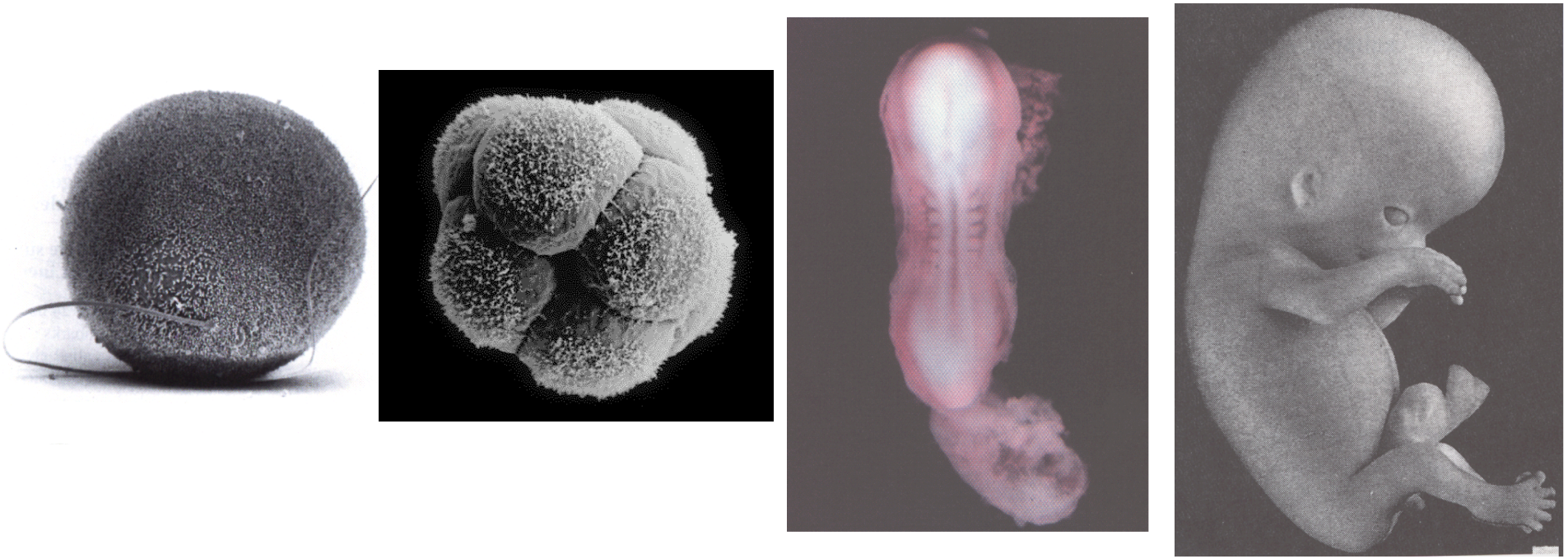
Human Development



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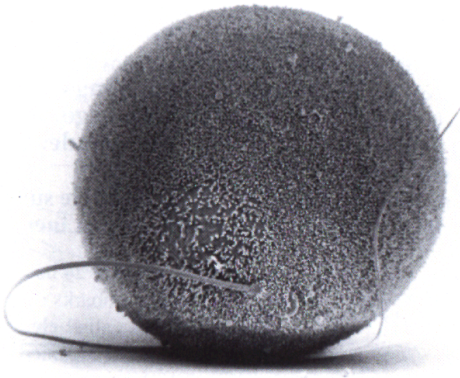
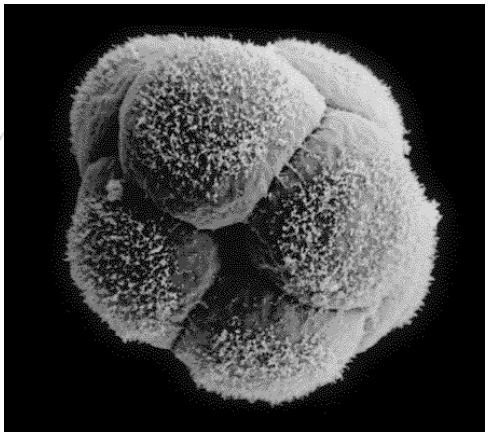
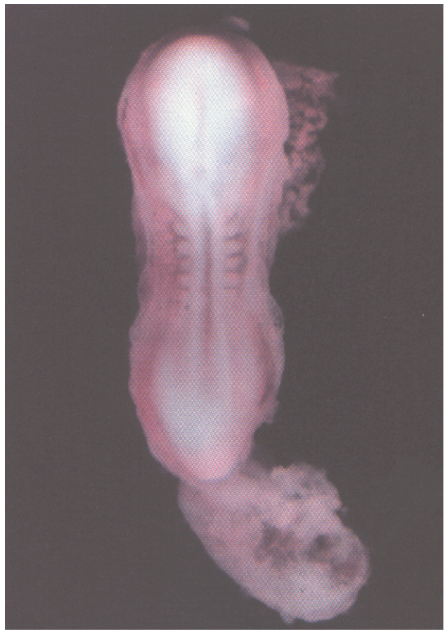
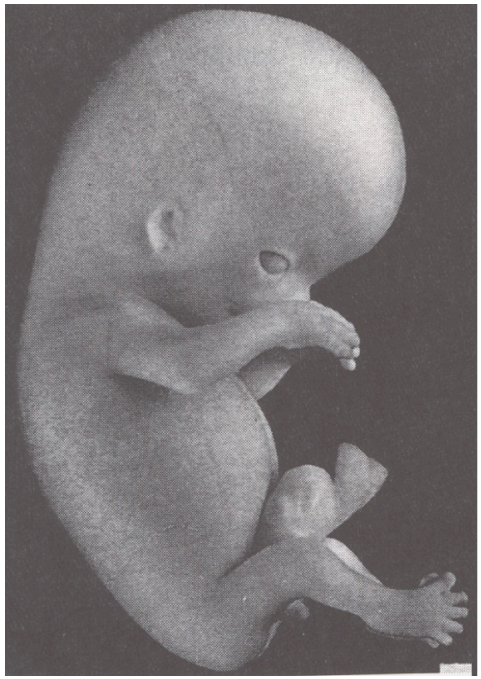

Michael Shen, PhD
Patricia Ducy, PhD
Michael Gershon, MD
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Lori Sussel, PhD
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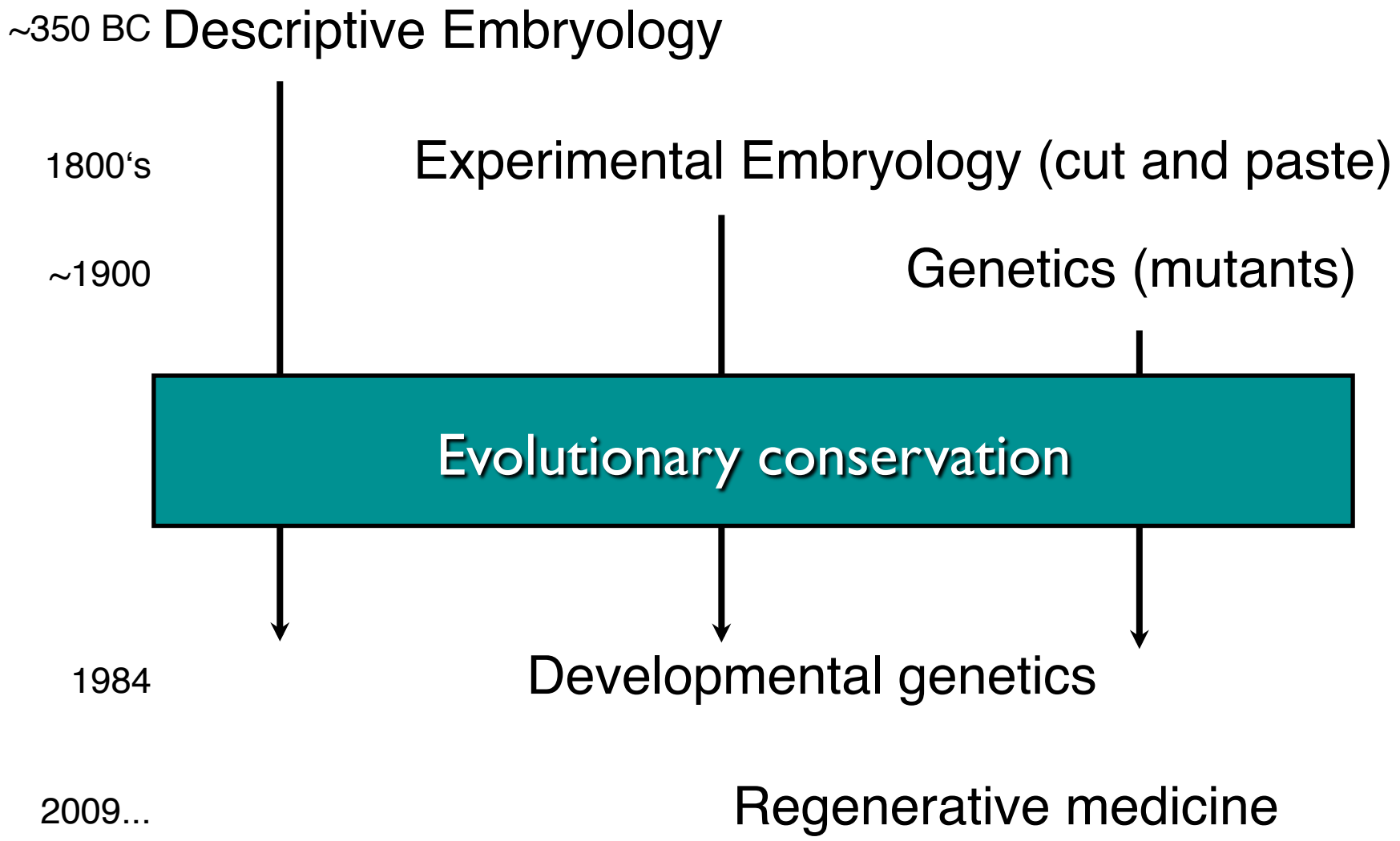
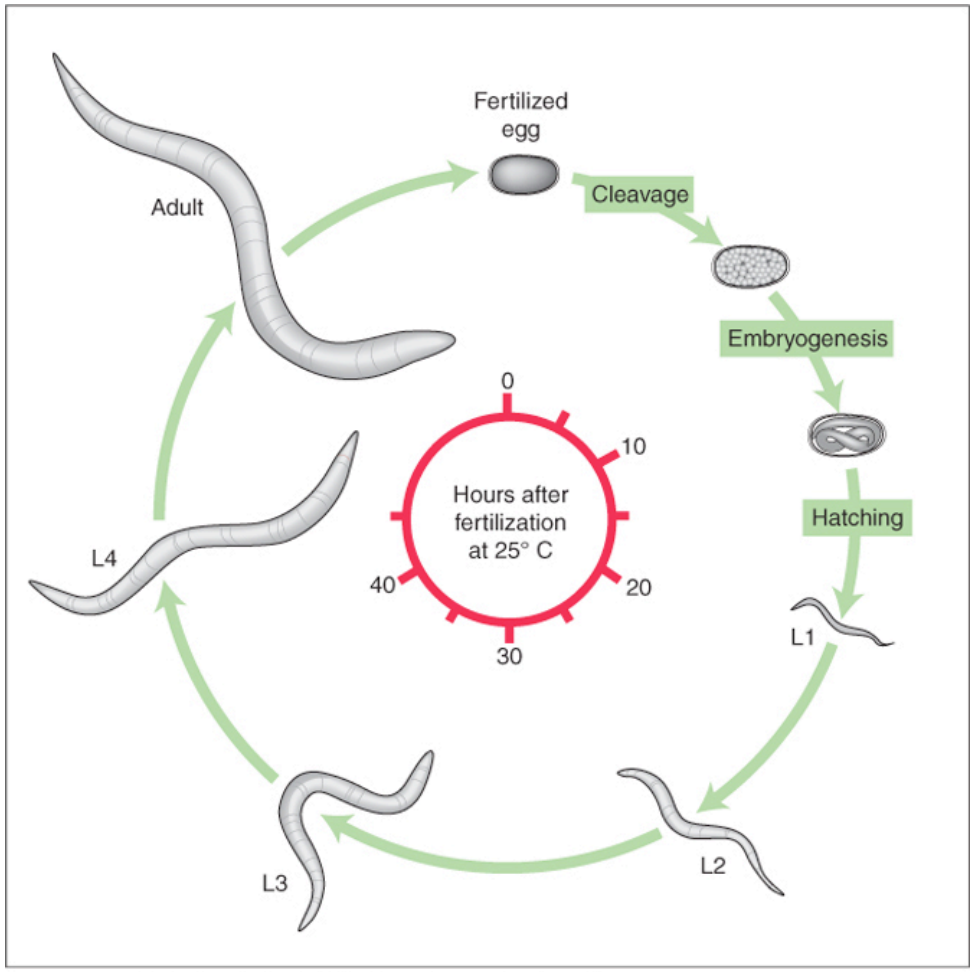
Foundations of modern developmental genetics

