

**Critical Thinking in Genetics and Genomics**  
**Spring 2005**  
**GMS GE 705**

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This class is designed to chronologically follow the development of a field of study in genetics to allow students to explore the logical evolution of a coherent line of scientific inquiry. The individual meetings build on the background studies discussed in previous meetings, examine apparent discrepancies in experimental results, critique the approaches employed by the authors, and consider the logical follow-through experiments for the results at hand.

The first class serves as an overview of the areas generally relating to the cell cycle, the field of focus in this class. Subsequently, we deal with papers on normal cell cycle regulation, regulation of DNA synthesis, responses to DNA damaging agents, and other aspects of checkpoint regulation. Throughout these studies, we emphasize the connection between oncogenes and tumor suppressor genes in cell cycle regulation to cancerous misregulation. For each paper, the students go through the exercise of formulating a new hypothesis and suggesting experiments to test these hypotheses. Often, hypotheses that the students formulate are tested in the subsequent papers that we read, which allows the students to be more engaged in understanding the progression of the field. Utilizing these methods, the students become proficient in carefully thinking about a complete body of scientific research and in addressing critical questions that arise from this type of global analysis of a field.

Students are evaluated based on their performance in paper presentations, contributions to in class discussions, written weekly homework, and a mid term assignment. The weekly writings ask the student to identify and to critically examine the papers' initial hypotheses and the scientific approach the authors took to test this hypotheses. After analyzing these elements of the scientific method, the students revise the initial hypothesis and propose experiments to test it. Furthermore, the mid term assignment consists of students analyzing papers with apparently contradictory conclusions (see week 5 readings) and suggesting experiments to resolve the discrepancy. The details for the individual meetings follow.

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**Week 1**

Introduction to cell cycle, DNA replication and DNA damage responses.

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**Week 2**

CSF1 regulates novel cyclins during the G1 phase of the cell cycle. *Cell* 65, 701-713 (1991)

Overexpression of mouse D-type cyclins accelerates G1 phase in rodent fibroblasts. *Genes Dev.* 7, 1559-1571 (1993)

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**Week 3**

The retinoblastoma protein is phosphorylated during specific phases of the cell cycle. *Cell* 58, 1097-1105 (1989)

Functional interactions of the retinoblastoma protein with mammalian D-type cyclins. *Cell* 73, 487-497 (1993)

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**Week 4**

Expression of transcription factor E2F1 induces quiescent cells to enter S-phase. *Nature* 365, 349-352 (1993)

Regulation of the cyclin E gene by transcription factor E2F1. *PNAS* 92, 12146-12150 (1995)

Ectopic Expression of Cdc25A Accelerates the G1/S Transition and Leads to Premature Activation of Cyclin E- and Cyclin A-Dependent Kinases. *Mol Cell Biol.* 19, 6183-6194 (1999)

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**Week 5**

Growth regulation of a cellular tumour antigen, p53, in non-transformed cells. *Nature* 308, 199-201 (1984)

Microinjection of monoclonal antibody to protein p53 inhibits serum-induced DNA synthesis in 3T3 cells. *PNAS* 79, 6309-6312 (1982)

WAF1, a potential mediator of p53 tumor suppression. *Cell* 75, 817-825 (1993)

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**Week 6**

Cell type-specific responses of human cells to inhibition of replication licensing. *Oncogene* 21, 6624 - 6632 (2002)

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Human replication protein Cdc6 prevents mitosis through a checkpoint mechanism that implicates Chk1. EMBO 22, p704-712 (2003)

Human replication protein Cdc6 is selectively cleaved by caspase 3 during apoptosis. EMBO Reports 3, 780-784, (2002)

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### **Week 7**

Inactivation of Cdc7 kinase in mouse ES cells results in S-phase arrest and p53-dependent cell death. EMBO 21, 2168-2179 (2002)

Stability, chromatin association and functional activity of mammalian pre-replication complex proteins during the cell cycle. EMBO 20, 4263-4277 (2001)

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### **Week 8**

Human ORC large subunit is degraded by ubiquitin-mediated proteolysis after initiation of DNA replication Molecular Cell 9, 481-491 2002

Defective S-phase chromatin assembly causes DNA damage, activation of the S-phase checkpoint, and S-phase arrest. Molecular Cell 11, 341-351 2003

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### **Week 9**

Dual Mode of Degradation of Cdc25A phosphatase. EMBO 21, 4875-4884 (2002)

Tip60 is targeted to proteasome-mediated degradation by mdm2 and accumulates after UV irradiation.

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### **Week 10**

Polo Like kinase-1 is a target of the DNA damage checkpoint. Nature Cell Biology 2, 672 (2000)

Multiple centrosomes arise from tetraploidy checkpoint failure and mitotic centrosome clusters in p53 and Rb pocket protein-compromised cells. PNAS 99, 9819-9824

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### **Week 11**

S-phase-specific interaction of the Fanconi anemia protein FANCD2 with BRCA1 and Rad51. Blood 100, 2414 (2002)

Interaction of FANCD2 and NBS in the DNA damage response. Nature Cell Biology 4, 913 (2002)

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