The number one cause of vision loss in working-age Americans comes from diabetic retinopathy, which is damage to the retina caused by diabetes. Ultimately, it can lead to total blindness. Although this aspect of diabetes is sometimes considered a niche, retinopathy’s impact on the quality of life of individuals in this country, in particular, is extremely powerful. In the mid-2000s, I first decided to focus on diabetic retinopathy, because it affects so many people, not just in this country, but around the world as well.

As a basic scientist, I was always interested in the mechanisms of diseases and their treatments. Therefore, it came as no surprise that, at the University of Oklahoma Health Sciences Center, I began an independent research program in retinal biology to investigate the mechanisms of diabetic retinopathy. Since then, the subject matter has been a major aspect of my career. I have the American Diabetes Association to thank for much of the support I have received in this field.

My experience with the Association and its Research Foundation stems back to 2006 when I applied for my first Basic Science Award. The Association was the first national funding agency to provide me with a basic science grant for a project titled “Retinal Müller cells in neovascularization and diabetic retinopathy.” The study was a great success, having demonstrated a genetic system to study the mechanisms of neovascularization (the formation of microvascular networks) in the retina.

As someone whose original training was in mouse genetics rather than diabetic retinopathy, it was very important to my career that the Association treats newcomers very well. Outsiders often need more time for the research community to recognize their work, which affects the ability to get published in high-impact journals and obtain subsequent research grants from agencies.

Additionally, the Association encourages the idea of “potential” in each of its scientists and puts a policy emphasis on supporting junior investigators. That said, I believe my first Association-funded award jump started my independent research career. It was through that grant that my research began to be noticed. In 2007, I presented my findings at the American Diabetes Association’s 67th Annual Scientific Sessions in Chicago.

As a result of the successful poster, a journal for practicing ophthalmologists, Retina Today, featured my work in a cover story editorial. Further evolving, the article was then noticed by a specialty pharmaceutical company that offered me a contract for my research.

Yun Zheng Le, PhD

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Professional Focus: Ocular Complications

Outside Interests: Basketball, table tennis, volleyball

Research Funding: Basic Science Award
“Diabetic Complication in the Eye”

Amount Awarded: $333,500
company that focuses on ophthalmologic drugs. Since then I have been working with this company to discover a treatment for diabetic retinopathy. Recently, our paper was accepted by *Investigative Ophthalmology & Visual Science*, in which I was the academic corresponding author.

I have the Association to thank for helping me make my transition from a junior investigator to a mid-career scientist who is now funded by a variety of agencies. This track is highly coveted, as I can spend more time today researching than applying for grants because of this level of financial security.

In 2010, four years after my first Association award, I received my second and current Basic Science Award, which is titled “Diabetic Complication in the Eye.” Dealing specifically with a particular cellular mechanism of diabetic retinopathy. My hope is—at the conclusion of the project—our understanding of diabetic macular edema (major vision loss in the retina of diabetic patients) will have increased significantly.

The eye is a complicated and important organ—one on which much of our daily functioning and happiness are based. The retina (the light-sensitive tissue lining the eye) is a thin layer of neurons that creates and processes visual signals. Two blood circulations, called retinal (inner blood-retina barrier) and choroidal (outer blood-retina barrier) vessels, support the livelihood of the eye. Diabetic retinopathy occurs when abnormal formations of retinal vessels appear and when leakage occurs from blood-retina barriers.

Abnormal formations of retinal vessels and the leakage from inner blood-retina barrier have been studied for quite some time, but the leakage from outer blood-retina barrier has not. Specifically, choroidal vessels bring oxygen and nutrients to the retina and the retina’s photoreceptor cells. They are responsible for approximately 70 percent of the blood circulation in the eye.

In my laboratory’s current Association-funded study, we will define how much the leaked fluid and proteins from the choroidal circulations affect the overall pathology of diabetic retinopathy. The retinal pigmented epithelium (RPE) is a major component of the outer blood-retina barrier. The vascular endothelial growth factor (VEGF) produced by the RPE is increased during diabetic conditions. Therefore, we think that the RPE-produced VEGF may be responsible for the diabetes-induced breakdown of the outer blood-retina barrier.

Our laboratory will study this in mice that have genetically altered genes for blood barrier function. These genes include VEGF and its receptor, VEGF receptor-2 (R2). It has been suggested that up-regulating VEGF signaling is a major cause of vascular abnormalities in the diabetic eye. The mice we work with are genetically engineered to have deleted VEGF or its receptor-2 specifically in the RPE. We are using these mice to determine the role and mechanisms of VEGF in diabetes-induced breakdown of the outer blood-retina barrier.

Additionally, we are also determining the role of the RPE-derived VEGF in retinal neuron survival during diabetes. Our work looks promising, and we hope to publish soon. I have recently spoken to the Biannual Meeting of Association for Ocular Pharmacology and Therapeutics about the work we are doing and look forward to further sharing my research with the diabetes arena.

My current study funded by the Association will hopefully lead to resolving a 30-year dilemma in the understanding of this mechanism in a subset of individuals who have diabetes and macular edema. The knowledge we glean from this work will be very useful in the diagnosis of diabetic macular edema and for screening for drugs to treat the disorder. I hope to derive important diagnostics and therapeutics for this disease as a result of this generous award. Our next steps would be to work with imaging engineers to bring our work to life.

I genuinely thank the donors who support the American Diabetes Association and its Research Foundation for allowing me to focus on an area of great importance to millions of individuals who struggle with diabetic retinopathy. Know that generous gifts to the Research Foundation are used wisely and the results of successful projects are widely publicized to the benefit of everyone in the field.

In addition to supporting my colleagues in diabetes science, I aim to dedicate myself to the millions of people who struggle with this illness. Diabetes and its complications affect many people who are close to us, which is why research in this area is and always will be my personal mission.

Yun Zheng Le, PhD, right, is a recipient of a Basic Science Award.
INSIDE:

- Investigating vitamin D’s impact on glycemic control
- Establishing new hypotheses in beta-cell research
- Training the next generation in diabetic complications
- Investing in the health of Japanese Americans

Cross-sectional image of muscle fibers, labeled with two molecules required for fatty acid uptake in red and green.
Fatty acid uptake in tissues other than fat cells (such as muscle and liver) is an important component in the development of insulin resistance and type 2 diabetes. This cross-sectional image of muscle fibers shows FATP1 and CD36 in red and green, two molecules required for fatty acid uptake. The muscle cell membranes are labeled in blue.

Submitted by: Andreas Stahl, PhD, Associate Professor, Nutritional Science and Toxicology, University of California, Berkeley. From the following publication: (Wu Q., Ortegon A.M., Tsang B., Doege H., Feingold K.R., and Stahl A. FATP1 is an insulin-sensitive fatty acid transporter involved in diet-induced obesity. MCB, 26:3455-67, 2006. PMC1447434).

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