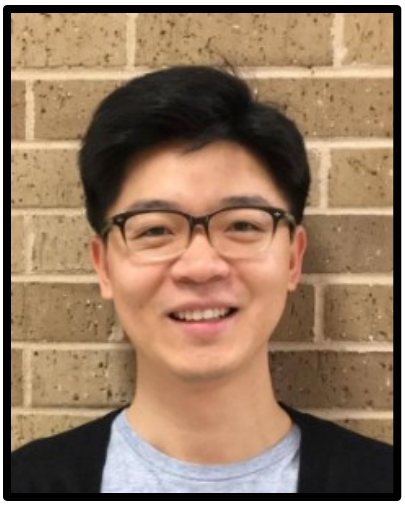
THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

YOUNGHWA SHIN

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

Wednesday, January 25, 2017, 1:00 p.m.
Room 272, Basic Science Education Building, OUHSC



Studies on two proteins of retinoid metabolism in vertebrate eyes: RPE65 and RDH10

COMMITTEE IN CHARGE: Jian-xing Ma, M.D. Ph.D, Chair, Robert Anderson, M.D. Ph.D., Michael Elliott, Ph.D., Courtney Griffin, Ph.D., Raju Rajala, Ph.D.

ABSTRACT: The visual cycle refers to a biochemical cascade in vertebrate eye in which vitamin A is utilized to generate light sensitive chromophore 11-*cis*-retinaldehyde (11-*cis*-RAL). The visual cycle is comprised of many enzymes located in both the retina and the retinal pigmented epithelium (RPE), but the majority of enzymatic reactions occur in the RPE. Oftentimes genetic mutations in the genes of the visual cycle lead to a spectrum of retinal disorders such as Leber's congenital amaurosis (LCA), retinitis pigmentosa (RP) and age-related macular degeneration (AMD). In fact, a key enzyme of the visual cycle RPE65 alone has over 100 mutations reported on it, most of which associate with autosomal recessive LCA and/or RP. We have studied RPE65 in two different contexts: (1) the first dominant mutation of RPE65 D477G was investigated by generating and characterizing a mutant knock-in mouse model, and (2) CU239, a novel inhibitor of RPE65, was tested on Light-Induced Retinal Damage (LIRD) model to examine its therapeutic potential for AMD. Our data indicate that our knock-in mouse model partially recapitulates clinical symptoms in human patients, most notably by disturbing visual chromophore regeneration and delaying dark-adaptation recovery. In addition, we have demonstrated that CU239 is a competitive inhibitor of RPE65 and confers a protective effect on LIRD model by modulating the visual cycle.

We have also studied Retinol dehydrogenase 10 (RDH10) to understand its role in the visual cycle. Although we initially expected RDH10 to be one of the 11-*cis*-retinol dehydrogenases (i.e. the enzymes responsible for the last step of the visual cycle), our data from RDH10 conditional knock-out mice demonstrated insignificant role of RDH10 in the visual cycle. Instead, we found that RDH10 may be an important retinoic acid (RA) synthesis enzyme for the neonatal ocular growth, as early deletion of *Rdh10* demonstrated a mild bilateral microphthalmia. RA is an important morphogen responsible for proper organogenesis and development of many organs including the eye. Collectively, our data suggest that RDH10 may be more important as a RA synthesizing enzyme in neonatal stage than as a visual cycle enzyme in adult.