



### Human Development

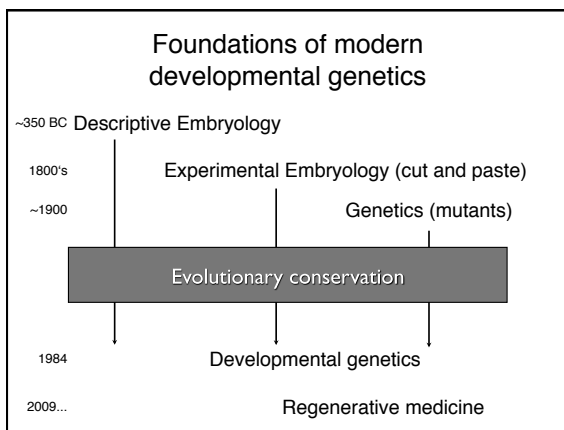


Ed Laufer, PhD [Course Director\\_elaufer@columbia.edu](mailto:elaufer@columbia.edu)  
 Ping Feng [Course Administrator\\_pf2013@columbia.edu](mailto:pf2013@columbia.edu)

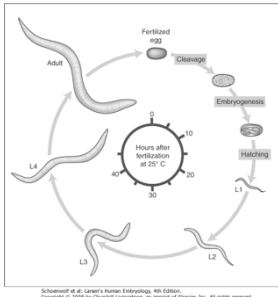


Michael Shen, PhD  
 Patricia Ducey, PhD  
 Michael Gershon, MD  
 Cathy Mendelsohn, PhD  
 Richard Schlusssel, MD  
 Lori Sussel, PhD  
 Lori Zeltser, PhD  
 Jeanine D'Armiento, MD, PhD

Lloyd Greene, PhD  
 Letty Moss-Salentijn, DDS, PhD  
 Jan Kitajewski, PhD  
 Deborah Yelon, PhD  
 Kimara Targoff, MD  
 Ben Ohlstein, MD, PhD  
 Wendy Chung, MD, PhD



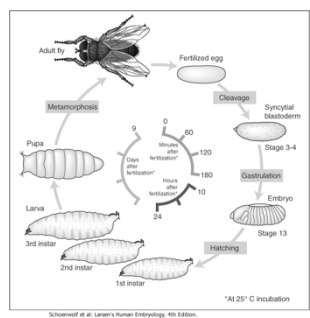
### *Caenorhabditis elegans*



Superb genetics  
 Fixed cell lineages  
 Rapid development

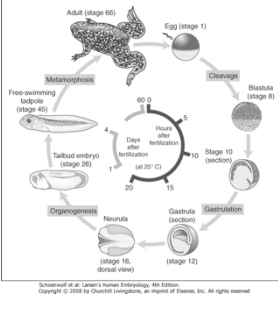
00132.013

### *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

Schoenwolf et al. Larner's Human Embryology, 4th Edition. Copyright © 2008 by Churchill Livingstone, an imprint of Elsevier, Inc. All rights reserved.

### Zebrafish (*Danio rerio*)

Transparent embryo  
Rapid development  
Good genetics

Schoenwolf et al. Larner's Human Embryology, 4th Edition. Copyright © 2008 by Churchill Livingstone, an imprint of Elsevier, Inc. All rights reserved.

### Mouse (*Mus musculus*)

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

Schoenwolf et al. Larner's Human Embryology, 4th Edition. Copyright © 2008 by Churchill Livingstone, an imprint of Elsevier, Inc. All rights reserved.

### Development of the embryo: from one cell to many

Fertilization      Preimplantation      Gastrulation and Patterning      Organogenesis and Growth

## Fate, determination, specification and lineage

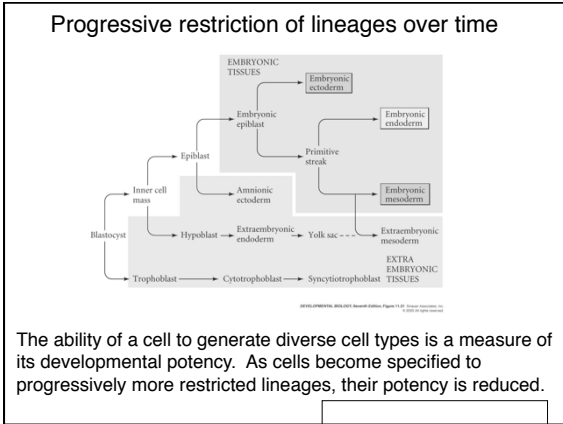
These are four related concepts having to do with cell identity.

- A cell's fate is defined as the cell types of its 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. 4.5 Tests for fate, specification and determination.** (a) The labelled region will normally contribute to the tail-dorsal part of the animal (fate). (b) When isolated this tissue will form a tail (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).

