1. What is the study of development?

• The process by which a fertilized egg transforms itself into a complex organism is one of the most exciting and complex mysteries in the field of biology! How does it happen?? Each of us sitting in this room developed from a single egg.

• Developmental Biology is the study of a PROCESS whereby a single cell divides and selectively activates expression of genes to produce a complex organism composed of many cell types.

• Ex ovo omnia=all from the egg. William Harvey (1651) was the first to propose that all animals originate from eggs.

• What are the types of PROCESSES required for development?

2. A central idea of development that we will talk about many times the rest of the semester is DIFFERENTIATION: ALL CELLS HAVE THE SAME DNA, BUT DIFFERENT CELLS EXPRESS DIFFERENT GENES.

Since different cell types express different genes, different cell types possess different cellular machinery. Different cells specialize to do different jobs. We will learn how this happens, how cells learn to activate different sets of instructions that lead to production of different proteins.

DIVERSITY: Earth's myriad animals & plants display an incredible diversity of body plans, and yet share many conserved developmental mechanisms, evidence of their evolution from a common ancestor. Our challenge is to understand both this diversity and this unity.

3. This PROCESS is studied using TOOLS, many of which you have already heard about in Bio202 and the first half of Bio205:

   a) Cell Biology - how cells are made, move, and talk to each other
   b) Genetics - what is the role of specific proteins? study the effect of mutations on developmental processes
   c) Molecular Biology - how cells selectively activate a subset of genes that will produce a unique set of cellular traits

What does this mean? You will now take your box of biological tools and use them to understand how development occurs.

Before we get into developmental mechanisms, let’s REVIEW THE BASICS

1. The body is made of millions to billions of cells.
   a) Each cell has a specialized task, e.g. muscle cell, nerve cell, etc.
   b) To carry out these specialized tasks, each cell has special machinery
   c) Nerve cell has machinery for transmitting electrical and chemical signals
   d) blood cell has machinery to transport oxygen
1. **Cellular machinery is largely made up of proteins**
   Proteins are long chains of amino acids. Each protein molecule has evolved to carry out a particular task. For example:
   i. hemoglobin in the blood binds to and carries oxygen
   ii. actin forms filaments that make up the cytoskeleton
   iii. ribosomal proteins help make up the ribosome, the cell's protein factory
   iv. insulin is secreted by cells of the pancreas and serves as a signal to other cells.

2. **Because of their different tasks, different cells contain different proteins**
   While some proteins are found in all cells (actin), others are made only in specialized cells
   i. e.g. muscles make myoglobin to store oxygen for work
   ii. lymphocytes make antibodies to neutralize foreign invaders
   iii. skin cells make cytokeratin which serves as the structural element of skin and hair

3. **Proteins are made up of chains or sequences of amino acids, and these amino acids are “encoded” in the cell’s DNA**
   a. DNA is organized in very large segments known as chromosomes, but each chromosome is a package of thousands of genes
   b. 1 gene encodes 1 protein
   c. Thus there is a myoglobin gene, an actin gene, an insulin gene etc. Genes are the instructions to make individual cellular machines.
   d. Mutations in single genes thus result in failure to produce single proteins, and mutant cells are thus lacking a particular protein machine

4. **All cells have the same DNA but different cells express different genes**
   a. Different sets of cellular instructions are activated in different cells, leading to the production of different proteins
   b. hemoglobin genes are only active in red blood cells
   c. the insulin gene only in the β-cells of the pancreas
   d. the pepsin gene only in stomach cells

5. **Development occurs at an unfamiliar scale.**
   • A mouse (3 inches = 7.5 cm = 750 mm) is about 100,000 times bigger than a cell-10-30 µm = 0.01-0.03 mm
   • A gene is 10,000 times bigger than a protein, which are generally 2-10 nm long = 0.001 µm = 0.000001 mm. A gene averages 1-10µm in length when unwound, but is only about 2nm wide when wound up with histones etc (it is extremely folded up to fit in cell since there are 15-30,000 genes per cell).

   **Another way to think of this**
   In other words if a mouse were the size of Chapel Hill (10 miles)
   • a cell would be about the size of a basketball (8 inches),
   • and a gene would be on average about an inch long.

   If a cell were the size of Chapel Hill (10 miles):
   • an average protein would be the size of a Volvo (10 feet)
   • an average gene would be about 1.5 miles long but the strand of DNA would only be a few feet wide.
DEVELOPMENTAL MECHANISMS AND THE EVOLUTION OF MULTICELLULARITY

1. Differentiation mechanisms- Two extreme models (REALITY INVOLVES BOTH!)
   a) MOSAIC DEVELOPMENT/autonomous specification: cells become progressively committed to particular cell fates: there’s no looking back! In other words, cells acquire fixed identities that they then maintain without influence from neighbors; when isolated their descendants only develop into particular parts of the body.

