

**7.27-2006
PROBLEM SET #1**

QUESTION 1.

Dan and Alice Stern have three children – 12 year old Tom, 8 year old Sarah and 6 year old Damien. At the age of 3, Damien was discovered to have unilateral retinoblastoma and the affected eye was surgically removed. There is no history of retinoblastoma in either Dan or Alice’s families and Tom and Sarah are also tumor-free.

A) Draw the pedigree for the Stern family.

B) Based on the family history, what is the most likely mechanism by which Damien’s retinoblastoma arose? Your answer should include a brief discussion of how the relevant gene mutation(s) might have arisen.

Damien’s parents read on the internet that individual’s with retinoblastoma can have an increased probability of developing other tumors types (e.g. osteosarcoma) relative to the general population.

C) Based on the mechanism you proposed above, what would you advice them about Damien’s risk? Briefly explain how you arrived at your answer.

Damien grows up, marries and has a son called Simon. By 16 months of age, Simon has developed tumors in the retinas of both eyes.

E) Add Simon to the Stern family pedigree.

F) Given this situation, what would you now conclude about the most likely mechanism by which retinoblastoma arose in (i) Damien and (ii) Simon. Briefly explain how you arrived at your answer.

Question 2.

You are interested in established a mouse model to study the development, and ultimately, treatment of melanoma. Someone suggests that you engineer a mouse model that expresses the B-raf V599/600 point mutant.

A) What is the rationale for using the B-raf V599/600 point mutant for your model?

B) What are the issues you will need to worry about in the design of your B-raf V599/600 mouse? Briefly describe how you would engineer the optimal B-raf V599/600 “melanoma” mouse.

You successfully generate your mouse and find that it is susceptible to developing pre-neoplastic melanotic lesions, called nevi, but it does not develop malignant melanoma. You remember that people who inherit a p16 germline mutation are predisposed to develop malignant melanoma. Thus, you wish to introduce a p16 mutation into your mouse model. You are able to get a p16 heterozygous mutant mouse from a colleague to cross with your B-raf V599/600 “melanoma” mouse.

C) Describe what p16 does and why the p16 gene mutation might be expected to cooperate with the B-raf V599/600 mutant to promote tumor development.

D) Describe the genotype of the animals you would generate to test the affect of p16 mutation in your B-raf V599/600 “melanoma” mouse. Your answer should include the breeding scheme and show the “test” versus “control” animals.

You find that the combination of the B-raf and p16 mutations gives you malignant melanomas at very low frequency. You compare the genotype of these tumors with that of normal tissue.

E) What do you predict about the genotype of (i) the B-raf V599/600 and (ii) p16 in the tumor versus normal tissue? Briefly explain how you arrived at your answer.

F) Would you expect to find ras mutations these tumors? Explain how you arrived at your answer.