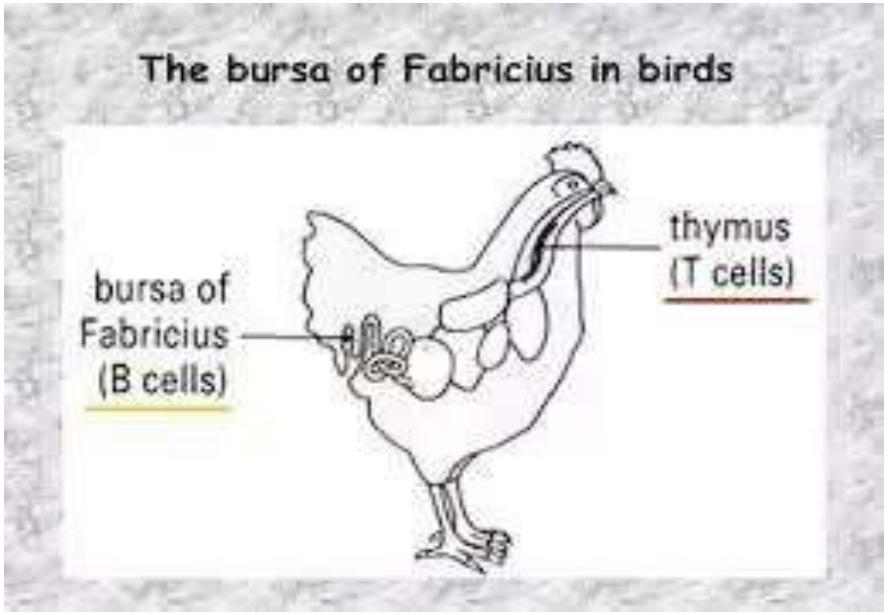
John Sulston

Model Organisms

Throughout history, and today:
Model organisms

Mouse, chick, *Xenopus*, zebrafish, *drosophila*, *c. elegans*, *arabidopsis*

Advantages: *In ovo* development, history of use, amniote.
Disadvantages: Genetic manipulation not (yet?) possible; large 'n's difficult.



2019 Lasker Awards highlight the invaluable role of animal research

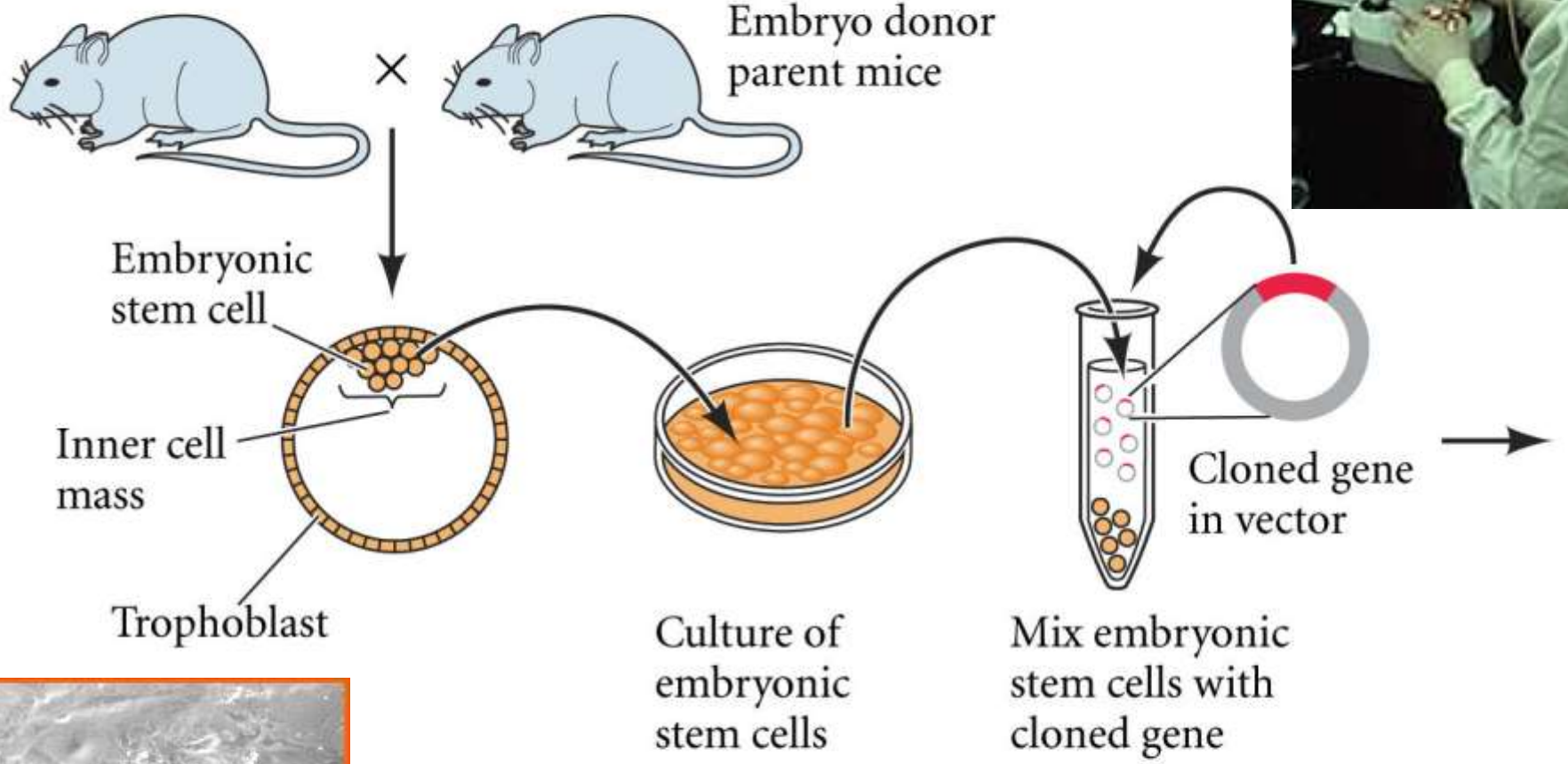
The Lasker Awards are among the most prestigious prizes in medicine in the U.S. Awarded annually, these awards given by the Albert and Mary Lasker Foundation serve to "**shine a spotlight on fundamental biological discoveries and clinical advances that improve human health, and to draw attention to the importance of public support of science**." The Lasker awards are so highly regarded, they have been nicknamed "America's Nobels."

