SHILEY EYE INSTITUTE WELCOMES **DOROTA SKOWRONSKA-KRAWCZYK, PH.D.**

Dorota Skowronska-Krawczyk, Ph.D. is originally from Lodz, Poland. She was awarded her Ph.D. at the University of Geneva and conducted post doctoral research at the Eye Hospital Jules Gonin and UCSD in the laboratory of Michael G. Rosenfeld, M.D., in the Department of Cellular and Molecular Medicine.

Dr. Skowronska-Krawczyk's studies have focused on molecular mechanisms' roles in retina development using molecular and cellular approaches. She has developed a state-of the art technology in retinas to study the in vivo association of transcription factors with target promoters and has applied this technology to study genomewide association of many transcription factors during organogenesis. She has also studied the role of intrinsic and extrinsic factors in retinal ganglion cell development.

In addition to her recent breakthrough research on glaucoma (see accompanying article), she has studied fetal brain development and how newly differentiated neurons undergo cell migration to reach appropriate bodily positions and form functional circuits. Dr. Skowronska-Krawczyk also has published on the nuclear organization and genome 3D structures that play prominent roles in the regulation of gene expression.

IDENTIFIED GENETIC INTERACTIONS OFFER POSSIBLE NEW TARGET FOR

GLAUCOMA THERAPY

It is fascinating to understand how transcriptional output, in this case expression of p16INK4a, can be modulated by subtle alterations in multiple pathways to mediate key changes in cell functionality and viability.

Dorota Skowronska-Krawczyk, Ph.D., newly appointed to the faculty of the Department of Ophthalmology and a team of scientists at the Shiley Eye Institute and the UC San Diego School of Medicine have elucidated a genetic interaction that may prove key to the development and progression of glaucoma, a potentially blinding disease that affects tens of millions of people worldwide and is a leading cause of irreversible blindness.

The findings, published in Molecular Cell (2015;59:921-40), suggest a new therapeutic target for treating the eye disease.

Primary open-angle glaucoma (POAG) is the most common form of glaucoma, affecting more than 3 million Americans, primarily after the age of 50. Pressure inside the eye (known as intraocular pressure) and age are the leading risk factors for POAG, resulting in progressive degeneration of retinal ganglion cells, optic nerve damage and eventual vision loss.

Genetics also plays a role. Recent genome-wide association studies have identified two genes – SIX1-SIX6 and p16INK4a – as strongly associated with POAG. SIX6 is required for proper eye development. P16INK4a irreversibly arrests cell growth, a phenomenon called senescence.

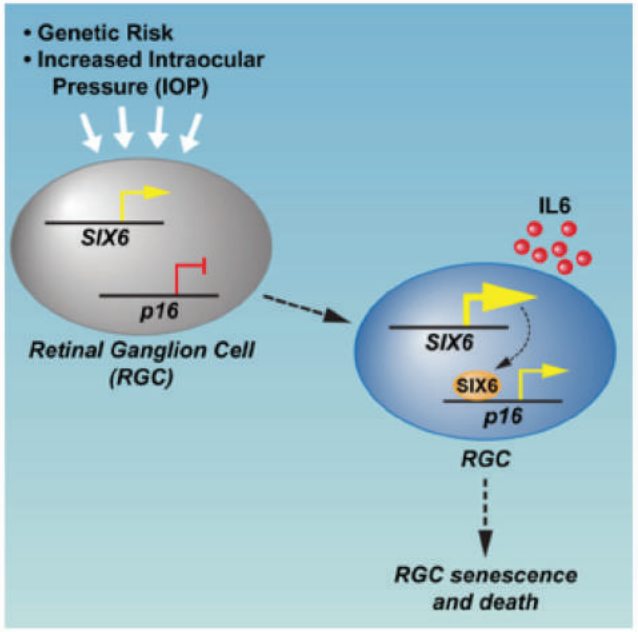
In their recently published article, the Shiley team reports that some variants of SIX6 boost expression of p16INK4a, which in turn accelerates senescence and death of retinal ganglion cells.

"We also show that high eye pressure in glaucoma increases expression of p16INK4a, making it a key integrator of inherent genetic and environmental risk factors that can result in glaucoma," said Kang Zhang, M.D., Ph.D., senior author and Professor of Ophthalmology.

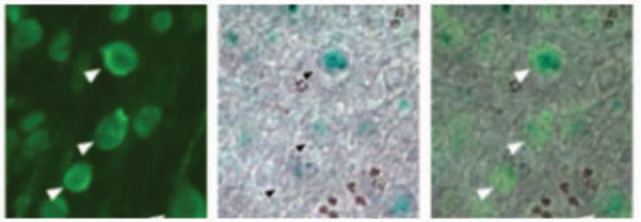
The findings suggest that inhibiting p16INK4a could offer a new therapeutic approach for glaucoma, which is currently treated by drugs that lower intraocular pressure. "Although lowering intraocular pressure can slow worsening of the disease, it does not stop it and prevent further cell death or possible blindness," said co-author Robert N. Weinreb, M.D., Distinguished Professor of Ophthalmology and director of the Shiley Eye Institute. The authors also note that earlier studies in mouse models have shown that selective elimination of p16INK4a-positive senescent cells can prevent or delay age-related tissue deterioration.

Dr. Skowronska-Krawczyk states, "It is fascinating to understand how transcriptional output, in this case expression of p16INK4a, can be modulated by subtle alterations in multiple pathways to mediate key changes in cell functionality and viability."

According to the Shiley research team, the next step is to conduct preclinical studies to assess the efficacy and safety of antisense oligonucleotides – strands of synthesized DNA or RNA that can prevent transfer of genetic information – which might inhibit p16INK4a expression and prevent worsening of glaucoma. "If they are effective, we may contemplate a human clinical trial in the future," Zhang said.



Model of sequence of events leading to RGC death upon Six6 upregulation in glaucoma indicating p16INK4a as a downstream integrator of diverse signals such a inherited genetic risk, age and eye pressure, in the pathogenesis of glaucoma.



IOP-treatment of Thy1-CFP retinas shows that the majority of SA-βgal-positive (senescent) cells are also Thy1-CFP positive (arrowheads - double positive RGCs; arrow- nonsenescent RGC).