   Wilhelm Roux’s experiment (1888) illustrates this. He killed two of the first four cells in a frog embryo with a hot needle, and allowed the remaining cells to develop.

   WHAT HAPPENS? The remaining two cells adopt the fates they would have in an intact embryo.

   b) "REGULATIVE" DEVELOPMENT/conditional specification: cells are flexible and able to adjust to alterations in their neighbors and environment; when isolated their descendants can develop into an entire organism.

   Hans Driesch’s experiment (1892) illustrates this. Separate the first four cells in a sea urchin embryo by vigorous shaking.

   WHAT HAPPENS? To his surprise, rather than finding the same results as Roux. Instead of each cell developing into a specific part, each cell senses its neighbors absence and regulates its fate to make an entire embryo.

   c) Most organisms combine both sources of information and develop as a combination of mosaic and regulative processes.

2. Another way to state the basic question of Development is: How do cells know which genes to activate as they go through development?

   Remember, different cells of the embryo will activate different genes. There are two sources of information cells can consult to decide which developmental pathway to take. These are:

   a) Information from your mother (cell)- e.g. Gene expression patterns, or Segregation of "determinants". All cells receive information from their mothers.

      i. Informational molecules (e.g. protein or mRNA).
      ii. Inherited patterns of gene expression.
      iii. Information can be passed on uniformly, or can be segregated to one of the progeny cells.

      example: in worms the cells that will form the germline (to make new organisms) get P-granules and the other cells in the worm do not get P-granules. P granules are ribonucleoprotein complexes that act as translation regulators (complex members =RNA helicases, translation initiation factors). They are segregated to the posterior end of the zygote, and only end up in the P1 cell after the first cell division. In subsequent cell divisions, they continue to be asymmetrically segregated (see Fig. 8.44)

   b) Information from your neighbors or environment- e.g. cell-cell interactions. The essence of multicellularity = cells have neighbors, which communicate with each other. This communication can be local, via direct cell-cell contacts, or global, via diffusible molecules. Cell-cell interactions can serve to:

      i. maintain neighbors in the status quo
      ii. incite neighbors to novel behaviors.
      iii. These differences can then be transmitted to cellular offspring.
3. Even unicellular organisms communicate!
   Unicellular organisms have to sense their environment, to find food, avoid danger, and to find like individuals for sex. They have developed complicated mechanisms both to detect environmental cues and to communicate with neighbors, similar to those used by cells within a multicellular organism.
   a) Yeast sex- an example of simple cell-cell communication. Baker's yeast, *Saccharomyces cerevisiae*, normally lives as a single cell. Haploid cells have one of two mating types, "a" or "alpha". When two cells of opposite mating types meet, mating ensues to form a diploid.
      i. Each mating type produces a different diffusible signal (a sex hormone)
      ii. Each mating type produces a different cell surface receptor
      iii. Hormones are recognized only by cells of the opposite mating type, because only they have the correct cell surface receptors.
      iv. In response to these signals two haploid cells of opposite mating types are able to find each other and fuse to form a diploid cell.
   b) Single-celled Slime molds get it together.
   Slime molds exist as single amoeboid cells, foraging on the forest floor for their bacterial prey. However, when life gets tough, the amoebae aggregate into a tiny, multicellular slug that crawls about looking for a place to sporulate. A slug contains up to 100,000 cells! When the slug reaches a favorable site, its constituent cells differentiate, some forming a foot plate, some the stalk, and some the fruiting body and the spores. When conditions improve, the spores germinate to repeat the cycle. Aggregation occurs by chemotaxis- starving cells produce the signal cyclic AMP, which binds to cell surface receptors on other amoebae, triggering them to travel toward its source.

EMBRYOGENESIS
1. Similarities between vertebrate embryos is especially apparent early in development.
2. As embryos develop they become less like each other.