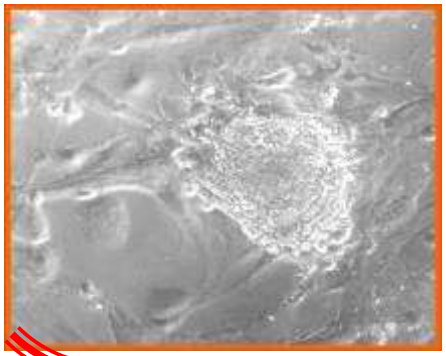
Mario Capecchi, Oliver Smithies és Martin Evans

2007 Nobel prize Psysiology and Medicine:

The Laureates have made a series of ground-breaking discoveries concerning embryonic stem cells and DNA recombination in mammals. Their discoveries led to the creation of an immensely powerful technology referred to as *gene targeting in mice*. It is now being applied to virtually all areas of biomedicine – from basic research to the development of new therapies.

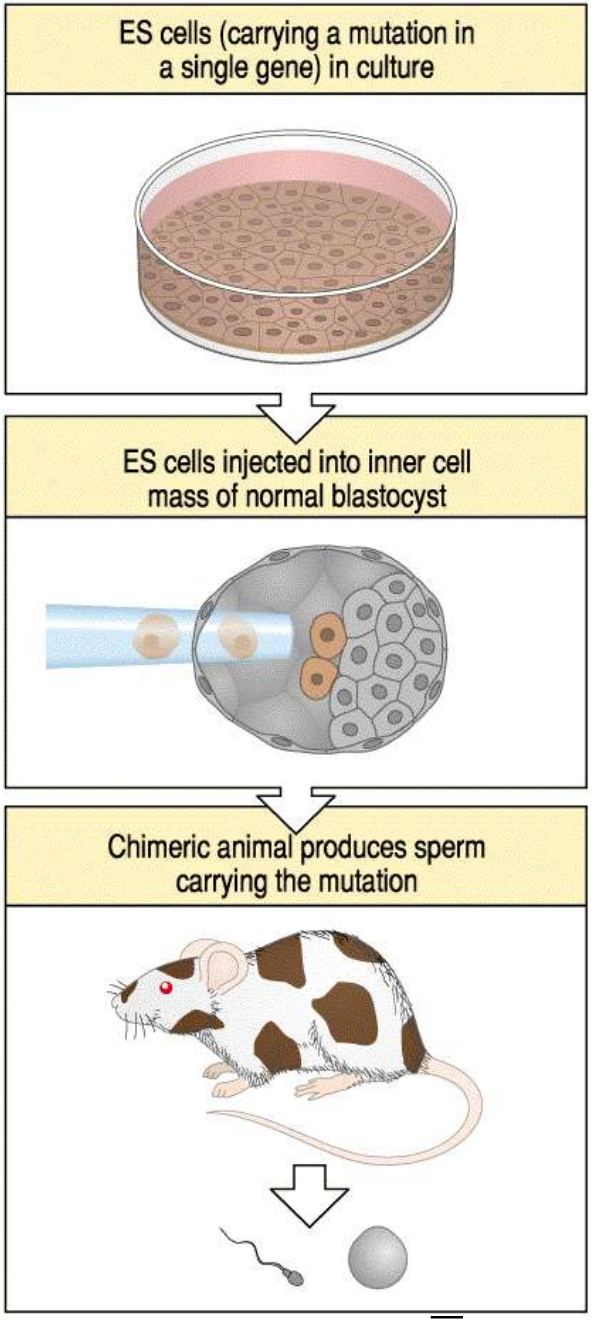
Mouse embryo: the transgenic (KO) mice

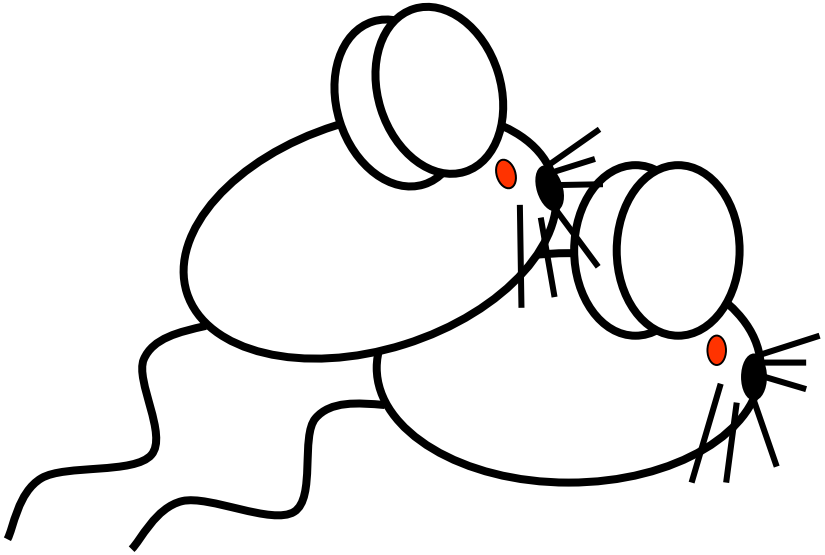




Chimeric mice

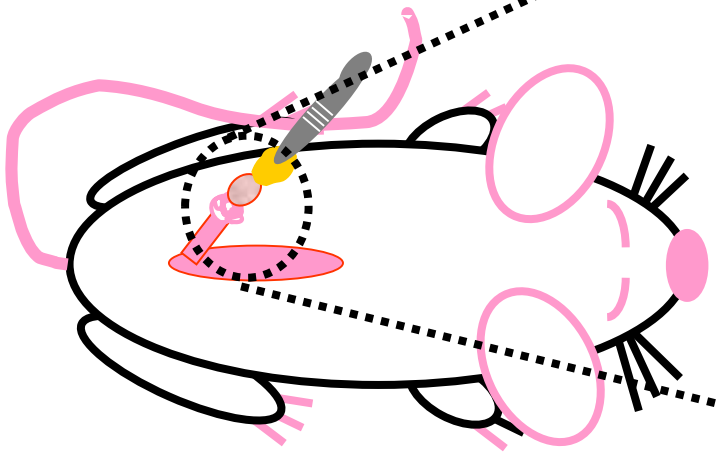
- Injection of inner cell mass cells from one mouse blastocyst to another will contribute to many tissues.
- Injection of genetically modified embryonic stem cells (ES cells) into a mouse blastocyst allows formation of transgenic chimeras which may breed to produce heterozygous (or homozygous) transgenic mice strains.
- Homologous recombination techniques can replace a gene with a defective (deleted) version of the gene to produce a “knock-out” mutant mouse strain.