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

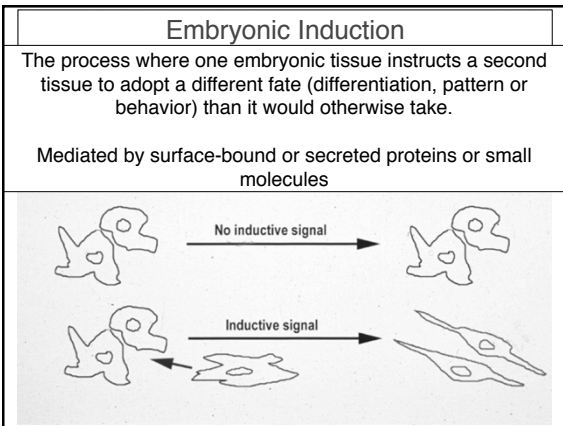


### Morphogenesis: the creation of ordered form

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.

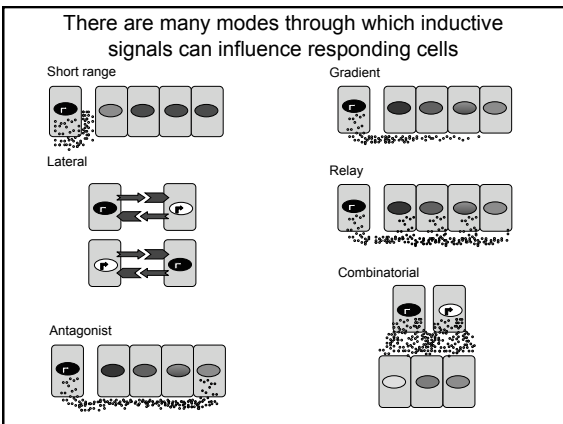


### Inductive signals can be permissive or instructive

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



### 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

<p><b>Secreted signals (long range)</b></p> <p><b>Hedgehog</b></p> <p><b>TGF<math>\beta</math>/BMP</b></p> <p><b>Wnt</b></p> <p><b>FGF</b></p>	<p><b>Membrane bound (short range)</b></p> <p><b>Notch/Delta</b></p> <p><b>Eph/ephrin</b></p>
--	---

### 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 fragments, 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 pleiotropic effects

Shh    Holoprosencephaly    Polydactyly

Copyright © 2008 by Churchill Livingstone, an imprint of Elsevier. All rights reserved.

### Tgf-beta/BMP signaling pathway

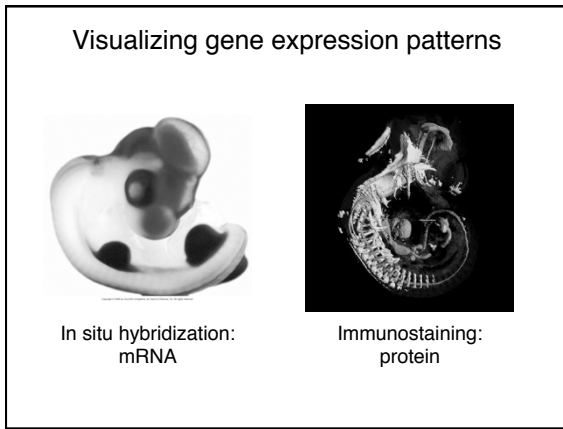
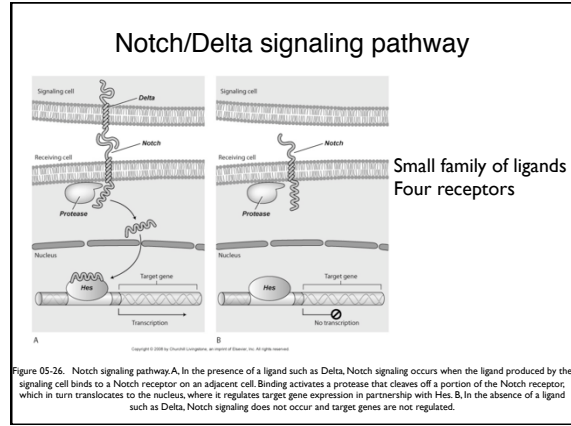
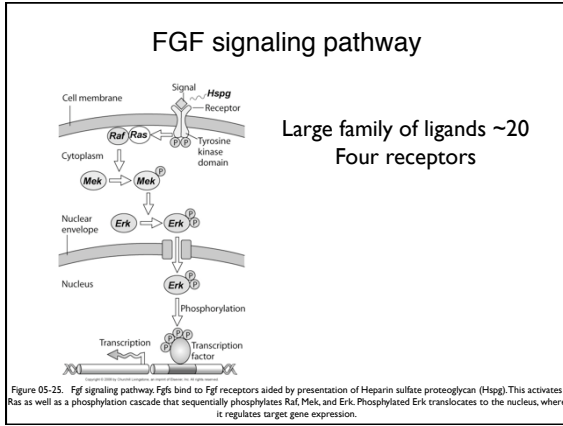
Large family of ligands >20  
Seven receptors  
Five positive Smads

