Tumor Suppressor Genes and Oncogenes
(Biochemistry/Molecular Biology Small Group)

OBJECTIVES
- Describe the differences between tumor suppressor genes and oncogenes, and give three examples of each.
- Describe the concepts of Knudson’s two hit hypothesis and multi-step carcinogenesis.
- Explain the basic biological differences, at a molecular genetic level, between cancers that occur in early childhood and those that occur in adults.
- Explain the difference between the pattern of inheritance of an inherited cancer at the physical level versus at the cellular level.
- Explain how to differentiate between sporadic and germline forms of retinoblastoma.

REQUIRED READING
Students should read the following syllabus sections before attending the small group discussion:
- Cell Proliferation and its Regulation
- Genes that Prevent and Cause Cancer: Tumor Suppressor Genes and Oncogenes

QUESTION 1
As scientists study the DNA changes seen in cancer cells, we have learned that certain genes are altered in many adult tumors. Among the genes that are commonly affected are genes encoding p53, cyclin D, Rb, p16, myc, and an EGF receptor (her2/neu). We have also learned that certain types of alterations are associated with each of these genes. For example, some of them are commonly activated while others are often inactivated.

a) What affect do each of the above gene products have on the cell cycle?
   (suggestion: Draw a schematic of the cell cycle and indicate where each gene product functions.)

b) Which of the genes named above are likely to be activated in cancers and which likely to be inactivated? What mechanisms are involved in activating or inactivating these genes?

QUESTION 2
Virtually all cases of retinoblastoma (both hereditary and sporadic) occur in children younger than six years of age. In contrast, colon cancer is rare under the age of 20. Even children who have the hereditary form of retinoblastoma cease
to be at risk for retinal tumors around the age of six, but they are at high risk of developing osteosarcoma throughout their lives.

a) How do the tumors arise in patients with retinoblastoma vs. with hereditary colon cancer? What does the difference in age of occurrence of retinoblastoma and colon cancer suggest about the underlying biology of these cancer types?

b) Why might there be an upper age limit for retinoblastoma?

c) The inherited form of retinoblastoma has an autosomal dominant pattern of inheritance (e.g. by pedigree analysis), yet mutations that inactivate tumor suppressor genes like Rb are recessive at the cellular level. How can the pattern of inheritance (phenotype) be dominant while the inherited mutation (genotype) is recessive? How could this also apply to dominantly inherited familial forms of colon cancer?

QUESTION 3
A 5-year-old boy, Nathan, was diagnosed with bilateral retinoblastoma at the age of 8 months. He was treated by enucleation of his right eye and cryotherapy of the tumor region in his left eye, and the vision in his left eye was saved. He is currently in good health. Nathan has 3 siblings (see pedigree below): an older sister age 8 years, a younger brother age 3 years, and a baby sister age 16 months. None of Nathan’s siblings have shown any signs or symptoms of retinoblastoma. Nathan’s father was diagnosed with unilateral retinoblastoma at the age of 2 years, and was successfully treated with radiation in the affected eye. Nathan’s mother is in good health, and there is no other immediate family history of retinoblastoma or other cancers.
a) Based on what you know about the genetics of retinoblastoma, is the father’s case likely to be sporadic or germline? Why?

b) Besides retinoblastoma, what other types of cancers are patients with Rb mutations at risk for developing? Why?

c) Is there still a risk of developing retinoblastoma or other cancers in any family members? What management do you suggest for Nathan’s father? For Nathan? For Nathan’s siblings?

Acknowledgements:
Sarah Morton, MSTP, 2006