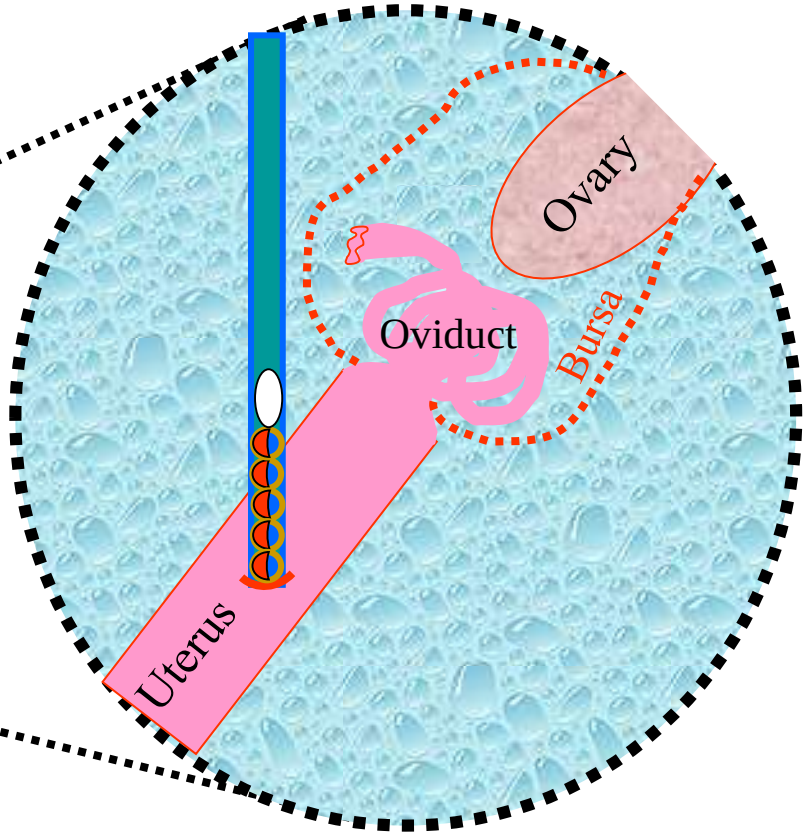


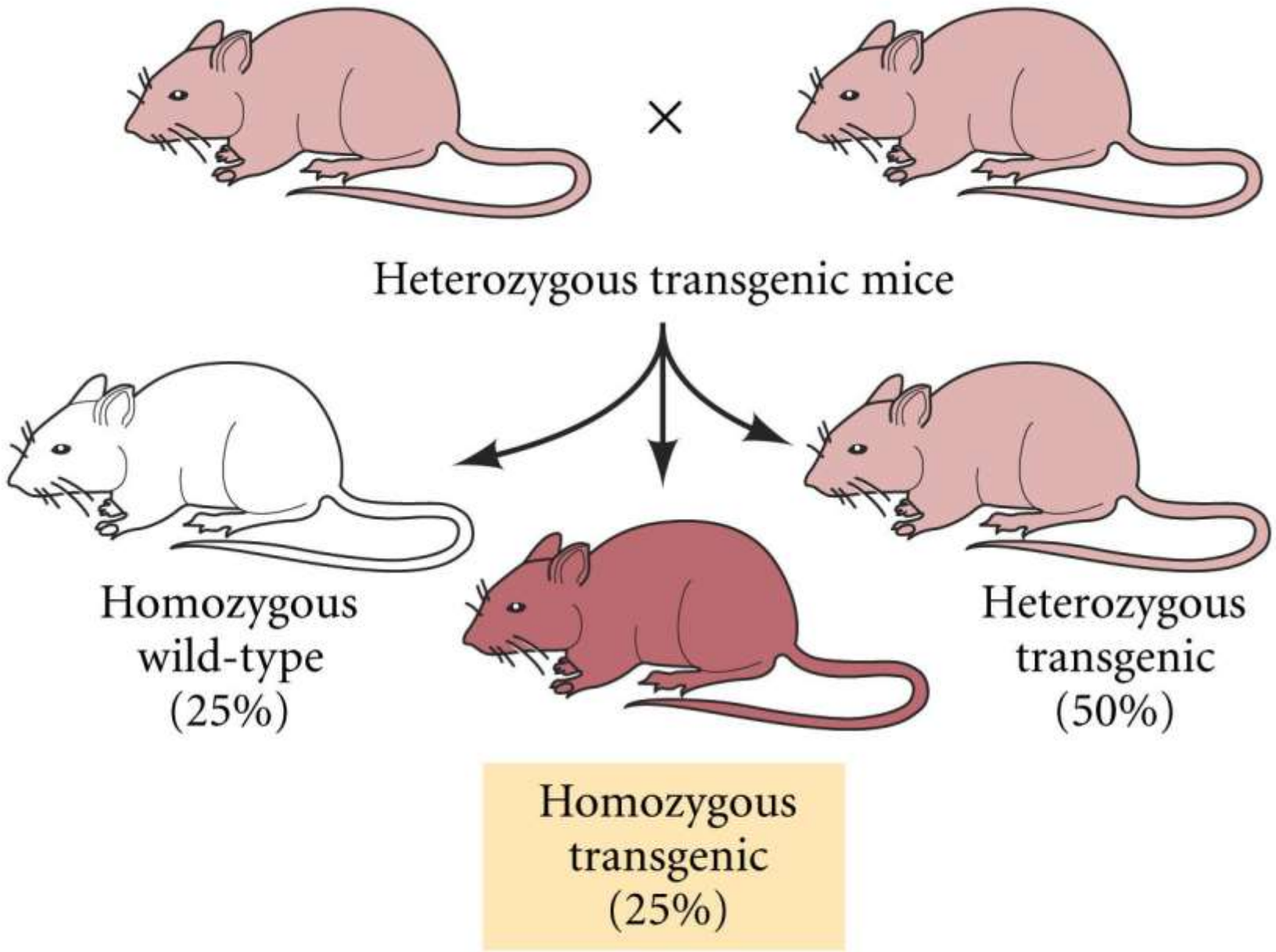


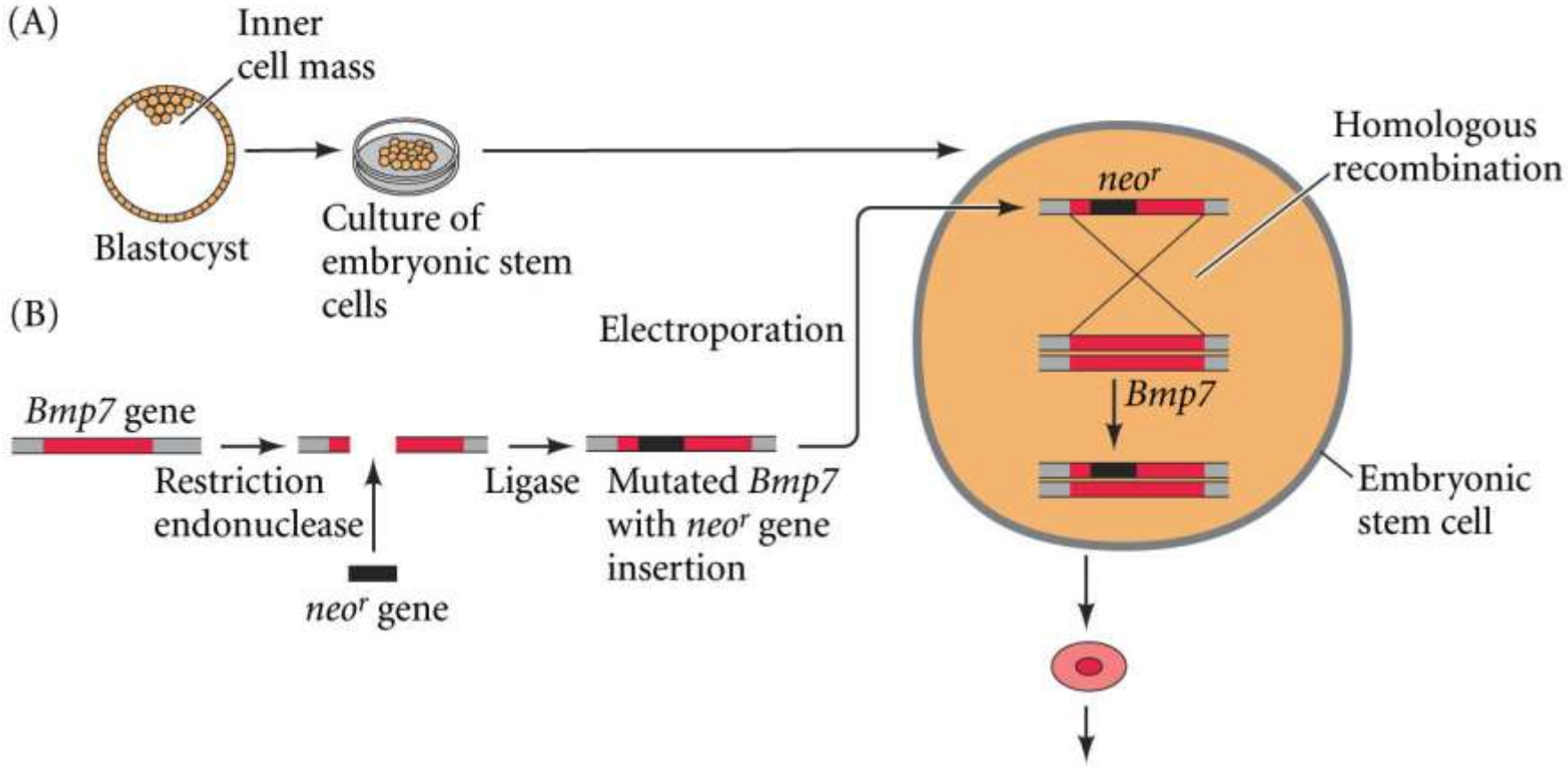
The recipient female is mated with a vasectomised male. Over the next 2 days, her uterine wall swells and vascularises, ready for implantation of blastocysts

