THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Angelica R. Harper

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Cell Biology

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BIOMEDICAL RESEARCH CENTER, ROOM 109

Identifying the Role of RALDH2 Mediated Retinoic Acid Synthesis in Visually Guided Eye Growth

COMMITTEE IN CHARGE: Jody A. Summers, PhD (chair); Doris M. Benbrook, PhD; Marie Hanigan, PhD; Raju Rajala, PhD; David Sherry, PhD

ABSTRACT: Emmetropization is a vision-dependent process that coordinates the growth of the eye such that the ocular axial length will align the retina with the focal plane to give clear vision. Abnormalities in this process can result in abnormal axial elongation of the eye, resulting in the development of myopia or nearsightedness. Based on research in animal models, such as the chick and primate, choroidal all-*trans*-retinoic acid (atRA) and retinaldehyde dehydrogenase 2 (RALDH2) have been implicated in the chemical cascade that modulates visually guided eye growth. Thus, the purpose of this project was to determine the role of choroidal atRA and RALDH2 in mediating visually guided eye growth. Studies revealed that RALDH2 is the sole RALDH isoform present in the chick choroid, that RALDH2 protein levels are significantly increased during recovery, and that the number of RALDH2 expressing cells increases in the proximal choroid following 1 – 7 days of recovery. Studies using human ocular tissue demonstrated the presence of active RALDH1 and RALDH2, found mainly in the choroid and/or RPE. Additionally, an intelligent drug design approach was employed to develop the first RALDH selective inhibitor, dichloro-all-*trans*-retinone (DAR) to directly test the

role of chick RALDH2 in postnatal ocular growth regulation. DAR was found to irreversibly inhibit chick RALDH1, 2, and 3 and did not inhibit the general, human mitochondrial aldehyde dehydrogenase, ALDH2. Further, *in vitro and ex vivo* experiments utilizing a cell line with doxycycline-inducible RALDH2 [$^{(Dox)}$RALDH2-eGFP 293], as well as choroidal lysates and tissue isolated from chick eyes following 4 days of recovery from form deprivation myopia resulted in significant inhibition of RALDH activity following pretreatment with DAR. Together, these data suggest that, during recovery, increased levels of choroidal RALDH2 result in increased levels of atRA, which may slow scleral and thus, ocular growth. As such, DAR exhibits promise as a potential therapy to inhibit RALDH2 and atRA synthesis in order to slow myopia progression in humans.