Genetics Day Poster Submission

Presenter: Molly Hulver

Category: Graduate Student

Authors: MOLLY HULVER, Paul Boutz

Title: MODELING CDK12 AND CDK13 LOSS-OF-FUNCTION TO INVESTIGATE THEIR ROLES IN ALTERNATIVE POLYADENYLATION AND NEOANTIGEN EXPRESSION

Abstract: CDK12 and CDK13 are cyclin-dependent kinases that phosphorylate Serine 2 (Ser2) of the RNA Polymerase II C-terminal domain (RNAPII CTD) repeat to signal for transcriptional elongation. Additionally, both kinases are mutated in various cancers. CDK12 has been identified as a 'BRCA-ness' gene-one that phenocopies BRCA1/2 LOF (loss-of-function) when mutated, resulting in loss of high-fidelity DNA double-strand break repair and promoting tumorigenesis. Further investigation has shown that both CDK12 bi-allelic LOF and heterozygous, dominant- negative CDK13 mutations can lead to increased intronic polyadenylation (IPA) of pre-mRNA transcripts, or to increased stabilization of IPA-isoforms, respectively. In zebrafish melanoma models expressing mutant CDK13, we have identified novel IPA-dependent peptide sequences. We hypothesize that a substantial pool of intron-encoded peptides could function as neoantigens as a result of IPA upregulation or stabilization in CDK12/13 mutated tumors. These neoantigens could potentially serve in an immunotherapy treatment, which CDK12 LOF patients have responded to positively in the past. Functions of CDK12 and CDK13, while similar, seem to target partially overlapping, but largely distinct transcripts. In order to distinguish the sets of transcripts affected by each kinase, we have developed mutations in both CDK12 and CDK13 that make each respective kinase resistant to the dual CDK12/13 inhibitor THZ531. Thus, allowing us to individually model CDK12 LOF while CDK13 is fully functional and vice versa. Using these model cell lines, we will characterize the effects of each kinase on global IPA site usage, intronically-encoded peptide expression, and display of potential neoantigens on tumor cell surfaces.