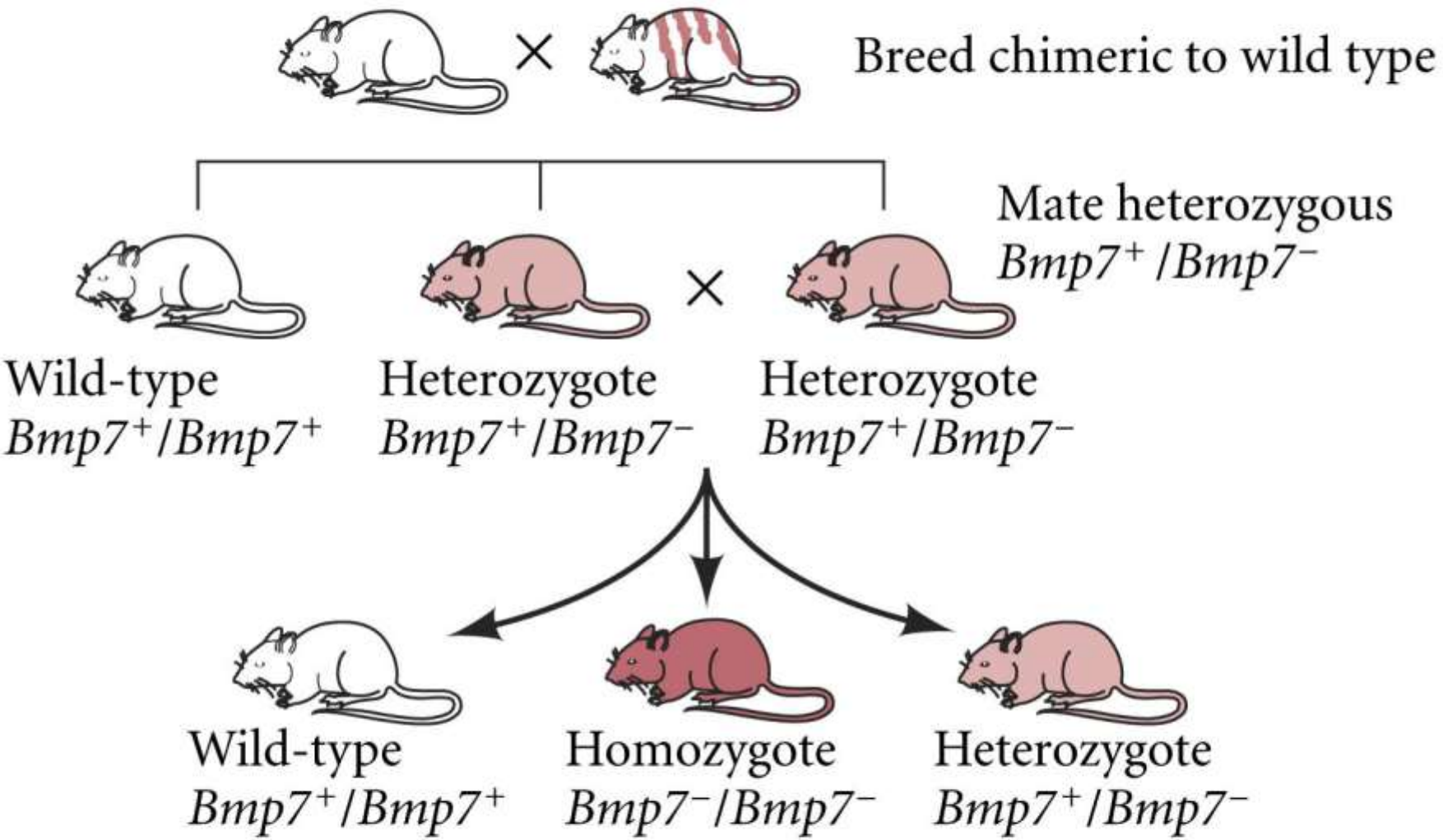
Uterine transfer of chimeric blastocysts