PRINCIPLES 1st proposed by Karl Ernst von Baer before Darwin

MODEL ORGANISMS USED TO STUDY DEVELOPMENT
1. To study development scientists use several different MODEL SYSTEMS.
   a. Why not just one? Because each model system has advantages and disadvantages for its use. Thus by having several a scientist can choose the model system that best suits her/his needs.
   b. We can use different model systems because developmental processes are shared by different organisms
   c. We know now that not only physical characteristics, but also specific molecules and their interactions with other molecules are shared among different model systems. For example: Wingless protein in the fly needed to make wings on a fly, and similar protein in the mouse used to help in limb development
   d. We classify model systems into invertebrate (worm, fly) and vertebrate (frogs, zebrafish, mouse) based on whether they have a backbone
2. A very brief introduction to six model systems widely used in labs today
   a. *Arabidopsis* advantages:
      i. its a plant!
      ii. small weed, member of the mustard family (cultivated members include cabbage, broccoli, cauliflower)
iii. cheap and easy to grow. Can fit thousands of plants into a small growth room indoors
iv. very short generation time for a plant: 6 weeks
v. history: most intensely studied model plant for past 15 years, genome completely sequenced, excellent genetics
vi. **DISADVANTAGE to Arabidopsis**: its a flowering dicot, so should study other model plants (ie. rice, corn, tomato, moss) as well if want to understand developmental processes specific to other types of plants (like monocots)

**DEFINE genome size**: megabase, gigabase

b. **Worm** (*C. elegans*) advantages:
   i. it is very small (adult = 1 mm long), so 10,000 worms can be kept on a Petri dish. They can be frozen for storage.
   ii. short generation time - 3 days from fertilization to adult. This makes genetic analysis easy because genes are passed from generation to generation.
   iii. embryo is transparent and develops outside the body in a short time - so can watch development in a microscope.
   iv. the adult has 1031 cells, and the lineage of each cell is known
   v. They are very cheap to keep.
   vi. **DISADVANTAGE to worms**: they are not vertebrates

c. **Fly** (*Drosophila*) advantages:
   i. small size (adult is less than 5 mm long). So, like worms, can keep large numbers (but hundreds not thousands) in a vial.
   ii. short generation time - 8 days from fertilization to adult. This makes genetics easy as for worms.
   iii. embryo develops outside the body in a short time - so can study development
   iv. lots of history - scientists have been doing genetics and getting mutations for many years (since 1910)
   v. They are very cheap to keep.
   vi. **DISADVANTAGE to flies**: they are not vertebrates

d. **Frog** advantages:
   i. they are vertebrates!
   ii. embryos develop outside the body in a short time - all of development to tadpole stage in 2-3 days
   iii. embryos are HUGE!! (can easily see with naked eye). So embryo manipulations are very easy. Thus many historical (and modern) experiments in cell fate, gastrulation movements, etc. have been done in frogs
   iv. relatively inexpensive because you can get lots of embryos from one female frog
   v. **DISADVANTAGE**: long time to sexual maturity, thus no genetics

e. **Zebrafish** advantages:
   i. they are also vertebrates!!
   ii. smaller than mice and frogs, larger than worms and flies. Each fish is about 2 inches long, can keep many in a tank
   iii. generation time is about 2 months, again longer than invertebrates but shorter than frogs, chickens or mouse. So can make mutations and screen.
   iv. embryo develops outside the body in a short time (24 hrs.) and is transparent - so development can be easily studied
   v. not so cheap as worms and flies but cheaper than mice
   vi. **DISADVANTAGE to zebrafish**: only recently used, so little history and genetics

f. **Mouse** advantages:
   i. they are also vertebrates!!
   ii. smaller than elephants, larger than worms, flies, zebrafish. Can keep 4 mice in a cage, many cages on racks in a room.
iii. generation time is relatively short, about 3 months, compared to chickens and frogs (2-3 years), so genetics can be done in the mouse

iv. lots of history - scientists have worked with mice for 100 years, and as long ago as ancient China the royalty had special mice with coat color mutations that they kept as pets and bred to keep the unique coat colors

v. there are lots of ways to change the genetic program in mice - we can introduce extra genes, or remove a specific gene, and study the effect on development

vi. **DISADVANTAGE to mice:** development inside the mother, hard to get at. expensive!
2. A very brief introduction to six model systems widely used in labs today
   g. Why model organisms? Kit example
   h. Megabase genome =1,000,000 (million) base pairs; Gigabase = 1 billion!

3. Rules of evidence
   There are three main types of evidence that are accepted in all of experimental biology
   when figuring out a gene’s function. It is important to KNOW THEM:
   • Correlative Evidence
     o You see a gene expressed in a tissue
     o Weak, but relatively easy
   • Loss of Function Evidence
     o You knock out the gene, the tissue fails to form.
     o Better, but a little harder.
   • Gain of Function Evidence
     o You express a gene in an inappropriate tissue, and transform it.
     o Best, but hardest of all
   Or to sum it all up, think of the motto: “Find it, Lose it, Move it”. [but use the formal terms
   above in an exam situation!!]