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

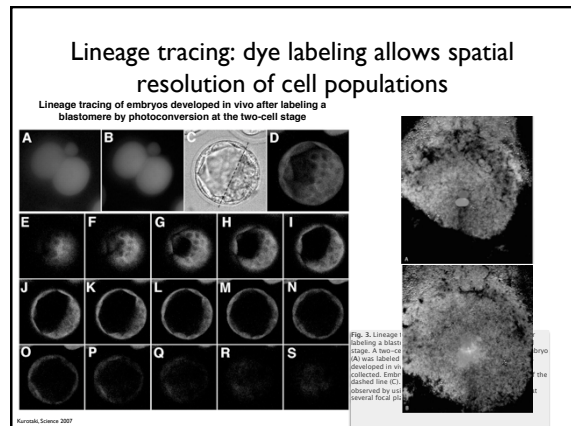
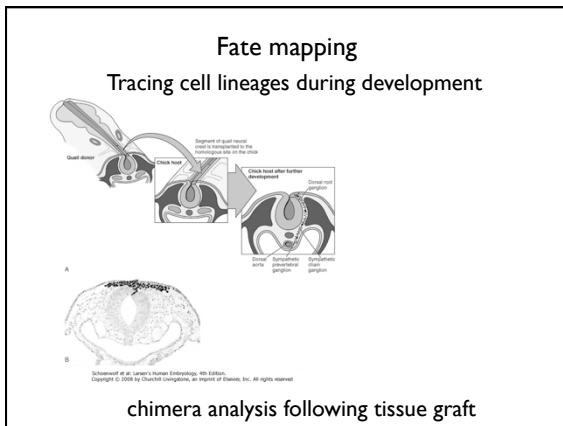
### Wnt signaling pathway

Large family of ligands ~20  
Multiple receptors

Figure 05-22. Canonical Wnt signaling pathway. In the absence of Wnt signaling (left),  $\beta$ -Catenin is degraded, but in the presence of Wnt signaling (right),  $\beta$ -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.

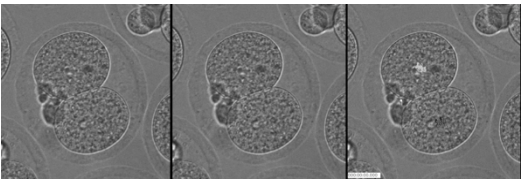


- ### Problems in Developmental Biology
- Differentiation: How do individual cell types form?
  - Morphogenesis: How are cells organized into tissues?
  - Medicine: How do errors in development lead to disease?



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

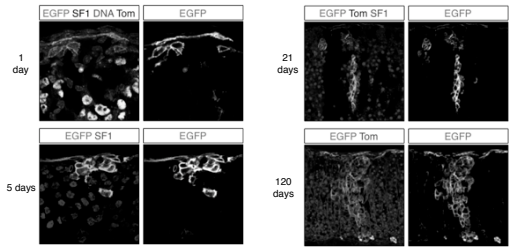
Lineage tracing of mouse embryo by videography from the two-cell stage; nuclei labeled with histone H2B-GFP



bright field      nuclei      lineages

Kurotaki et al., Science 2007

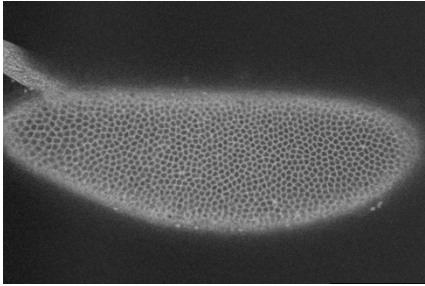
**Lineage analysis: genetic marking can be used to follow cell fates for a long time**



1 day      21 days

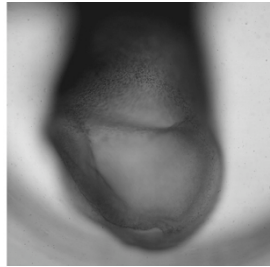
5 days      120 days

**Morphogenesis**



Cell movements and shape changes

**Morphogenesis**



**Some developmental disorders are genetic**



Copyright © 2008 by Elsevier Inc. All rights reserved.

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