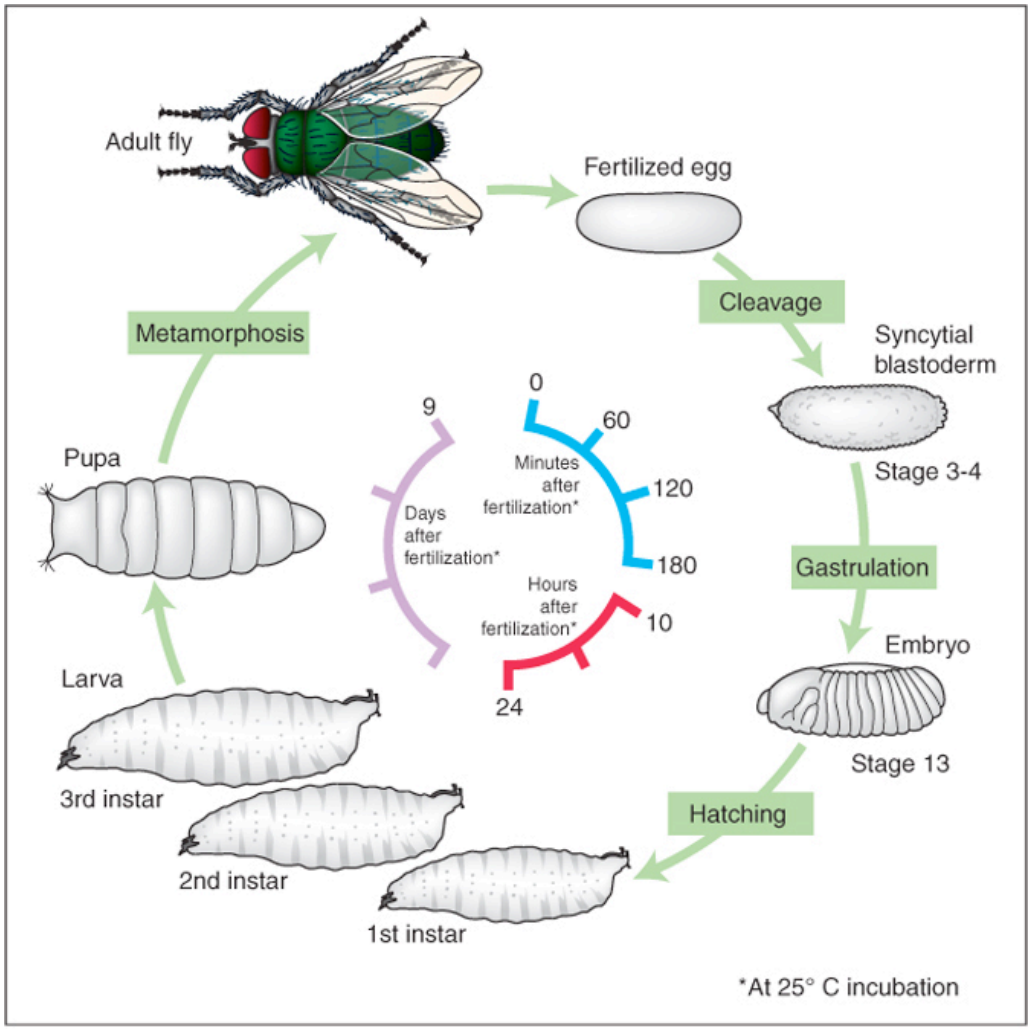


Caenorhabditis elegans



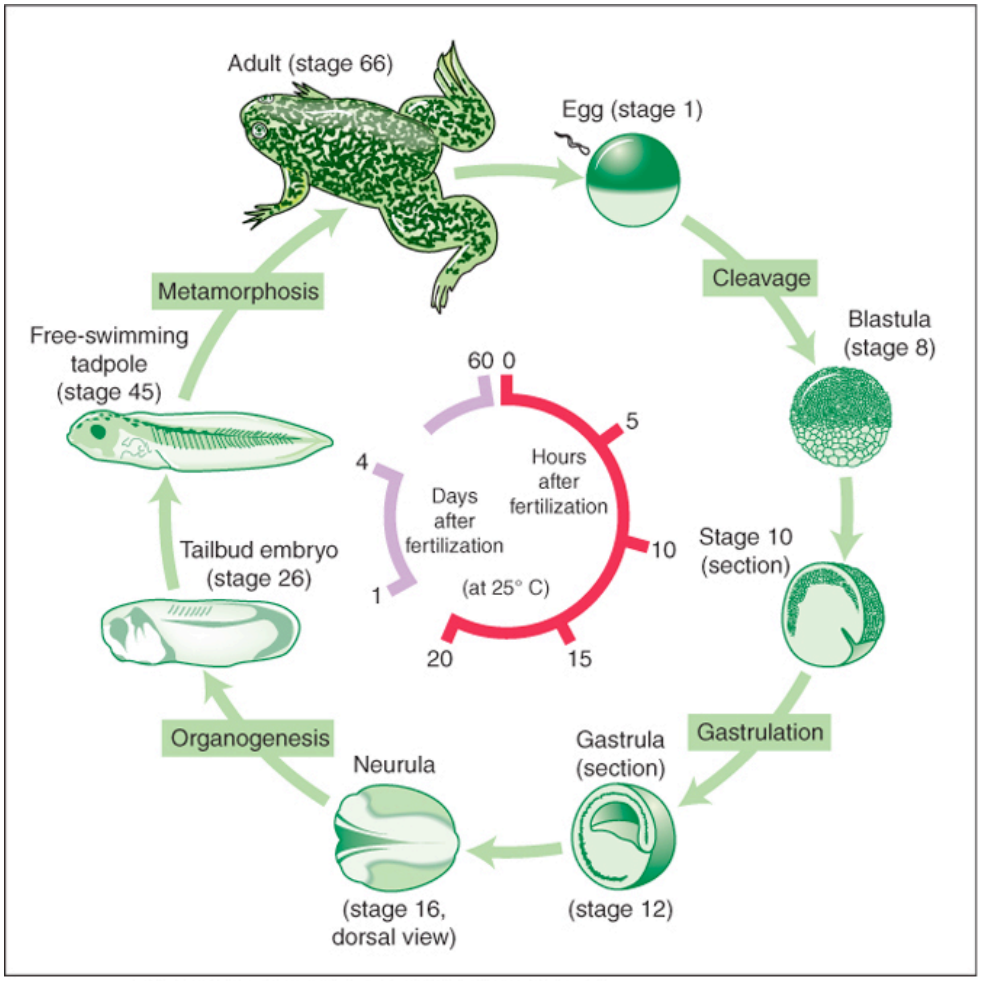
Superb genetics
Fixed cell lineages
Rapid development

Drosophila melanogaster



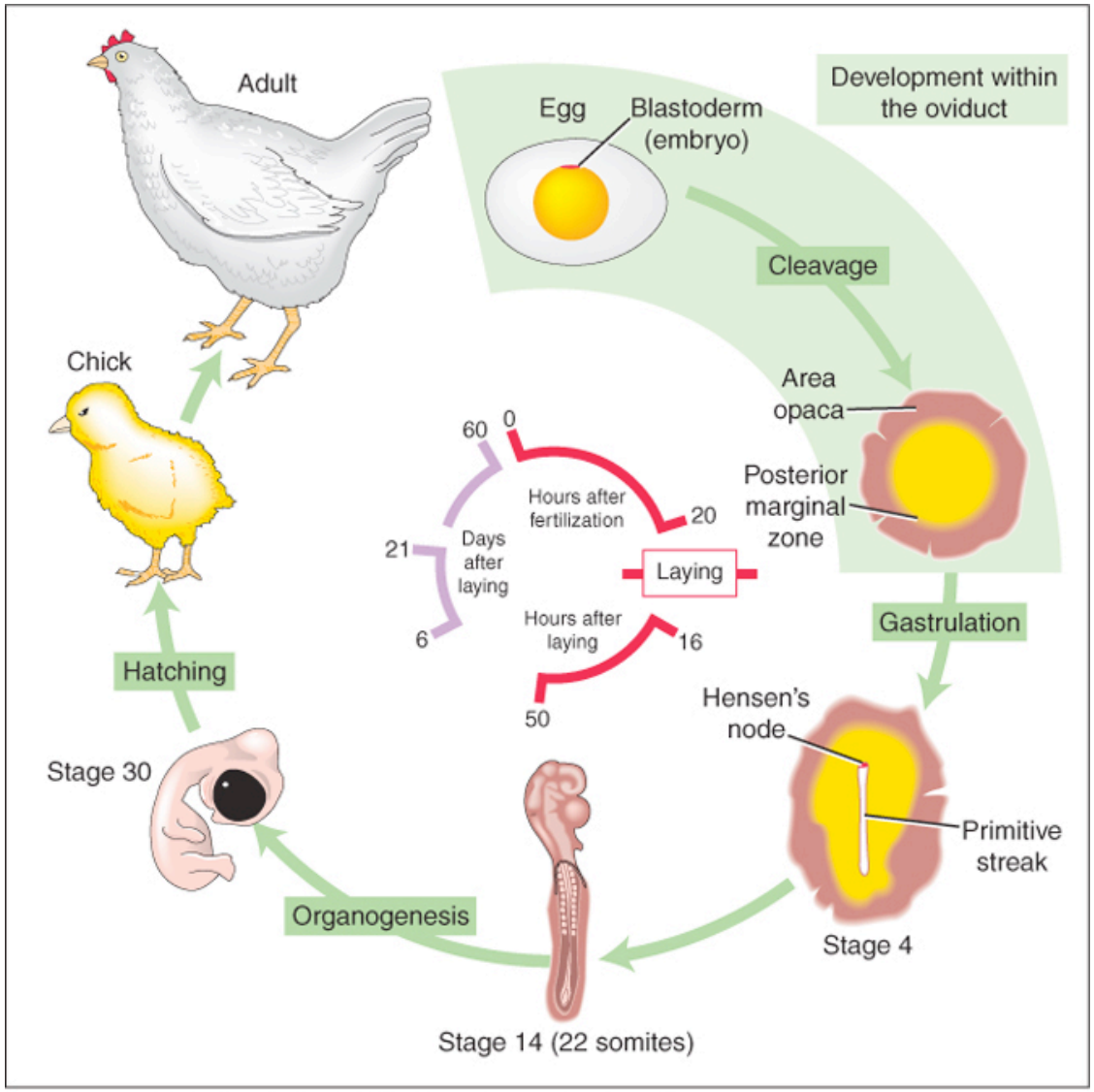
Superb genetics
Rapid life cycle

Xenopus laevis



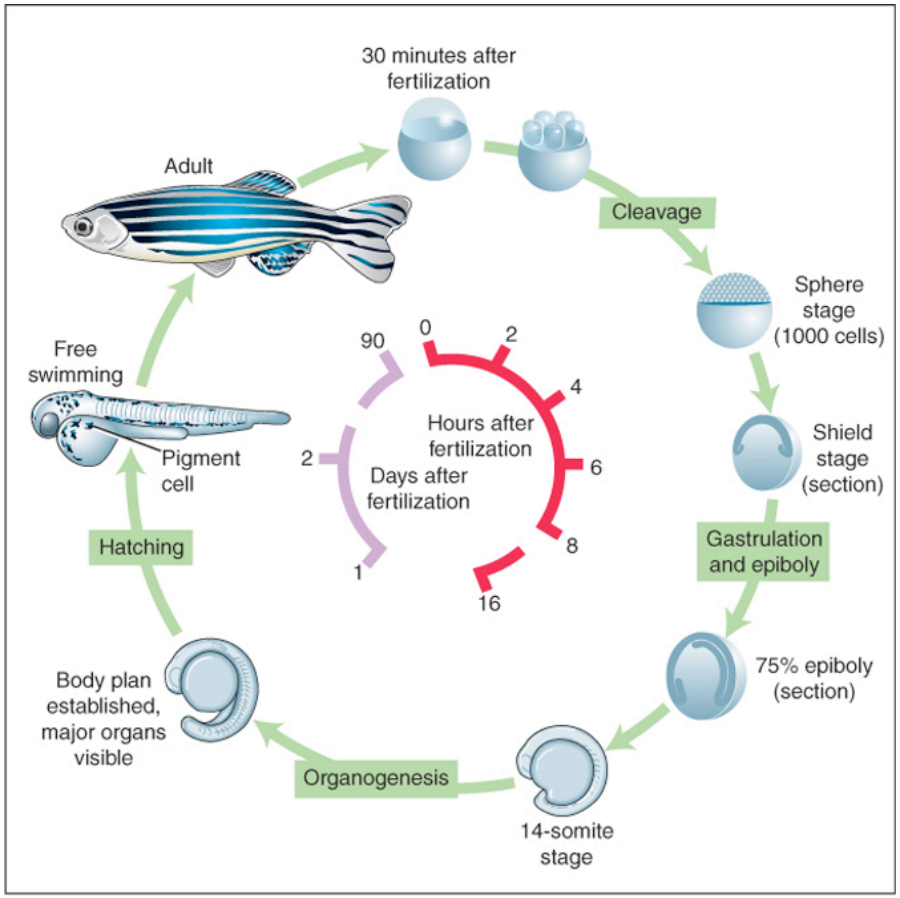
Rapid development
Large eggs (~1mm diam) easily manipulated
Well suited for studying earliest stages of development

Chicken (*Gallus gallus*)