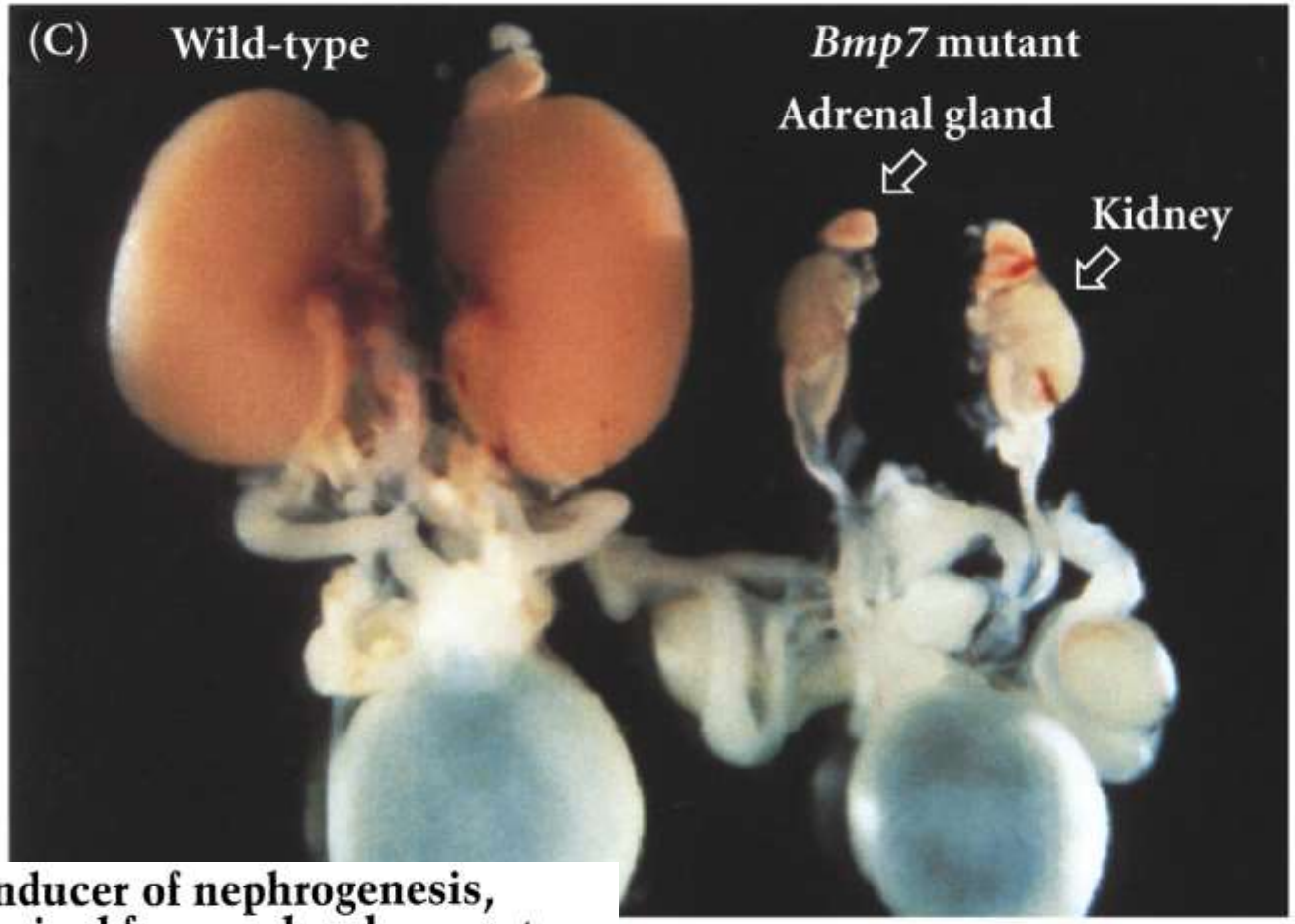










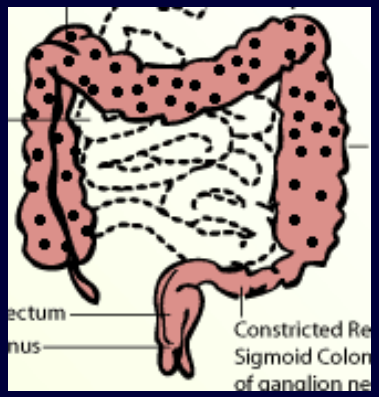


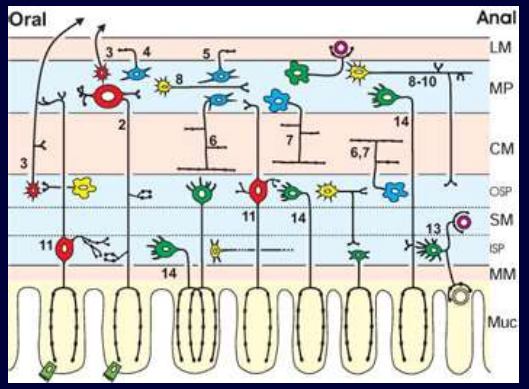
BMP-7 is an inducer of nephrogenesis, and is also required for eye development and skeletal patterning

Guangbin Luo,[1] Clementine Hofmann,[2,4] Antonius L.J.J. Bronckers,[1,5] Melanie Sohocki,[1] Allan Bradley,[3] and Gerard Karsenty[1,6]

[1]Department of Molecular Genetics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, 77030 USA; [2]Department of Biochemistry, [3]Howard Hughes Medical Institute-Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, 77030 USA; [4]GSF, Forschungszentrum für Umwelt und Gesundheit, Institut für Saugetiergenetik, Oberschleissheim, Germany D-85758

Hirschsprung Disease (congenital disease;1 in 5000 newborns; presents with failure to pass meconium, distension, vomiting)





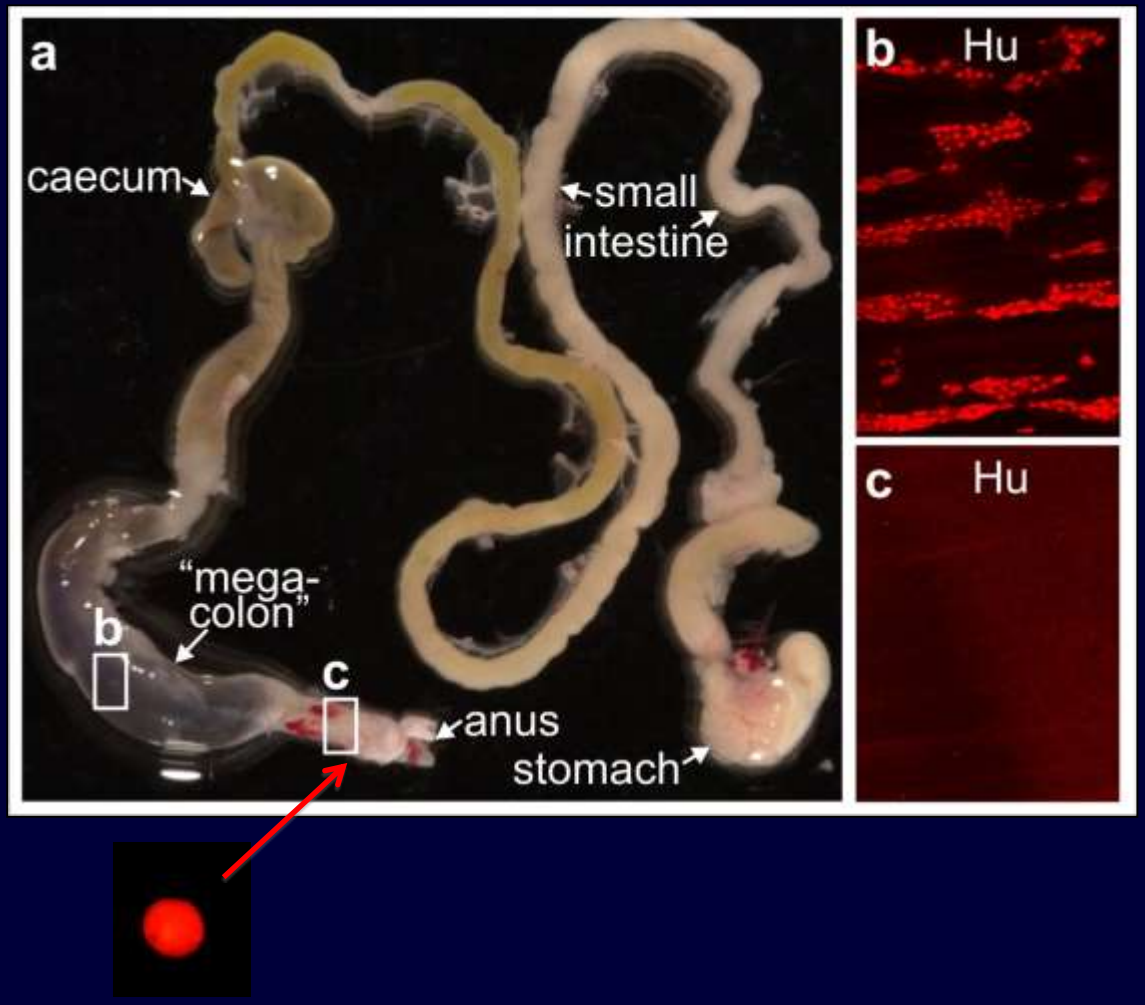
Enteric Nervous System (ENS)

- Intrinsic innervation of the gut
- Controls motility, absorption, secretion, blood flow, immune function, microbiota composition
- Hirschsprung disease is an intestinal disorder characterized by the absence of ENS in parts of the intestine. This condition occurs when the nerves in the intestine (enteric nerves) do not form properly during development before birth (embryonic development).
- can result from mutations in one of several genes, including the RET, EDNRB, and EDN3 genes

Hirschsprung disease model (EDN3 mutant mice)

