**Reading Guide for Journal Club 2**

**Background information, from the review article by J.W. Shea and W.E. Wright**

(you will need to understand this information in order to understand the research articles, and it will appear on the quiz, but we will not talk specifically about this article in class)

What is TERT? What is its normal function?

Do adult human cells express telomerase? Can you think of any exceptions for cell types that might express telomerase in adults?

Briefly summarize the role of telomerase in cancer.

What estimated percentage of malignant tumors express telomerase?

Explain this statement: “While telomerase does not drive the oncogenic process, it is permissive and required for the sustain growth of most advanced cancers.”

What is senescence? Why do normal cells senesce? What happens in cancer cells with regard to senescence?

What is the basic idea or hypothesis behind targeting telomerase as a therapy for cancer?

Below are the specific questions related to the two brief papers by Huang et al., and Horn et al. Please check the posted list to determine which question you will be responsible for during the in-class discussion.

*Highly Recurrent* TERT *Promoter Mutations in Human Melanoma* by F.W. Huang et al.

1. What is the central hypothesis for this work? (Why did they start this project? What, in the authors opinion, was the important question they were trying to address?)

2. Explain the statement “We systematically queried non-coding somatic mutations using published whole genome sequencing data”. What are non-coding somatic mutations?

3. What specific mutation(s) were found by analyzing the TERT promoter from melanomas (reference Figure 1A)? What does “dipyrimidine” mean?

4. What percentage of melanomas contained these mutations (reference Figure 1B)?

5. How do the specific mutations found relate to the type of cancer (melanoma) that is being studied? (Hint: it has to do with UV damage! What type of DNA damage does UV most often cause?)

6. What is an ETS transcription factor? What sequence does it bind to? Does is activate genes (turn them on) or repress genes (turn them off)?

7. The discovery of the ETS sequence created within the TERT promoter led to a new hypothesis about how cancer cells are able to grow out of control. What was this hypothesis? (Look in the center column of page 958).

8. The authors next wanted to see what types of cancers may contain ETS promoter mutations. What types of cancers seem highly likely to contain these mutations? Which types of cancers do not contain these mutations? (Refer to Figure 1D)

The final four paragraphs of the article summarize the conclusions and interpretations of the data by the authors.

9. Why do the authors feel these results are important? What is so novel (new and different) about their study? [Hint, there are two main points the authors claim are important about their work, found in the last paragraph, top left of page 959].

10. Is the approach taken by Huang et al in this study an example of forward or reverse genetics? Explain your answer.

TERT *Promoter Mutations in Familial and Sporadic Melanoma* by S. Horn et al.

11. How do the authors begin their study? What is their hypothesis? How does this differ from the hypothesis of Huang et al?

12. Is the approach taken by Horn et al an example of forward or reverse genetics? Explain your answer.

Examine the pedigree in Figure 1: What do the following symbols mean?

13. “Index”, #, \*, “L”,

14. 2-digit numbers, “rs”, gray boxes

15. What is the inheritance pattern of this hereditary melanoma? What are the important clues from the pedigree that led you to this conclusion?

16. What mutation did the authors identify in this particular family? Compare this mutation to those identified by Huang et al.

17. The authors next examine several cell lines and melanoma tumor samples from sporadic (non-hereditary) cases of melanoma. Do they find their familial mutation in cases of sporadic melanoma? What do they find instead?

18. How do these mutations found in sporadic melanomas compare to the mutations found by Huang et al? Are they the same?

Concluding thoughts (consider both articles, we will discuss these questions as a class):

What did you think of these two studies? Are they interesting? Are they important? Are there any parts that raise doubts or questions in your mind? What experiments might the authors do to extend their studies in the future? Are there important experiments missing from these studies? How do you think these articles will change cancer diagnosis and treatment (or will they?)