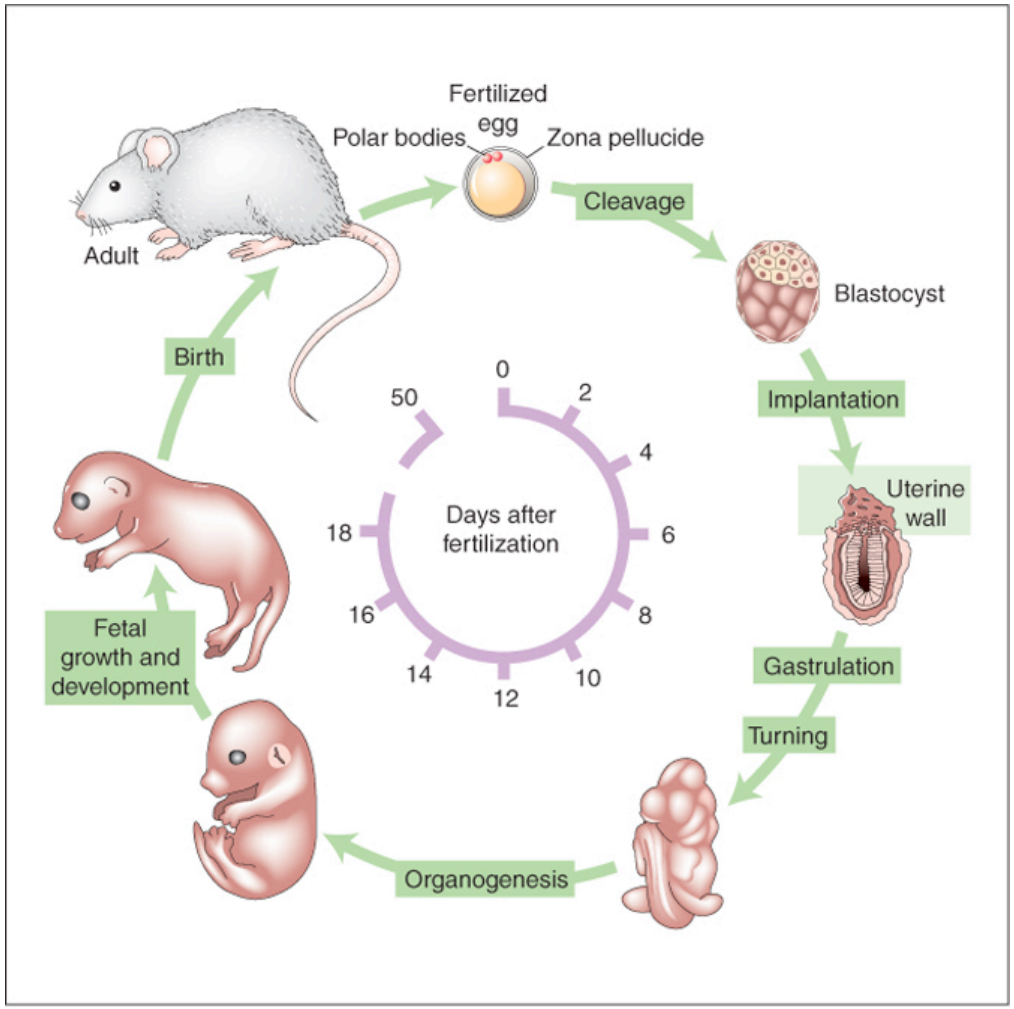
Easily manipulated, especially from gastrulation through organogenesis

Zebrafish (*Danio rerio)*

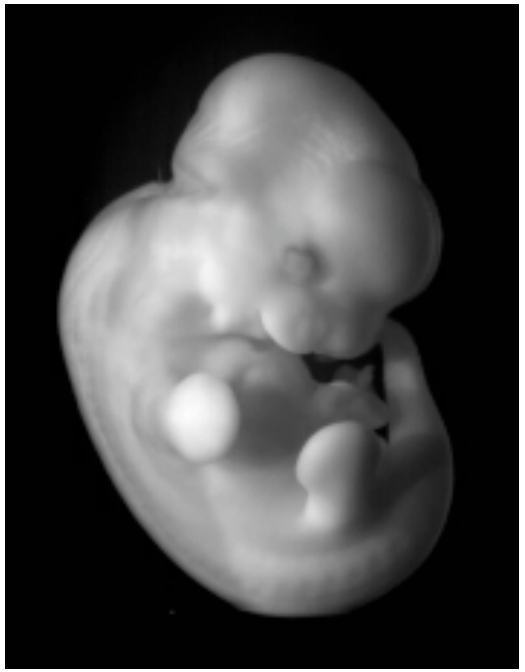


Transparent embryo
Rapid development
Good genetics

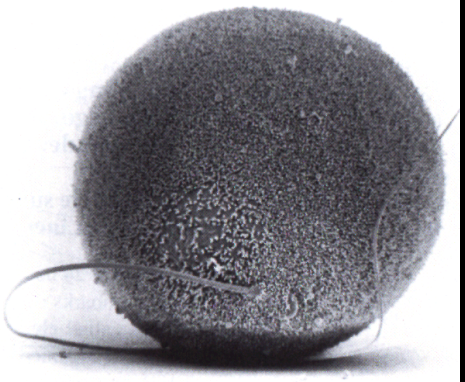
Mouse (*Mus musculus*)



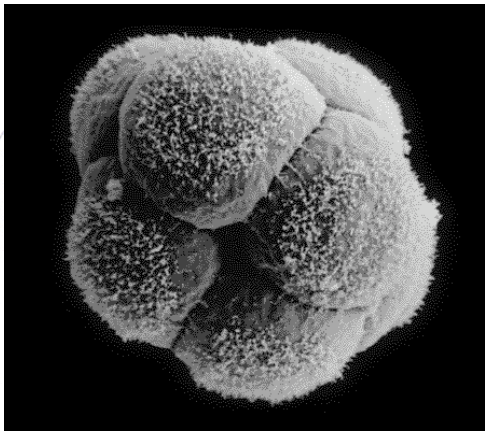
Excellent genetics
Can explant culture for tissue manipulation
Mammal: good disease model



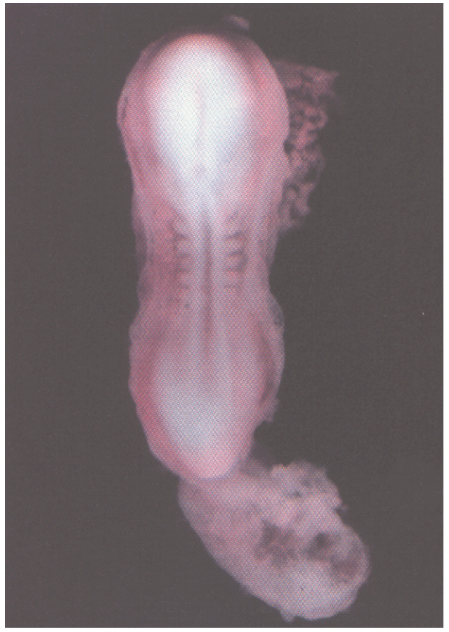
Development of the embryo: from one cell to many



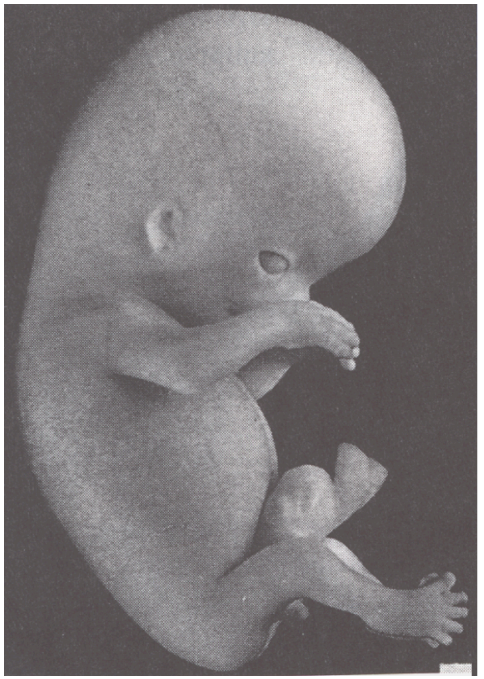
Fertilization



Preimplantation



Gastrulation
and
Patterning



Organogenesis
and Growth

Fate, determination, specification and lineage

These are four related concepts having to do with cell identity.

A cell's fate is defined as the cell types of it's descendants.

A cell's fate is specified when it generates those cell types if cultured in isolation: independent of external influences.

A cell's fate is determined if it gives rise to its normal descendants when exposed to abnormal influences. eg if transplanted to a different region of the embryo.

A cell lineage is the population of cells descended from a parent cell.

Specification vs. determination

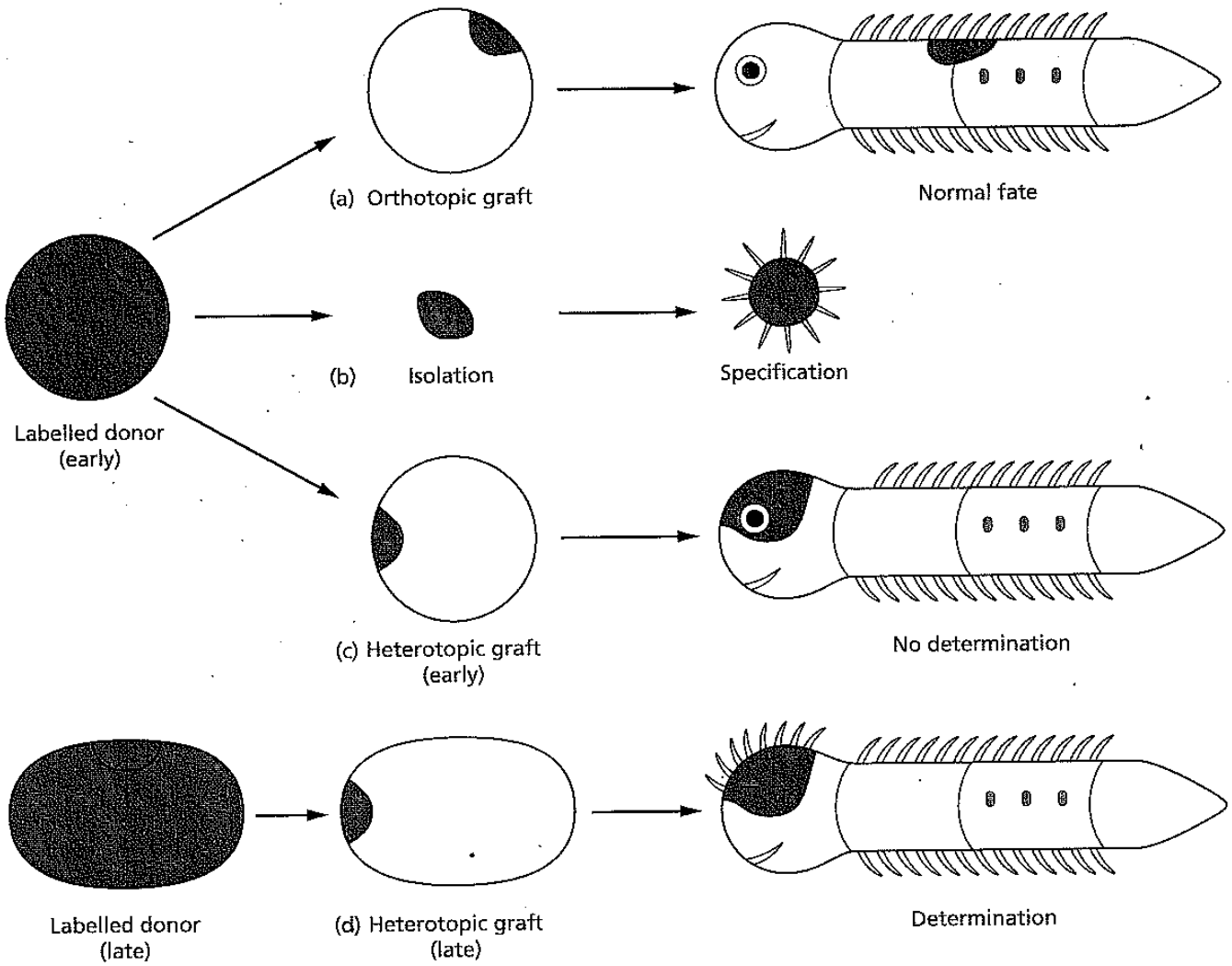
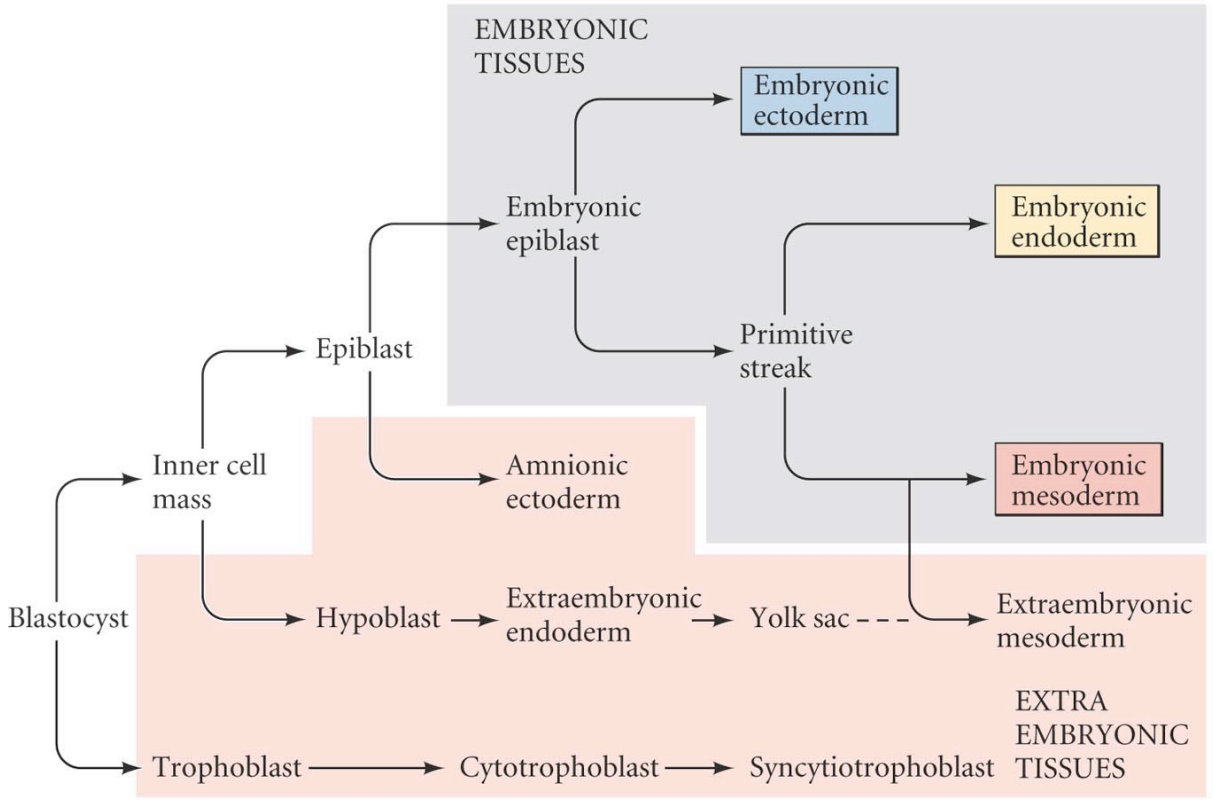


