An important unsolved problem is understanding the mechanism of enhancer-promoter specificity. For example, within a single TAD (topological associating domains), enhancers can target specific promoters for activation while not regulating other promoters, even if these other promoters are close to the enhancer. As mentioned in class, a high-throughput screen was done to find enhancers specific for either housekeeping or developmentally regulated promoters. Thousands of enhancers were found to be specific for one or the other type of promoter.

1) How would you validate the screen, e.g., convincingly show that the large-scale screen identified enhancers specific for one or the other promoter type?

2) How can you begin to address what is different about the enhancers that are specific for developmentally-regulated or housekeeping promoters? List at least two experiments or computational analyses that you might do. If you propose something computational, propose an experiment to validate the results of your analysis.

3) How can you begin to address what is different about developmentally-regulated and housekeeping promoters that allows them to be differentially regulated? List at least one experiment or computational analysis + validation.

4) Extra credit: Activators often target coactivators rather than directly targeting promoters. How do you think coactivators fit into the above enhancer-promoter specificity and how might you test your hypothesis?