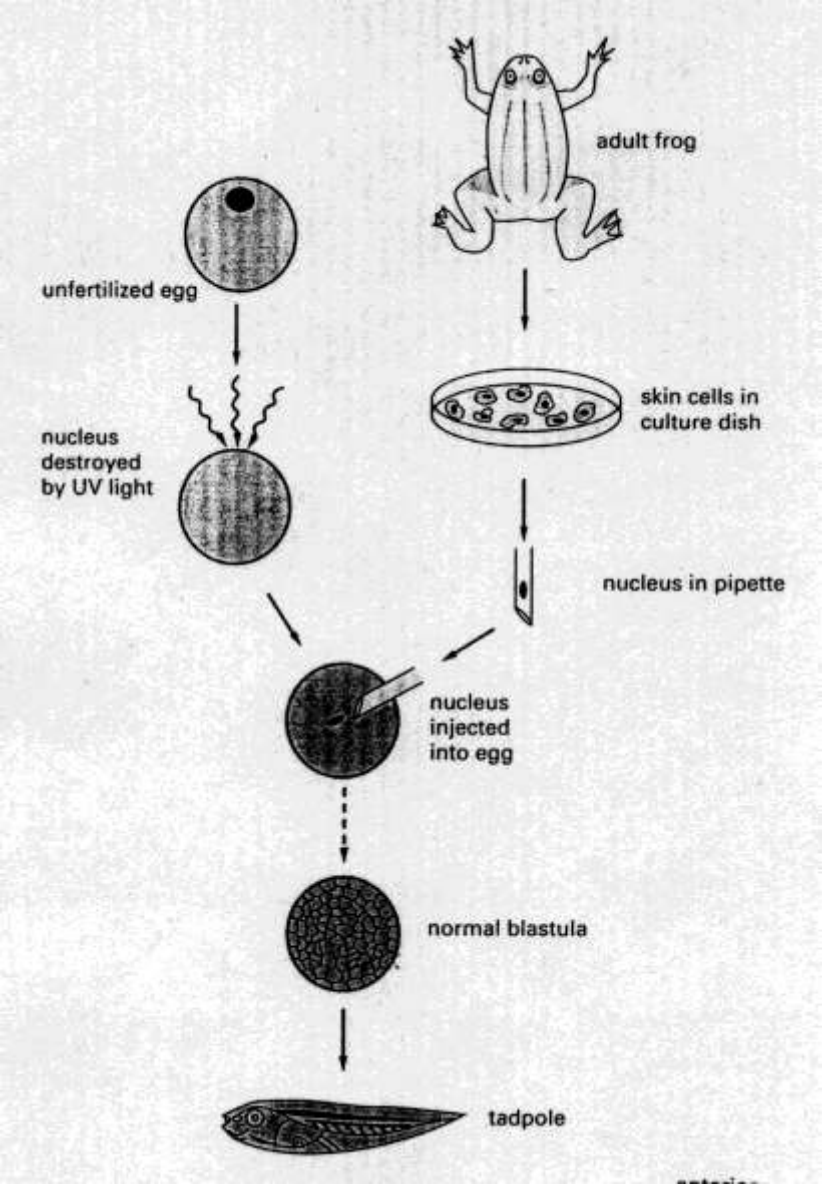
EDN3$^{-/-}$

(Endothelin Receptor B)



Summary

- The **mouse** is used in developmental biology partly because it is a small, cheap, mammal, which can be a good model for human genetic disease.
- It has been developed as a very sophisticated genetic tool that lends itself to forward and reverse genetic analysis.
- Disadvantages are practical and logistic – it is still not as cheap or small as some other models, and there are greater ethical issues than other models.
- Also embryogenesis is internal, not easily experimentally accessible.
- Most work on signalling during early embryogenesis up to around gastrulation has been easier in frogs, fish, and chicks (but they are not as genetically accessible).