Fig. 6.5 Tests for fate, specification and determination. (a) The labelled region will normally contribute to the spiny dorsal part of the animal (fate). (b) When isolated this tissue still forms dorsal spines (specification). (c) When grafted at an early stage to another region it differentiates according to the new position (not determined). (d) When grafted at a later stage to another region it differentiates according to its original position (determined).

Slack, J., 2001. Essential Developmental Biology, Blackwell

Progressive restriction of lineages over time



The ability of a cell to generate diverse cell types is a measure of its developmental potency. As cells become specified to progressively more restricted lineages, their potency is reduced.

Morphogenesis: the creation of ordered form

During embryogenesis cells divide, migrate and die
Tissues fold and separate
Organs are arranged in particular ways

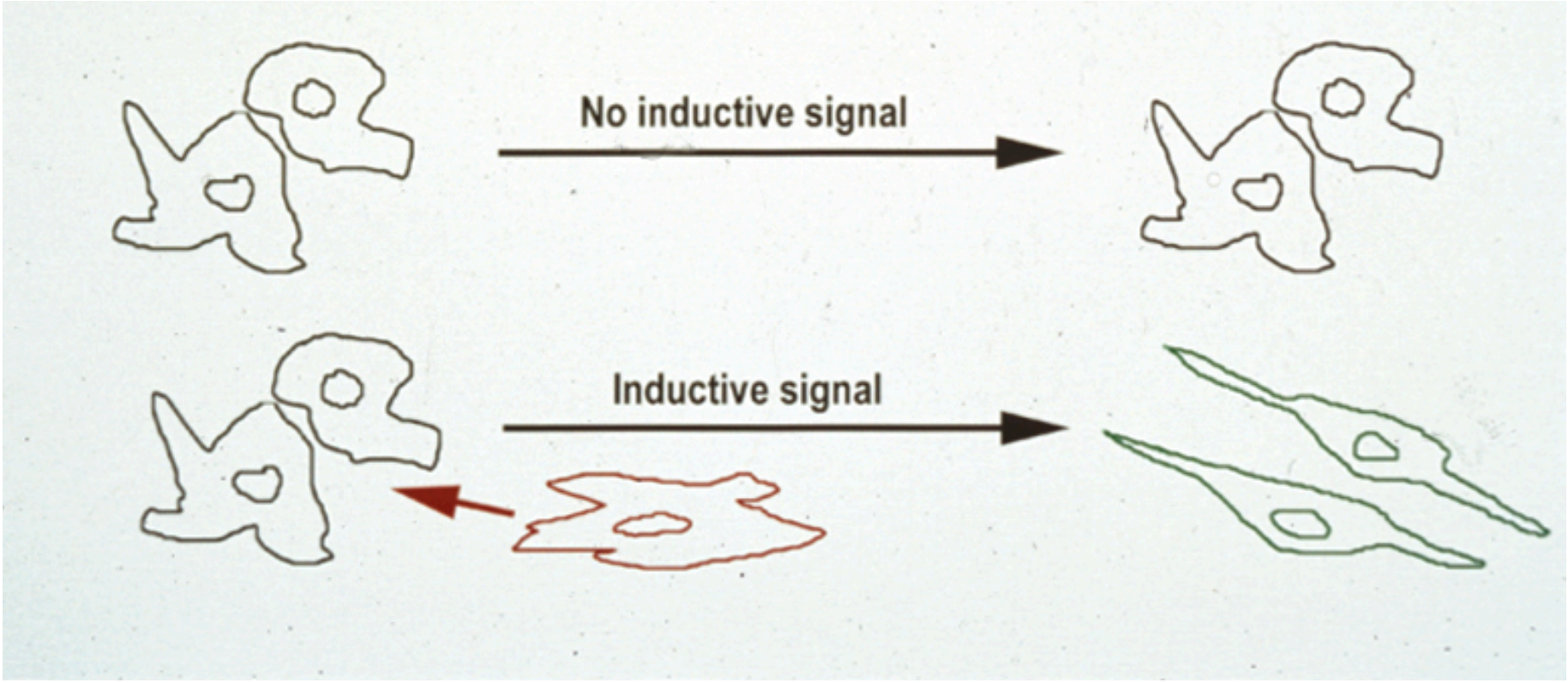
Development is the result of a combination of cell fate specification leading to differentiation of functional cell types in combination with morphogenetic processes.

These events do not happen in isolation. Rather they are the result of intricate interactions between cells and tissues.

Embryonic Induction

The process where one embryonic tissue instructs a second tissue to adopt a different fate (differentiation, pattern or behavior) than it would otherwise take.

Mediated by surface-bound or secreted proteins or small molecules



Inductive signals can be permissive or instructive

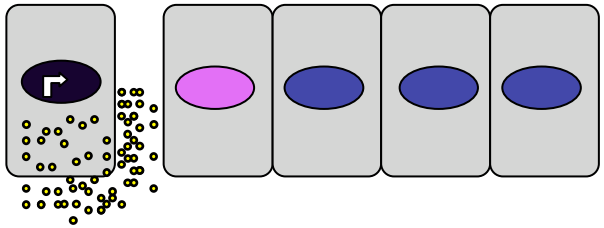
Permissive signals allow cells to reach developmental potential but do not direct their fate

eg. many cells need a solid substrate or lamina to develop, but the lamina does not affect the type of cell produced

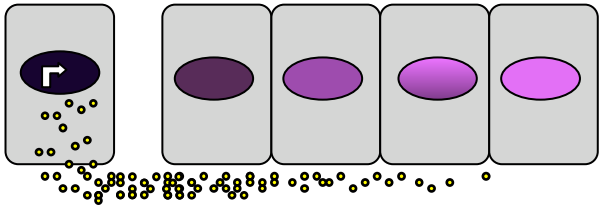
Instructive signals tell cells to adopt specific new fates

There are many modes through which inductive signals can influence responding cells

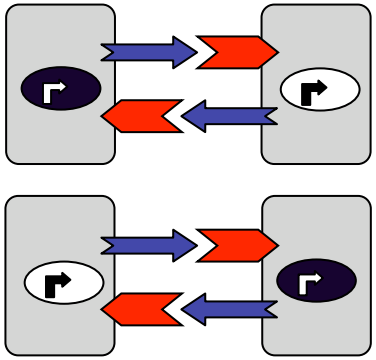
Short range



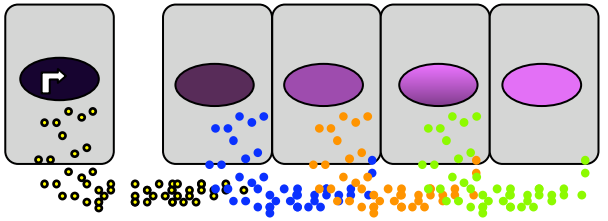
Gradient



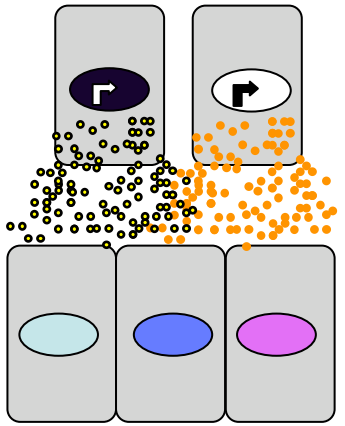
Lateral



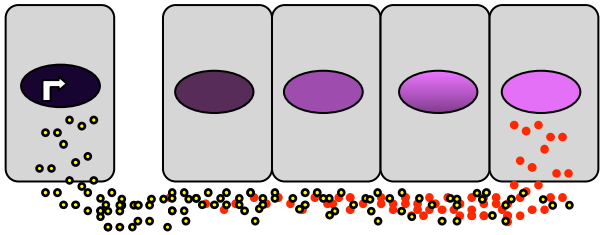
Relay



Combinatorial



Antagonist



Classes of inductive signals

While there are many known intracellular signals, surprisingly the major inductive cues for almost all developmental events turn out to be members of just a few families of proteins

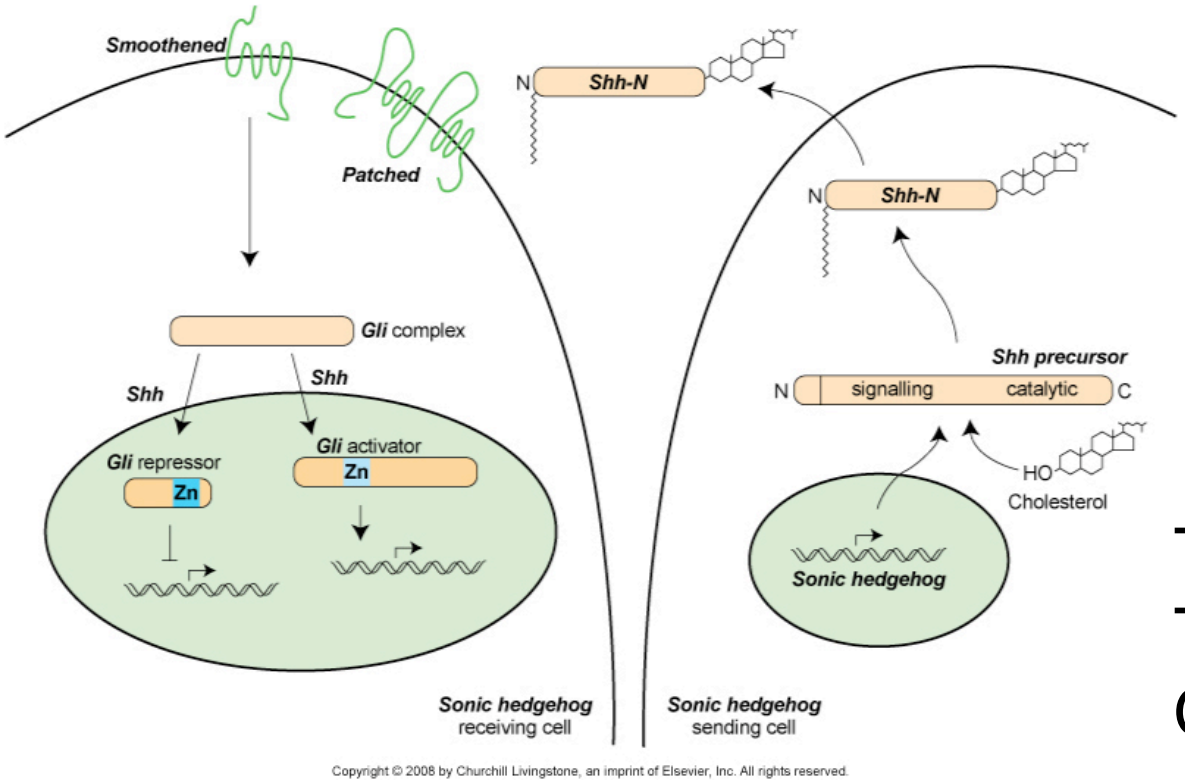
Secreted signals
(long range)
Hedgehog
TGFβ/BMP
Wnt
FGF

Membrane bound
(short range)
Notch/Delta
Eph/ephrin

Inductive molecules are reused for different tasks during embryogenesis

The same signal will induce different responses in different cell types, depending on which receptors and signal transduction molecules are present in a given cell, and on what other gene-regulatory processes are present at the same time (other activating or repressing transcription factors, chromatin state, etc.)

