UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

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FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF PATHOLOGY

Wednesday, December 14, 2016, 3:00 p.m.
Room 433, Hensley Library, BMSB, OUHSC

AN *IN VIVO* FUNCTIONAL GENOMICS APPROACJ TO IDENTIFY AND CHARACTERIZE PATHOLOGICAL GENETIC VARIANTS

COMMITTEE IN CHARGE: David Jones, Ph.D, Chair, Lorin Olson, Ph.D., J. Kimble Frazer, Ph.D., Maria Ruiz-Echevarria, Ph.D., Takemi Tanaka, Ph.D

ABSTRACT: Collective advancements in research technologies, methods to characterize patients, knowledge in genomics, and tools for health information systems has permitted the edifice of a new era in medicine – precision medicine. For the treatment of cancer, precision medicine is an approach to disease intervention that aims to match a tumor's genomic profile with targeted therapeutics. However, such an approach assumes that all proto-oncogenes, tumor suppressor genes, and their actionable variants have been identified and characterized. Large-scale next generation sequencing initiatives have revealed that tumors can harbor two to hundreds of mutations. And while 'hot spots' for mutations within a gene exist, in other genes missense mutations in all codons have also been identified. Therefore, the utility for mutational analysis in the clinic is limited by our small number of characterized mutations and understanding of their functional consequences. What is immediately needed is a clinically-time relevant and creative approach to sift through the deluge of patient genomic information.

The purpose of this thesis is to demonstrate an *in vivo* functional genomics approach to identify and characterize pathological mutations. Following identification of novel patient derived genetic variants, overexpression and knockdown studies in zebrafish embryos were carried out to determine their *in vivo* functional consequences. The results demonstrate two extracellular domain mutations in *PDGFRa* independently induce pathological consequences similar to a known constitutively active intercellular domain mutation. These findings establish the pathogenicity of the previously novel variants and suggest available targeted interventions may be clinically beneficial. This thesis also demonstrates how zebrafish are useful in elucidating the cellular and molecular mechanisms of cancer initiation and progression. Chemical knockdown and overexpression studies in embryo and adult zebrafish were used to elucidate how APC loss of retinoic acid biosynthesis in the colon contributes to induction of the proliferative response. These studies show that loss of retinoic acid biosynthesis results in an adaptive immune response independent of chronic inflammation that is required to induce proliferation. Globally, the above findings demonstrate zebrafish are a clinically-time relevant model system that can be used to elucidate the functional consequences of genetic variants that contribute to disease progression.