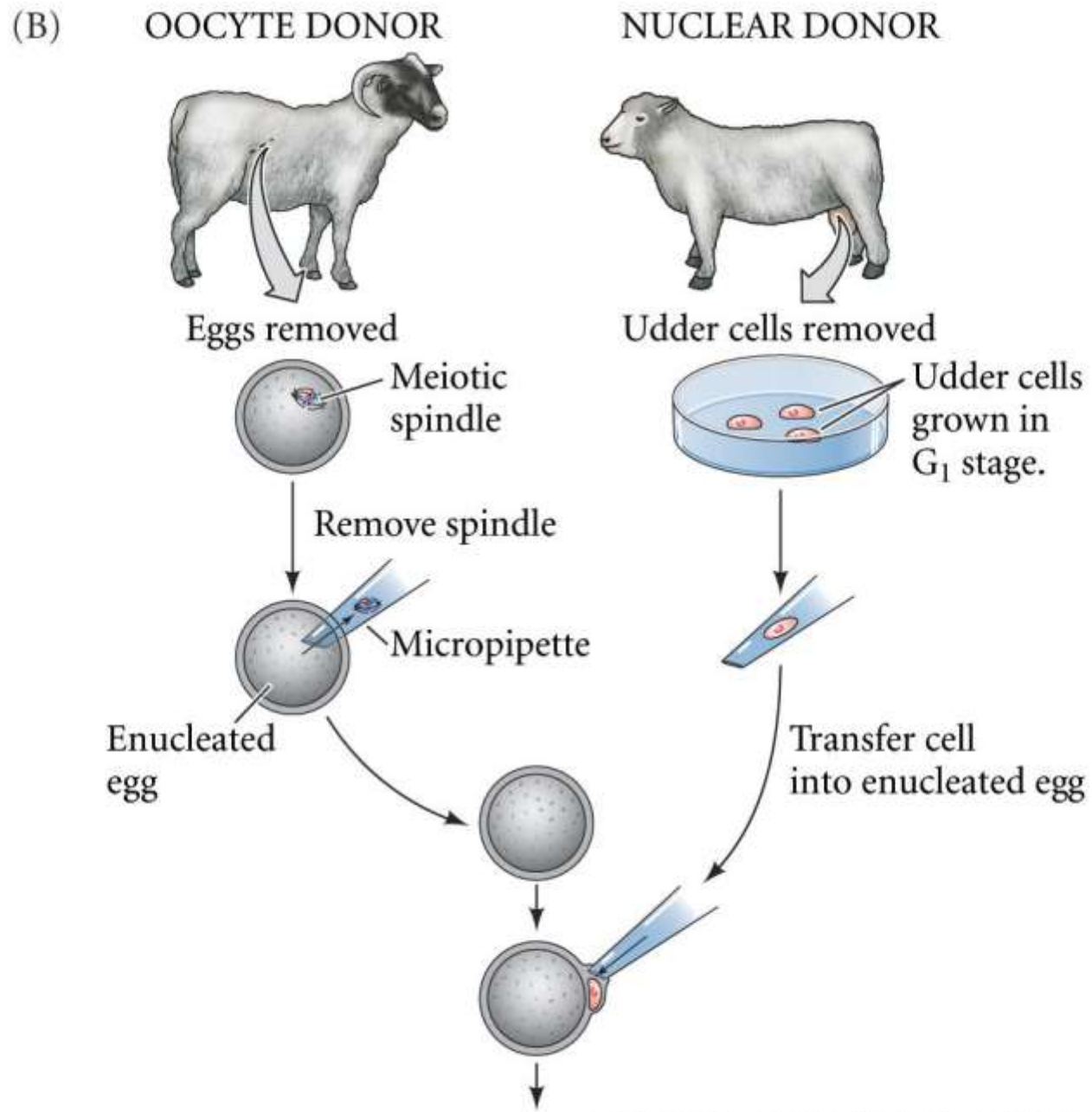
Transplantation experiment

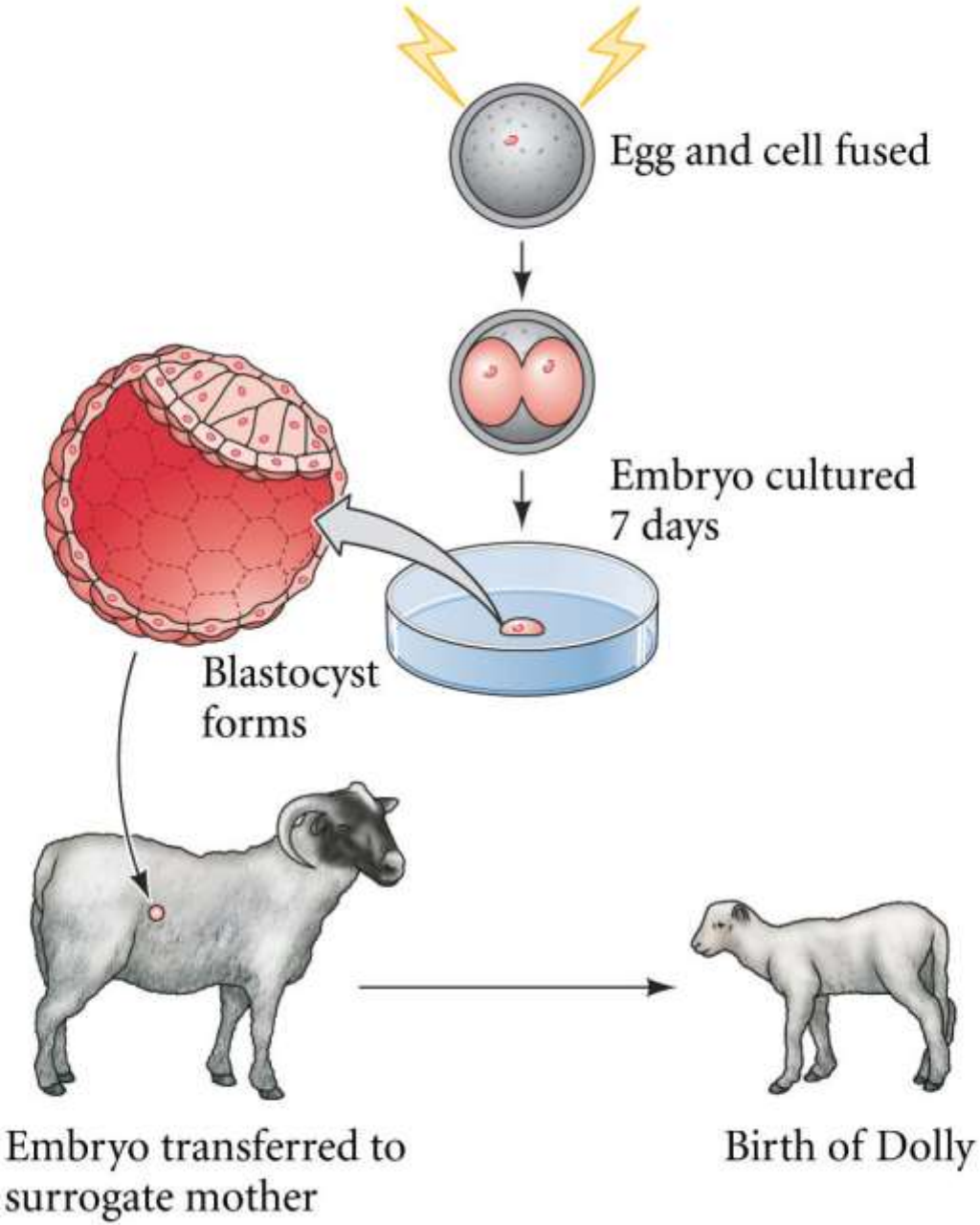
John Gurdon

cloning

(A)

Ian Wilmut





(1/434)

DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 4.8 (Part 3)

The Nobel Prize in Physiology or Medicine 2012

Sir John B. Gurdon, Shinya Yamanaka

Photo: Creative Commons Attr. 2.0 Generic license

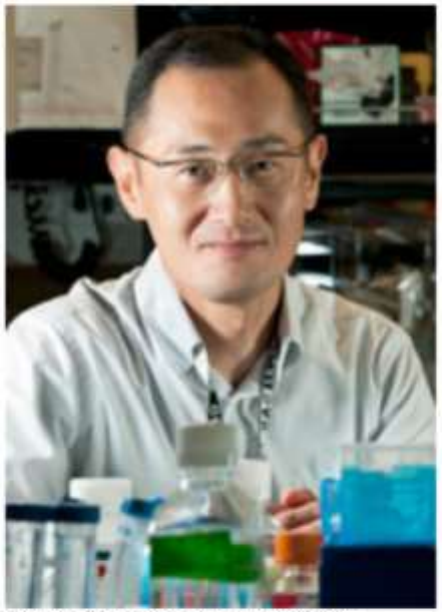


Photo: Gladstone Institutes/Chris Goodfellow

Sir John B. Gurdon

Shinya Yamanaka

The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka *"for the discovery that mature cells can be reprogrammed to become pluripotent"*