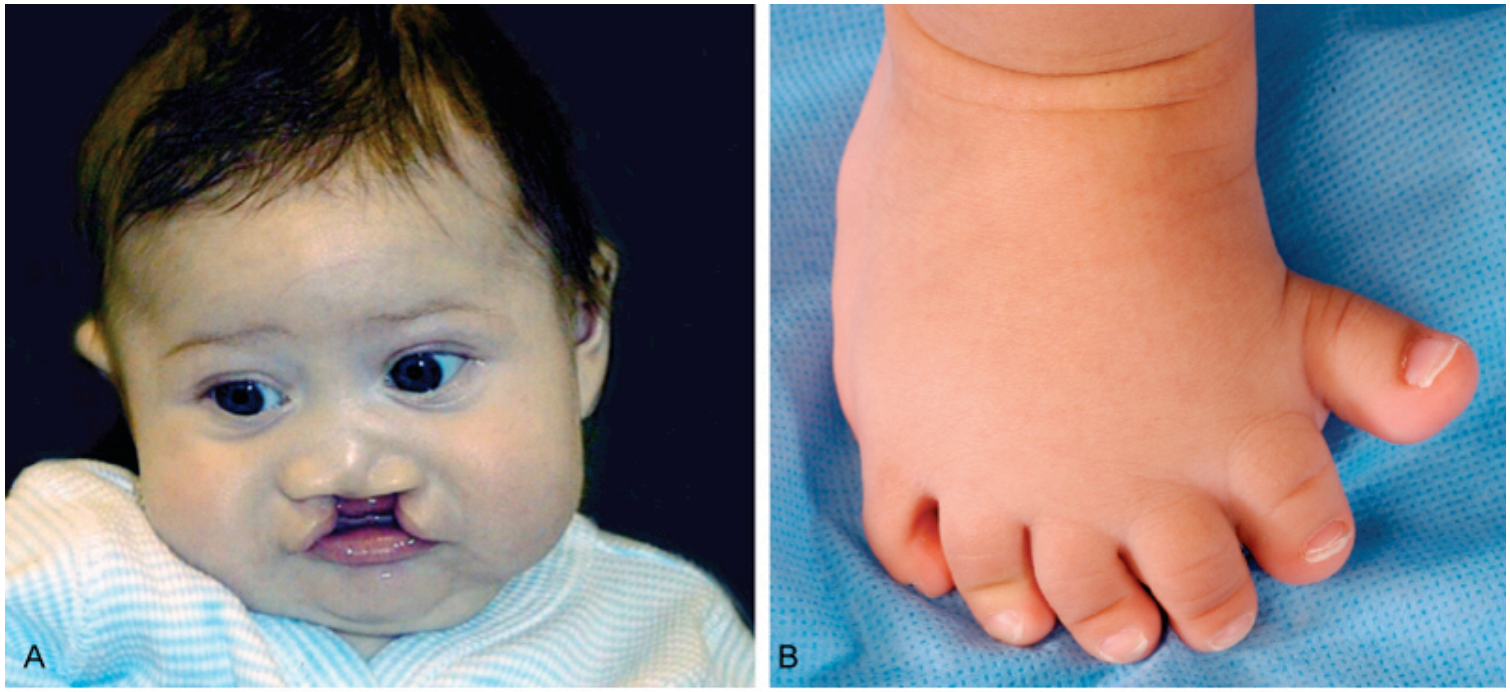
Hedgehog signaling pathway



Three ligands
Two receptors
One transducer (Smo)

Figure 05-23. Sonic hedgehog signaling pathway. The Sonic hedgehog sending cell synthesizes a precursor molecule that is cleaved into N- and C-terminal fragment, and cholesterol is added to the N-terminal fragment. The N-terminal fragment after secretion binds to Patched on the Sonic hedgehog receiving cell. This binding activates a signaling cascade involving Smoothened (which in the absence of the N-terminal fragment binding is inhibited by Patched) and a zinc (zn) containing Gli complex. Both Gli repressors and activators exist, and their relative amounts control which target genes are expressed in the presence and absence of Sonic hedgehog signaling.

Mutations that affect signaling pathways can have pleotropic effects



Shh Holoprosencephaly Polydactyly

Tgf-beta/BMP signaling pathway

Large family of ligands >20
Seven receptors
Five positive Smads

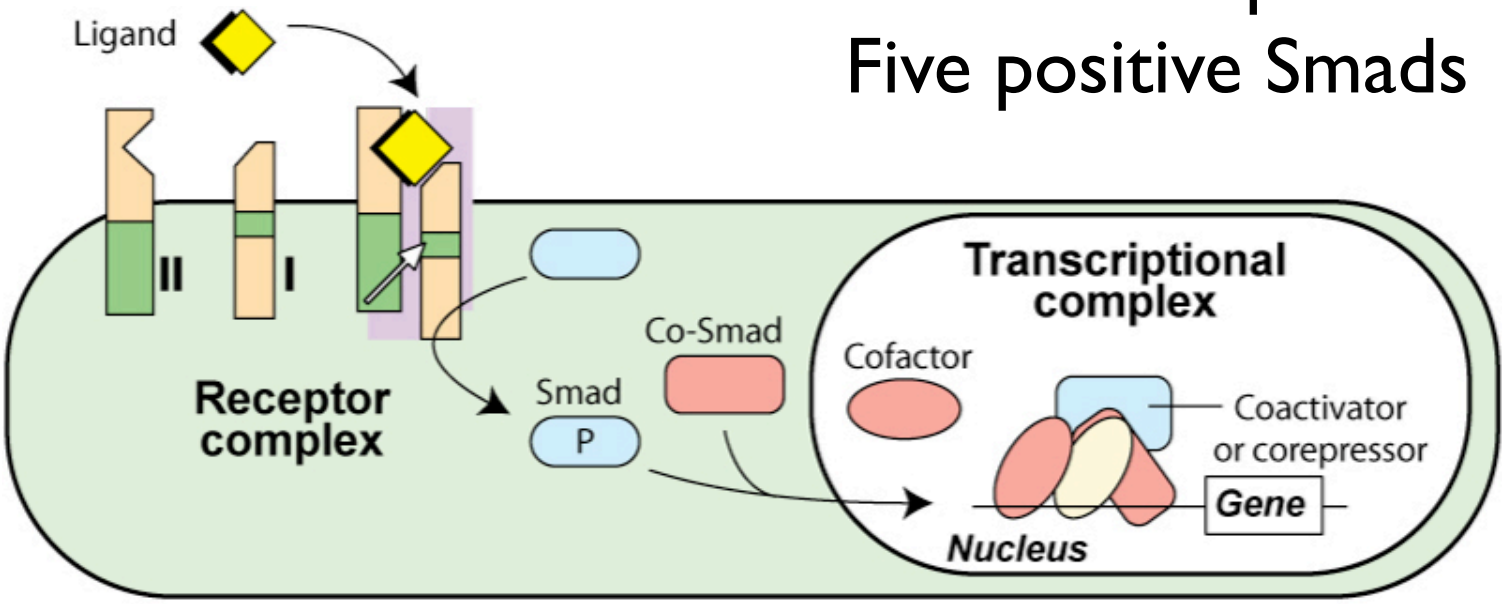
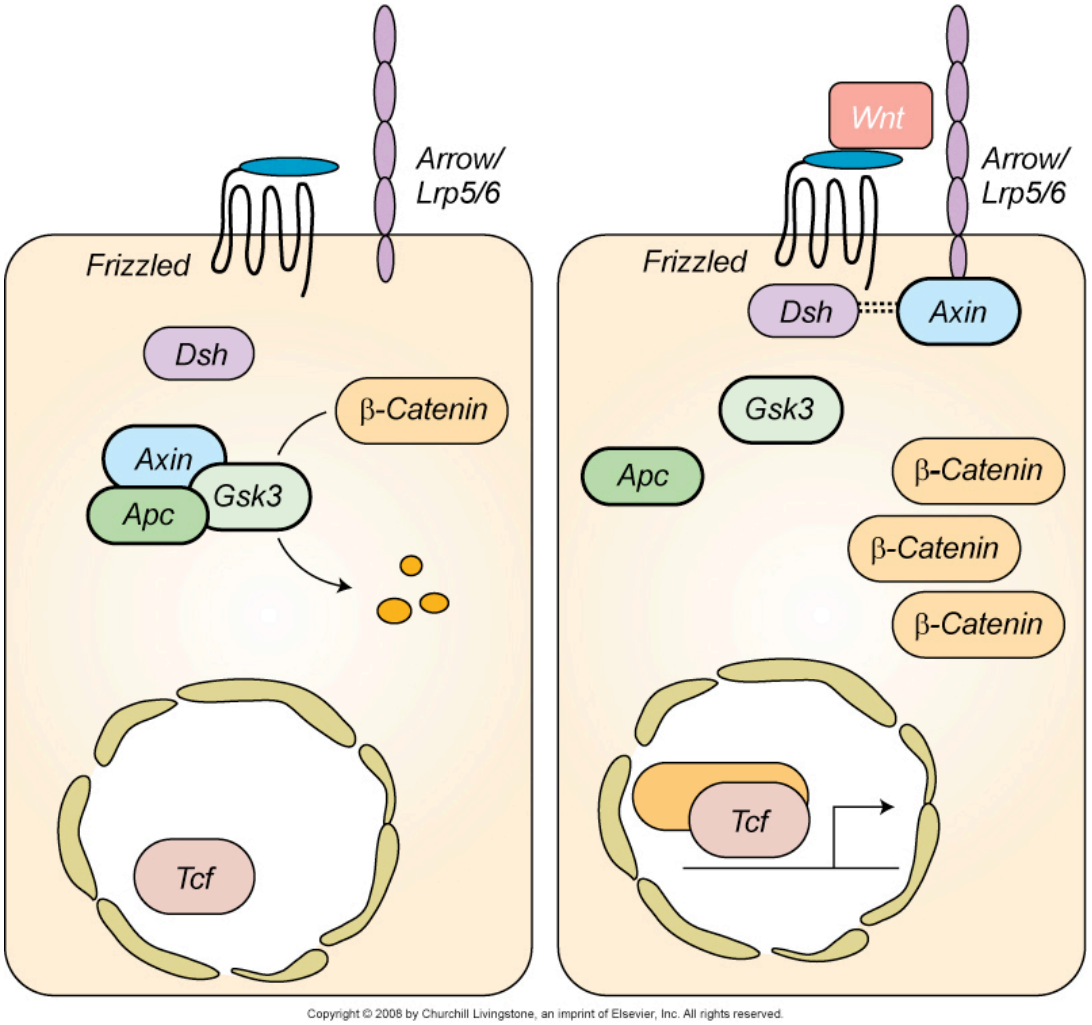


Figure 05-24. Tgf β signaling pathway. Ligand binding activates receptor dimerization and phosphorylation of Smads. Phosphylated Smads, along with Co-Smads, translocate to the nucleus to alter target gene expression.

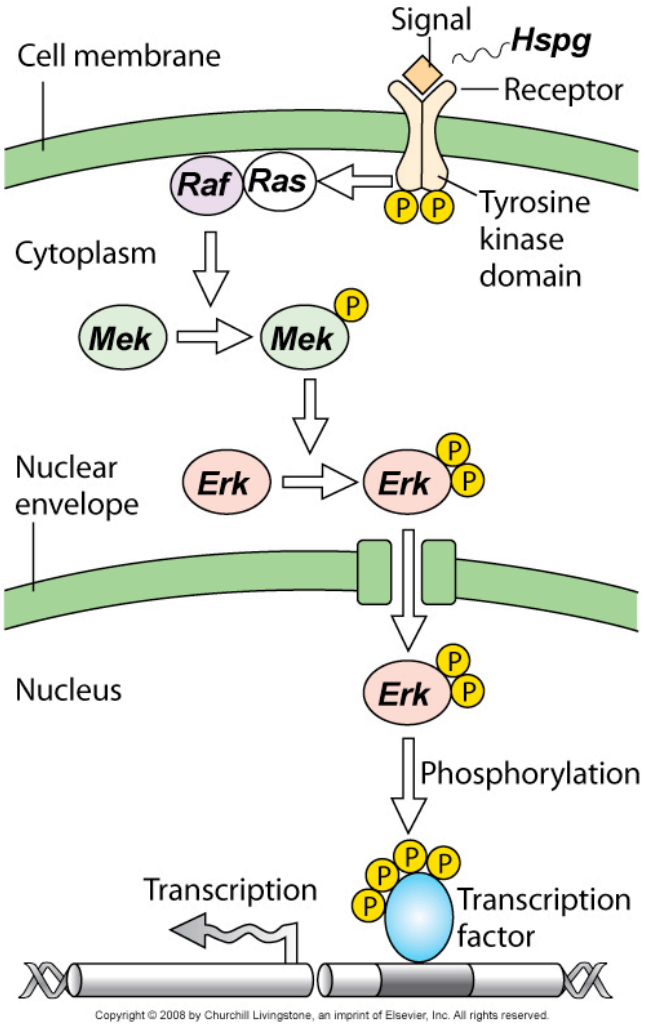
Wnt signaling pathway



Large family of ligands ~20
Multiple receptors

Figure 05-22. Canonical Wnt signaling pathway. In the absence of Wnt signaling (left), β-Catenin is degraded, but in the presence of Wnt signaling (right), β-Catenin accumulates and enters the nucleus, where in partnership with Tcf/Lef, gene expression is altered (i.e., Wnt target genes are activated). Arrow in nucleus indicates transcription.

