Lecture 1. MCB 141. S15. Tu Jan 20.

1. Overview of course. Profs Levine, Gerhart, Harland will present three sequential modules, each consisting of 8 or 9 lectures. There will be a midterm at the conclusion of each module.

2. The grad student instructors are: Rachel Kjolby and Jo Downes. They will run the discussion sections, but there are no sections this week. The discussion sections will begin next week, the week of Jan 26.

3. Your grade will be based on a total of 500 pts: 100 pts for each midterm, 100 pts for a comprehensive final, and 100 pts for participation and quizzes in the discussion section. Note that the final exam period will consist of two parts. Midterm 3 (100 pts) followed by the comprehensive final (100 pts).

4. The exam questions stem from material covered in class during the lectures. Recommended reading is intended to reinforce the information presented in class. We strongly advise you to attend the lectures and not rely on notes from other students.

5. The first set of lectures will focus on developmental processes in invertebrates, mainly insects, with an emphasis on mechanisms of differential gene expression. Profs Gerhart and Harland will present lectures on signaling processes in vertebrate embryos, stem cells, and organogesis.

6. Differential gene expression is the central foundation for our understanding of developmental biology. Most animals, from the lowly nematode soil worm to humans--the crown and summit of the animal kingdom—contain roughly 20,000 genes. These 20,000 genes appear to be regulated in increasingly more sophisticated ways as we move up the tree of animal life.

7. Differential gene expression usually refers to the synthesis of a protein in one cell type but not another. For example, the Hemoglobin protein is present in our red blood cells where it is essential for transporting oxygen. It is composed of two polypeptide subunits, alpha and beta. These are encoded by separate alpha-globin and beta-globin genes. Both genes are present in all 200 cell types of your bodies. But they are active, or expressed, only in red blood cells.

8. Most often, but not always, expression means transcription. Alpha and beta globin messenger RNAs are produced only in developing red blood cells and not in any other tissues. I will use the rest of the time today and the Thurs lecture to discuss the basis for differential gene expression during animal development. But first I want to summarize the evidence that all tissues contain the same set of genes, an invariant genome, also called nuclear equivalence.

9. The first compelling proof for nuclear equivalence came from studies by Gurdon in Xenopus. He was able to obtain a frog from an enucleated Xenopus egg injected with the diploid nucleus of an adult gut cell. This result showed that the differentiated intestinal cell retained the complete Xenopus genome, capable of producing all of the tissues of an adult frog.

10. A similar experiment was done with sheep, using the nucleus of a fibroblast cell from an adult. The most recent evidence for nuclear equivalence comes from the generation of iPS cells, induced pluripotent stem cells. It is now possible to convert just about any differentiated cell type into any other cell type using iPS cells.

11. The blastocysts of mammalian embryos, including human embryos, contain ~30 ICM (inner cell mass) cells. These 30 cells give rise to all of the tissues of adults during embryogenesis. Each ICM cells is said to be pluripotent. It can give rise to just about any cell type. ICM cells can be harvested and cultured, producing large quantities of pluripotent stem cells.

12. Earlier studies identified about 30 different transcription factors that are active in the ICM cells of blastocysts. Takahashi and Yamanaka showed that 3 of these are particularly important for the formation of ICM cells: Oct4, Sox2, and Nanog. The forced expression of the three genes encoding these transcription factors causes the transformation of any adult cell types into iPS cells, which are comparable to the normal ICM cells of blastocysts.

13. For example, expression of Oct4, Sox2, and Nanog in adult skin cells converts ("reprograms") them into iPS cells. Cultured iPS cells can then be injected into the blastocysts of normal mice, where they have been shown to function as normal ICM cells and form the different tissues of adult mice. The competence of adult cell types to be transformed into iPS cells, which in turn, can produce any tissue is a clear demonstration of nuclear equivalence. So, all of our tissues contain the same set of genes, but possess distinct morphologies and functions due to differential gene activity.

14. How do transcription factors such as Oct4, Sox2, and Nanog control development? They do so by binding to enhancer DNAs, which switch associated genes on and off. Enhancers are typically 500 bp in length and contain multiple binding sites for at least two different classes of transcriptional activators. They can work over very long distances to activate gene expression. For example, the ZRS enhancer of the mammalian sonic hedgehog gene maps approximately one million base pairs away from the promoter of the gene. Despite this distance, the ZRS is essential for the expression of sonic hedgehog in developing limbs.

15. Recent whole-genome studies suggest that the human genome is riddled with enhancers, with estimates ranging from 250,000 to over a million enhancers. This means that a typical gene in your genome is regulated by something like 10-40 different enhancers. As I said earlier, there is no correlation between gene number and organismal complexity. Simple worms contain the same number of genes as humans. It is possible that complexity scales with the number of enhancers. Humans appear to contain significantly more enhancers than worms.