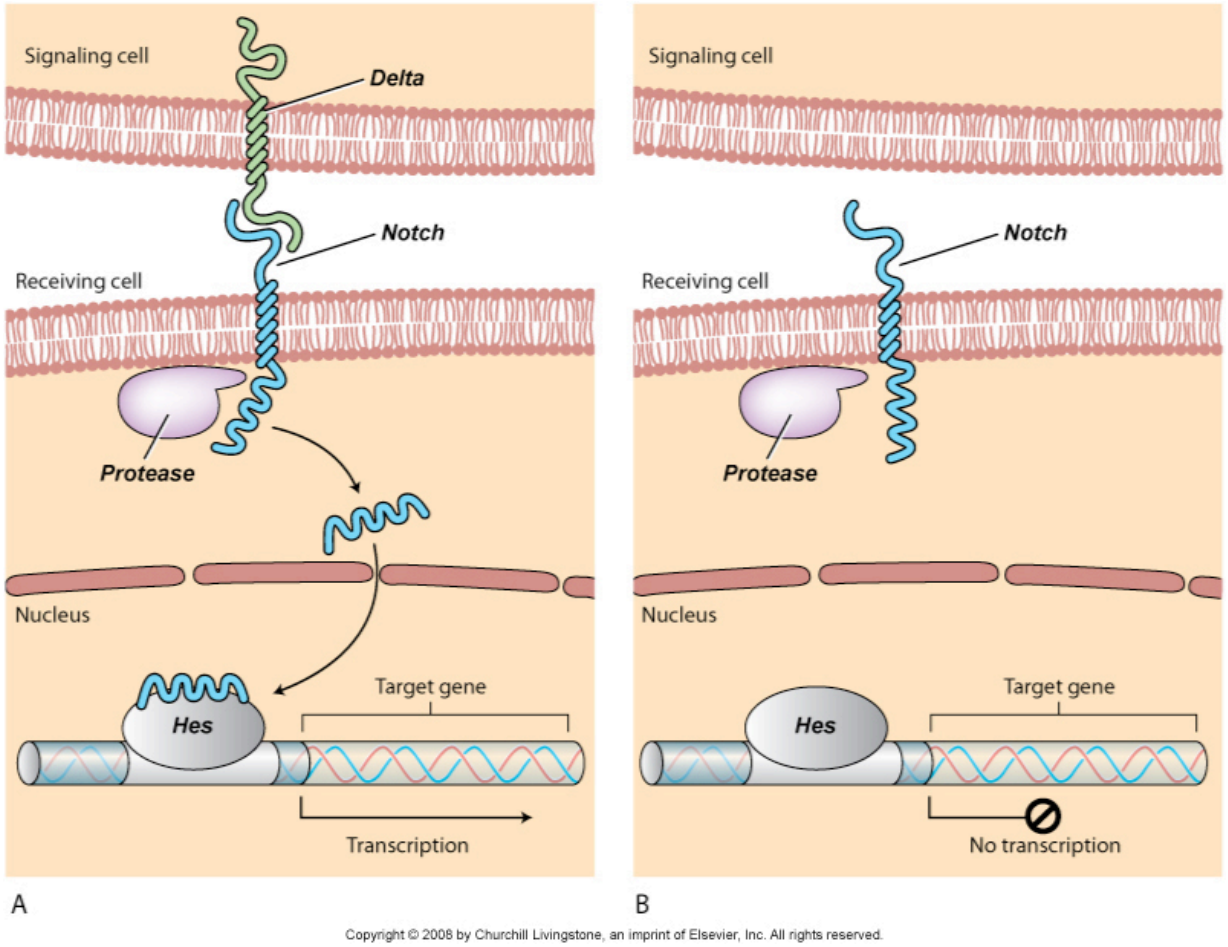
FGF signaling pathway



Large family of ligands ~20
Four receptors

Figure 05-25. Fgf signaling pathway. Fgfs bind to Fgf receptors aided by presentation of Heparin sulfate proteoglycan (Hspg). This activates Ras as well as a phosphylation cascade that sequentially phosphylates Raf, Mek, and Erk. Phosphylated Erk translocates to the nucleus, where it regulates target gene expression.

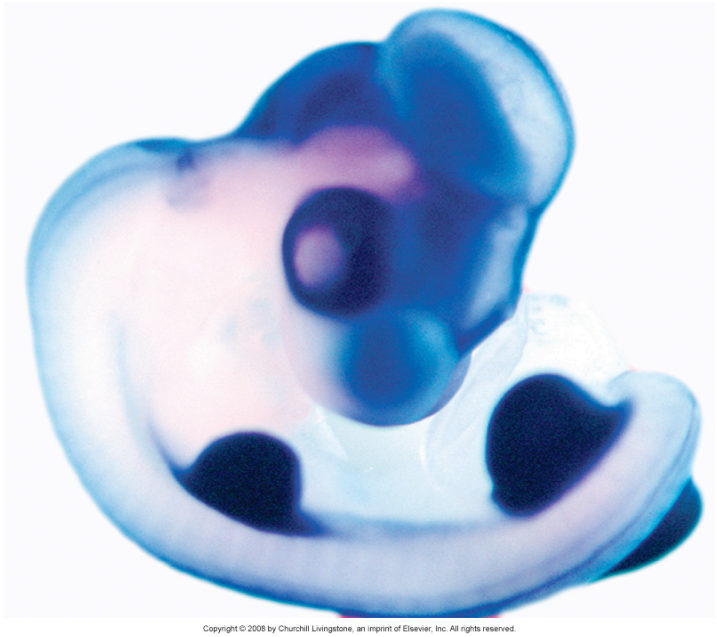
Notch/Delta signaling pathway



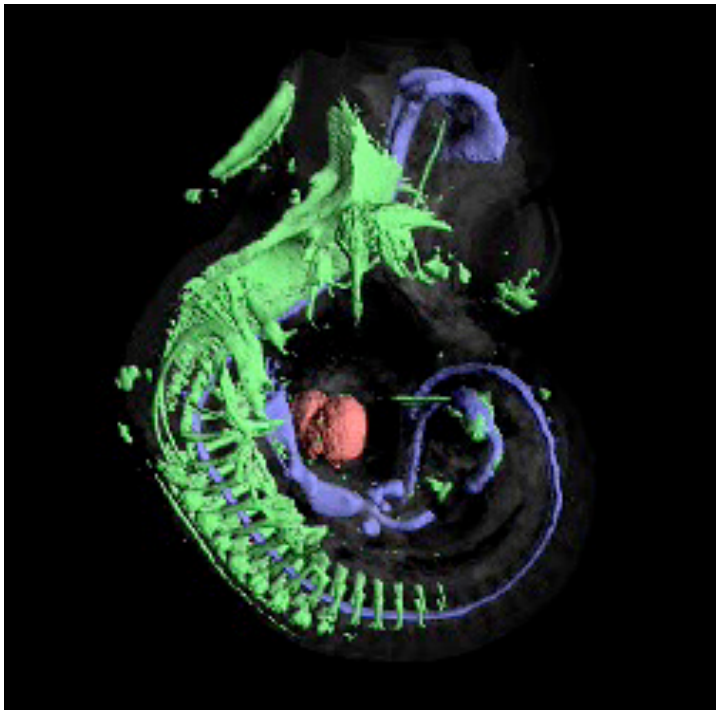
Small family of ligands
Four receptors

Figure 05-26. Notch signaling pathway. A, In the presence of a ligand such as Delta, Notch signaling occurs when the ligand produced by the signaling cell binds to a Notch receptor on an adjacent cell. Binding activates a protease that cleaves off a portion of the Notch receptor, which in turn translocates to the nucleus, where it regulates target gene expression in partnership with Hes. B, In the absence of a ligand such as Delta, Notch signaling does not occur and target genes are not regulated.

Visualizing gene expression patterns



In situ hybridization:
mRNA



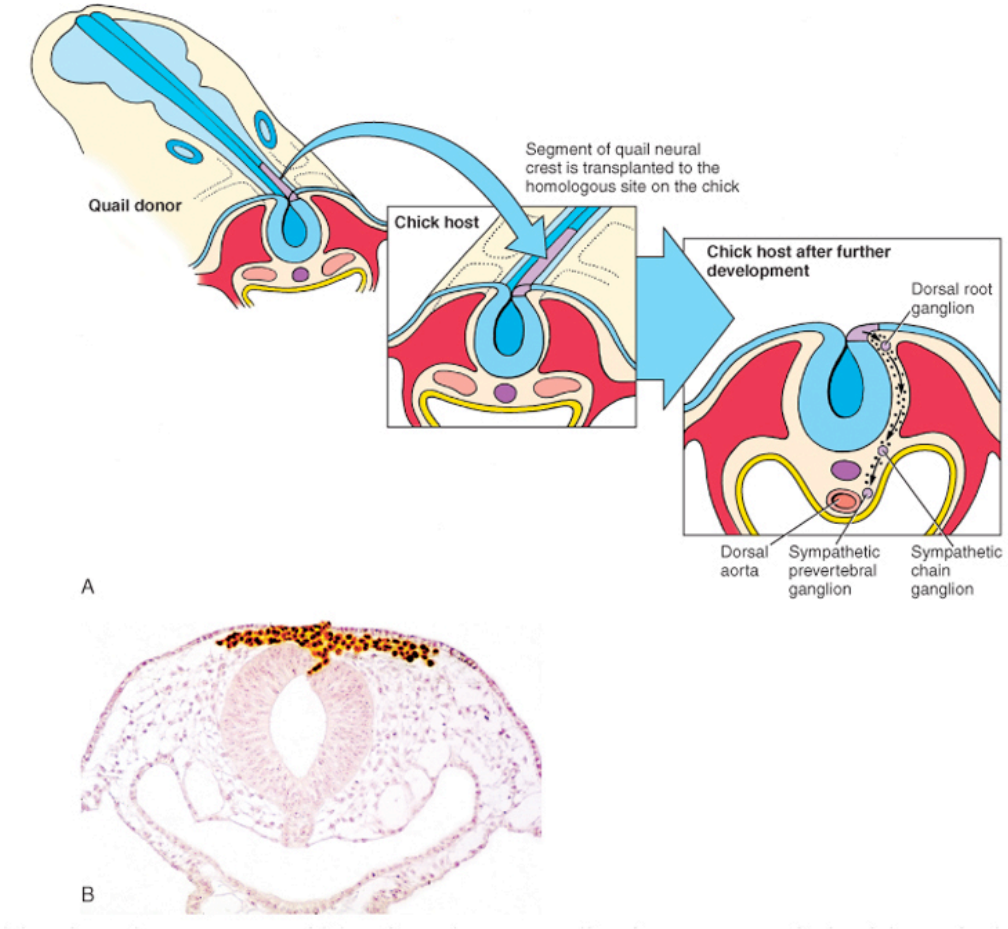
Immunostaining:
protein

Problems in Developmental Biology

- Differentiation: How do individual cell types form?
- Morphogenesis: How are cells organized into tissues?
- Medicine: How do errors in development lead to disease?

Fate mapping

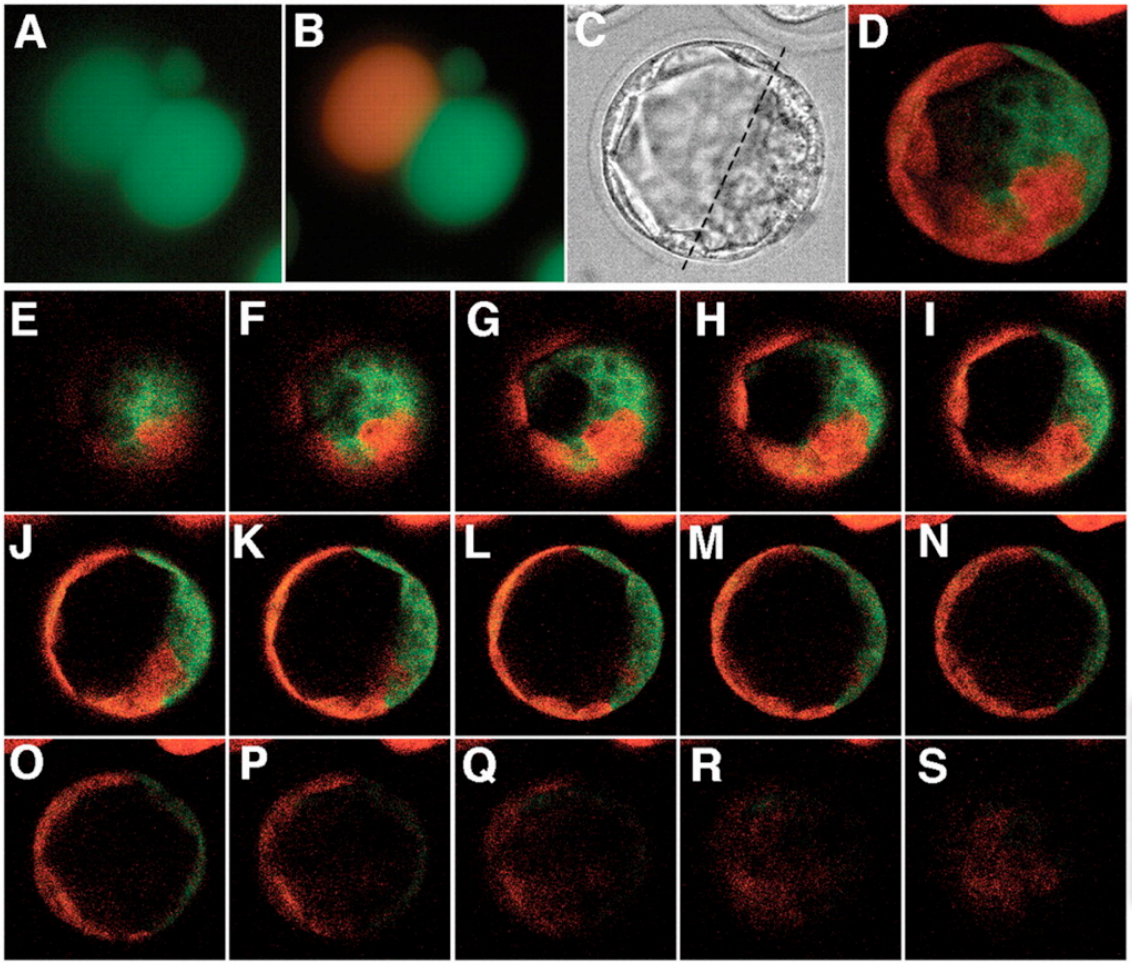
Tracing cell lineages during development

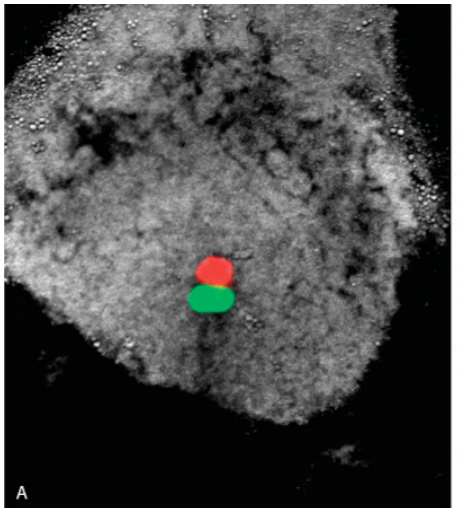


chimera analysis following tissue graft

Lineage tracing: dye labeling allows spatial resolution of cell populations

Lineage tracing of embryos developed in vivo after labeling a blastomere by photoconversion at the two-cell stage





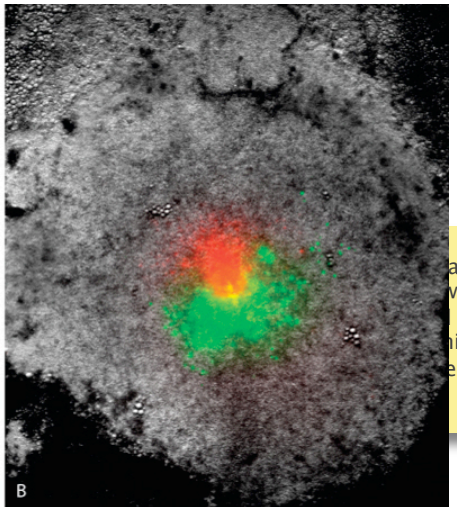


Fig. 3. Lineage tr
labeling a blasto
A two-cell blasto
labeled by photo
vivo to the blasto
regions are obse
distribution of la
scanning micros
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was
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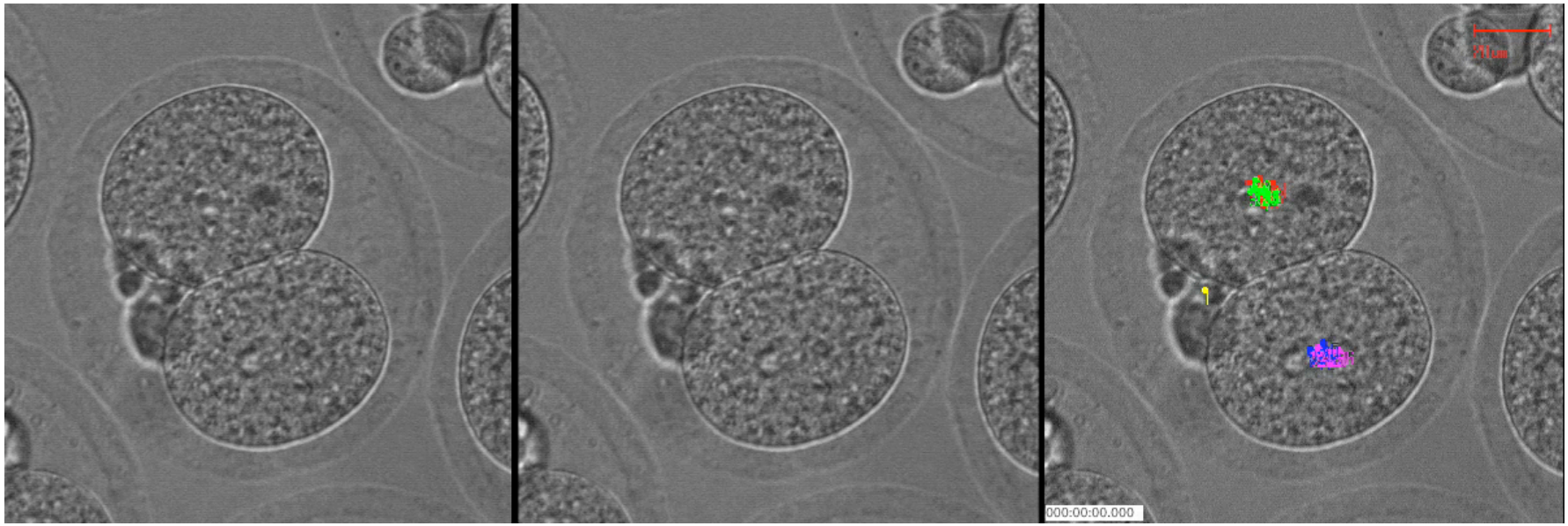
Kurotaki, Science 2007

Lineage tracing: movies allow us to follow dynamic cell behaviors within an individual embryo

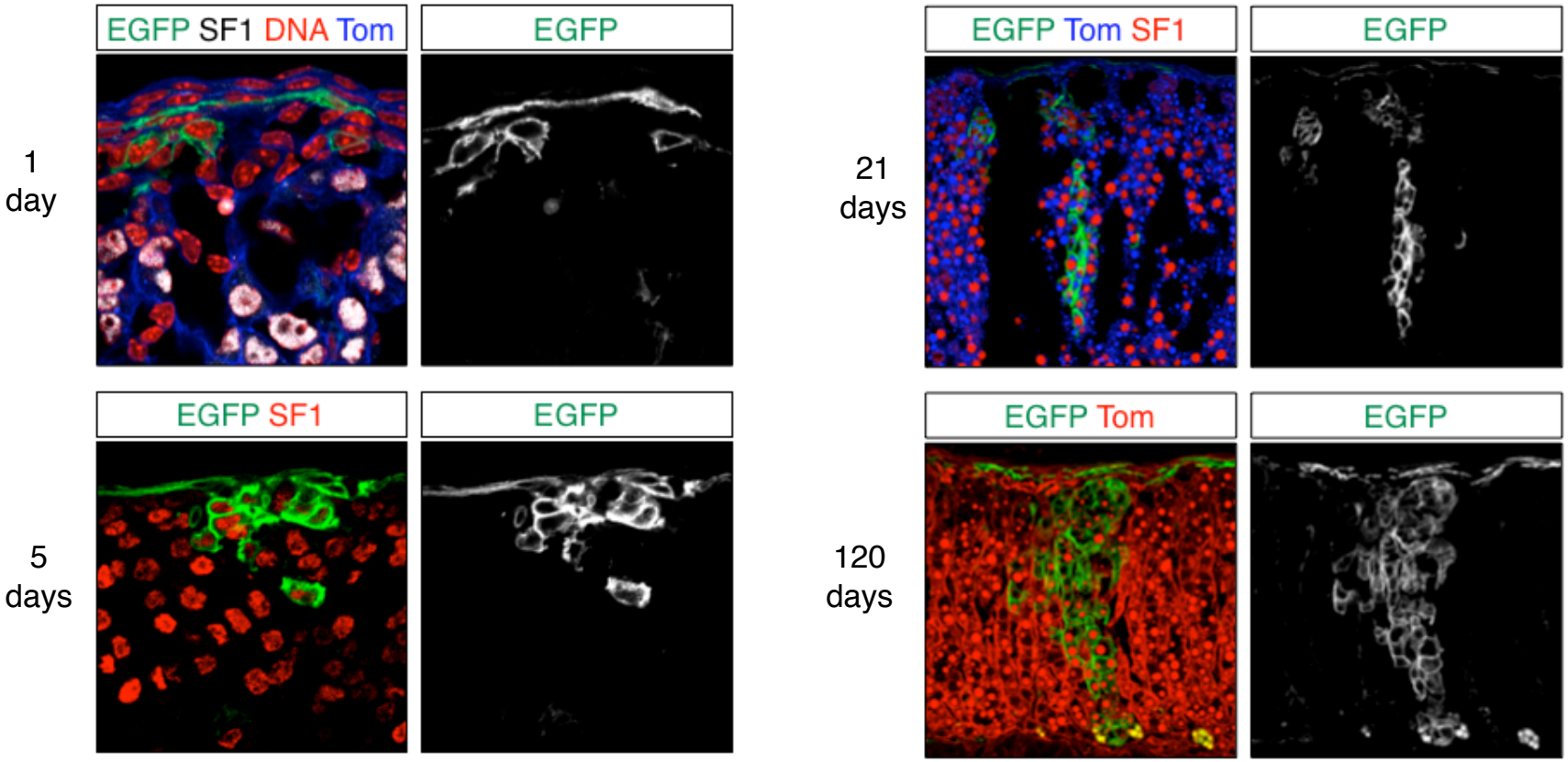
Lineage tracing of mouse embryo by videography from the two-cell stage; nuclei labeled with histone H2B-GFP



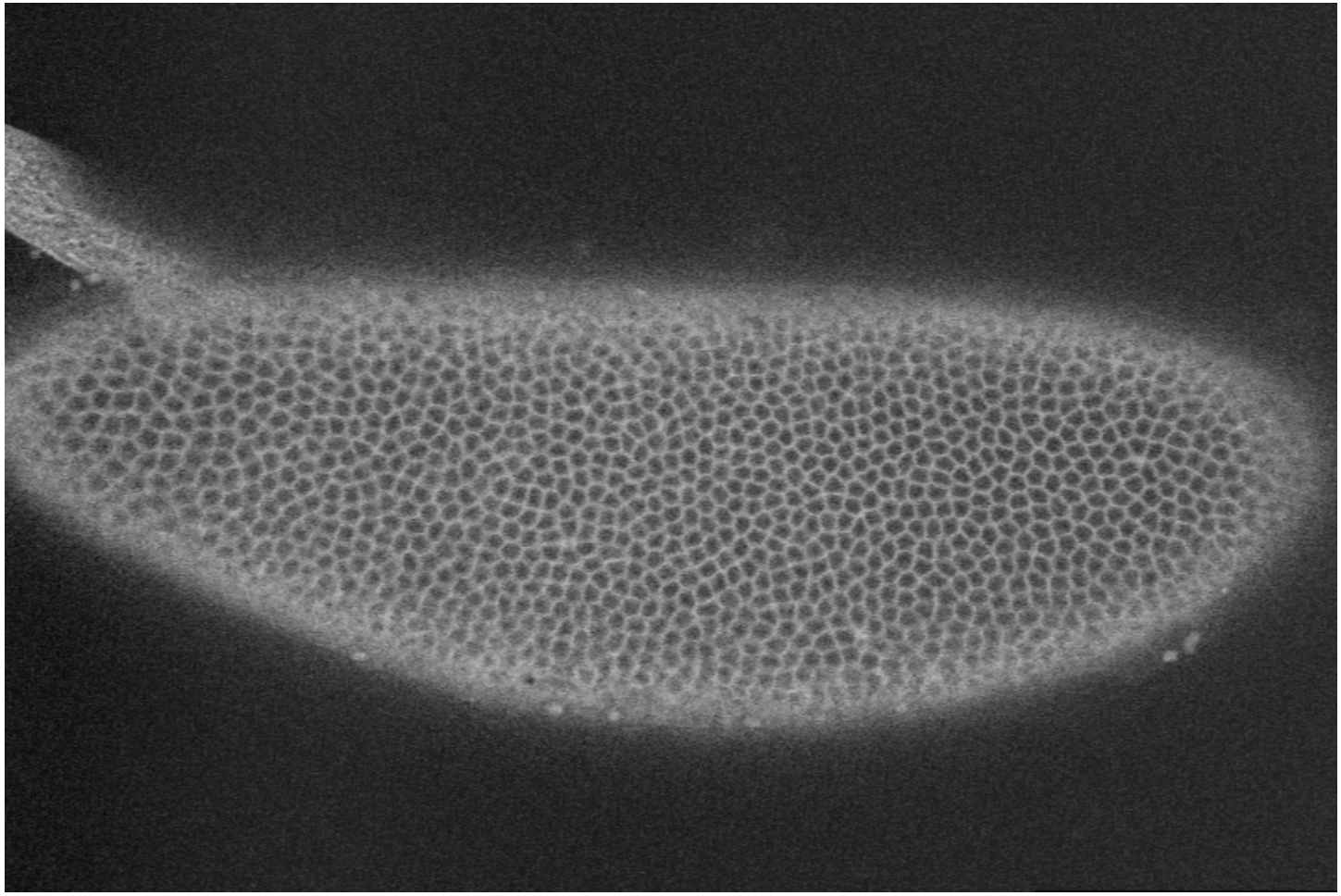
bright field nuclei lineages

Kurotaki et al., Science 2007

Lineage analysis: genetic marking can be used to follow cell fates for a long time

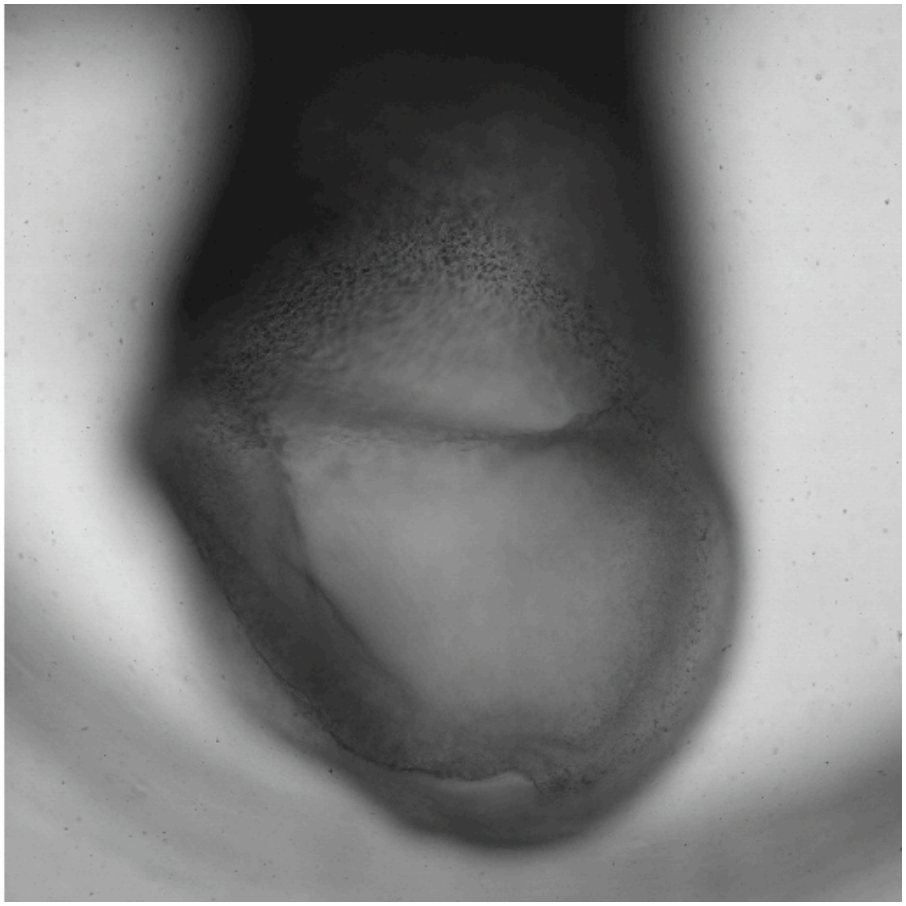


Morphogenesis



Cell movements and shape changes

Morphogenesis



Some developmental disorders are genetic

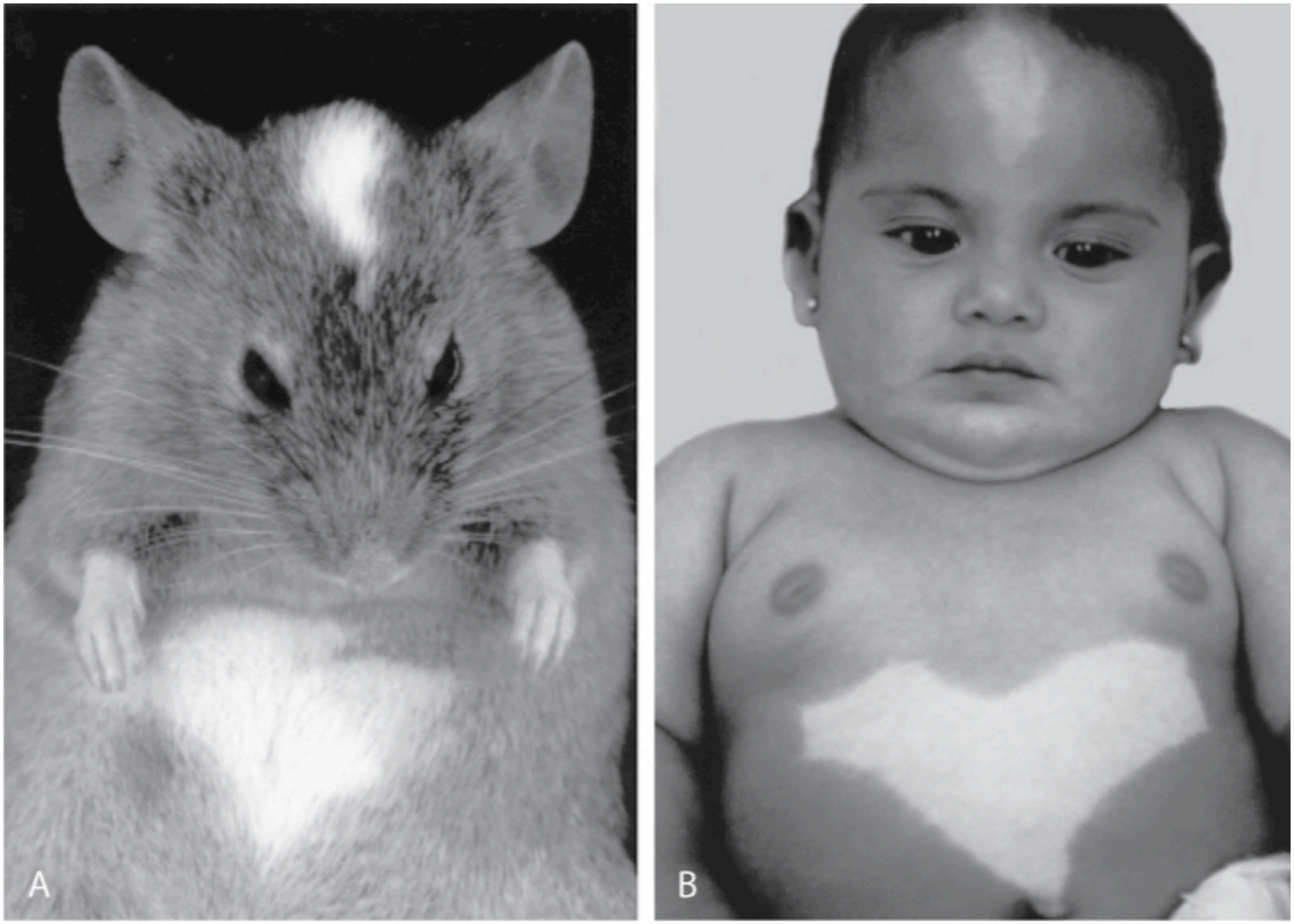
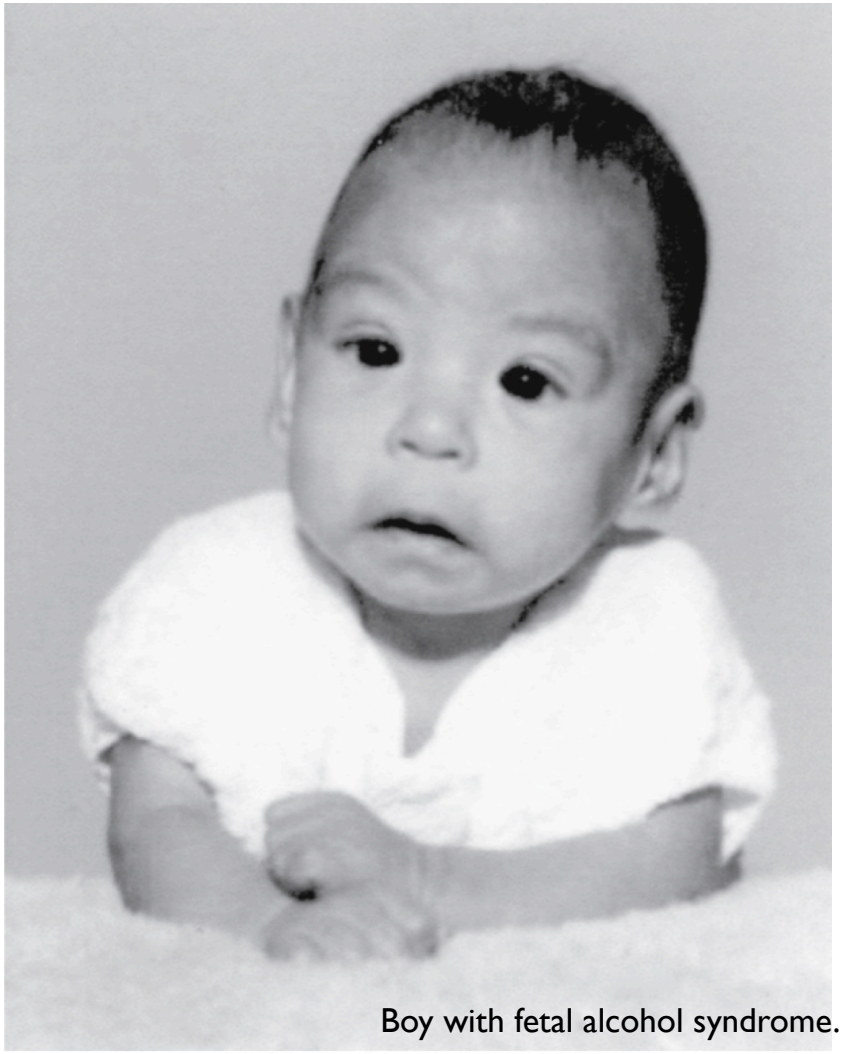
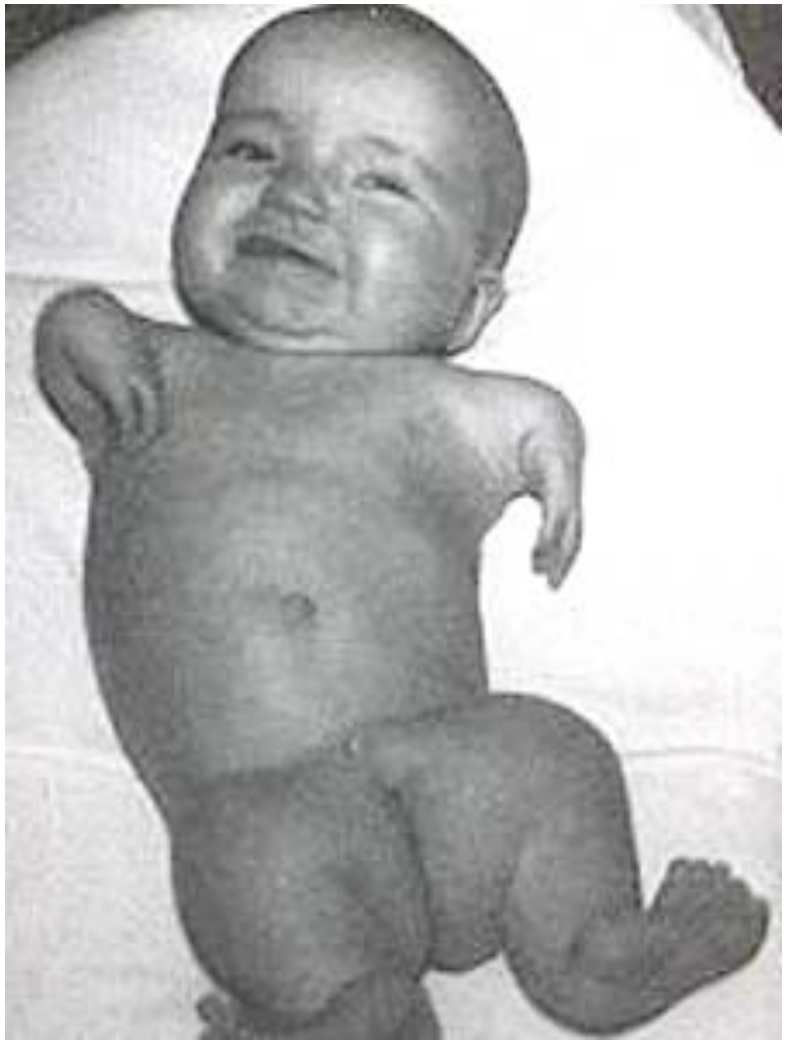


Figure 05-03. Animal models for disease can precisely phenocopy human diseases. A, Mouse with a mutation in the c-Kit gene shows pigmentation deficits on the forehead and chest. B, Child with a mutation in the c-Kit gene, a condition known as piebaldism, shows pigmentation deficits that are similar to those shown by the mouse model.

Some developmental disorders are caused by environmental insults



Boy with fetal alcohol syndrome.



Child exposed to thalidomide in utero