Team discovers new drugs with potential for treating world's leading causes of blindness in AMD, other diseases

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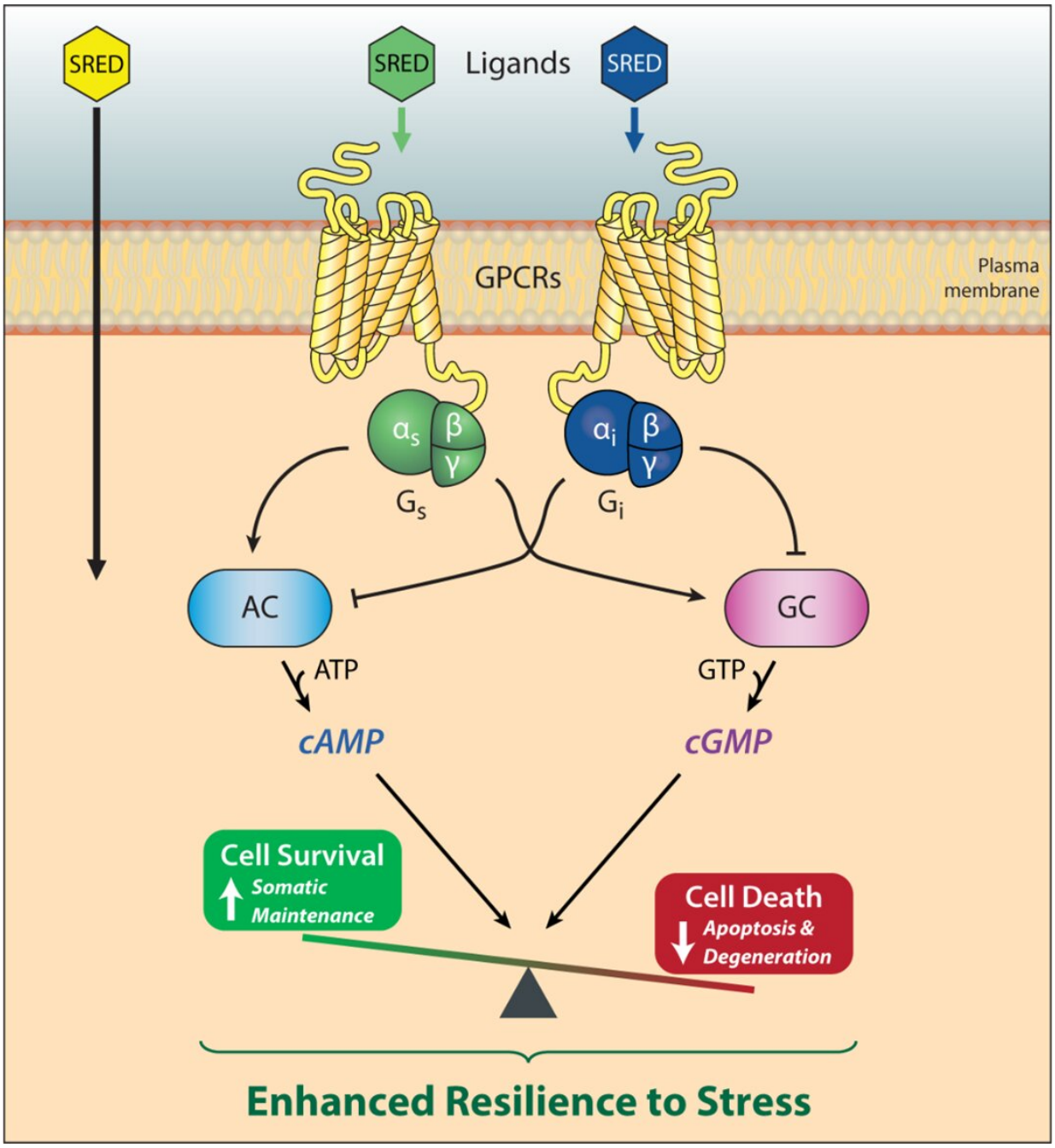

Molecular mechanisms of stress resilience-enhancing drug (SRED) therapy. Retinal degeneration involves a complex, multifactorial combination of genetic factors and environmental exposures that accumulate over a lifetime and eventually overwhelm intrinsic stress resilience mechanisms, which can be enhanced pharmacologically by SREDs to alleviate disease and preserve vision. Credit: UCI School of Medicine

In a University of California, Irvine-led study, researchers have discovered small-molecule drugs with potential clinical utility in the treatment of age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinitis pigmentosa (RP).

The study, titled, "Stress resilience-enhancing drugs preserve tissue structure and function in degenerating retina via phosphodiesterase inhibition," was published in the *Proceedings of the National Academy of Sciences*.

"In this study, we introduce a new class of therapeutics called "Stress Resilience-Enhancing Drugs" (SREDs) for the treatment of neurodegenerative conditions, specifically the world's leading causes of blindness in age-related and inherited retinal diseases," said Krzysztof Palczewski, Ph.D., Donald Bren Professor of Ophthalmology at the UCI School of Medicine and corresponding author on the study. "Through selective, pharmacological inhibition of cyclic nucleotide phosphodiesterases, our prototypical SREDs slowed or halted the development and progression of retinopathies in a number of genetic and environmental animal models."

Today, approximately 350 million people worldwide suffer from debilitating vision loss caused by either AMD or DR, and a large majority of these cases (>90%) have only minimally effective or no treatment options available. These chronic, progressive retinal diseases, including retinitis pigmentosa, arise from genetic and environmental disruptions of cellular and tissue stability. Such disruptions accumulate with repeated exposures to stress over time, leading to progressive visual impairment and, in many cases, legal blindness. Despite decades of research, therapeutic options for the millions of patients suffering from these disorders remain severely limited, especially for treating earlier

stages of disease when the opportunity to preserve the retinal structure and visual function is greatest.

To address this urgent, unmet medical need, the researchers in this study innovated a systems pharmacology platform that leverages state-of-the-art disease modeling and characterization to identify novel, mechanism-based therapies that mitigate disease at the root cause. The SRED therapeutic intervention enhanced resilience to acute and chronic forms of stress in the degenerating retina, thus preserving tissue structure and function across multiple models of age-related or inherited retinal disease. Taken together, these findings exemplify a systems pharmacology approach to drug discovery and development, revealing a new class of therapeutics with potential clinical utility in the treatment or prevention of the most common causes of blindness.

"SREDs represent a promising strategy for patients and clinicians to combat disease in earlier stages with superior efficacy over the current standard of care, augmenting the arsenal of ophthalmic medications presently available in anti-angiogenics, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs)," said lead author Jennings Luu, MD/Ph.D. Doctoral Fellow of Pharmacology in the Medical Scientist Training Program at Case Western Reserve University and Visiting Scholar at University of California, Irvine. "Ultimately, it is our expectation that SREDs will someday serve as a standard of care for human aging, effectively providing patients the means to diminish suffering from debilitating ailments for which there currently exist no viable therapeutic options, thereby extending human lifespan and healthspan irrespective of disease etiology."

Predicated in part on the discoveries highlighted in this publication, Luu and Palczewski have co-founded a seed-stage startup pharmaceutical company, Hyperion Therapeutics, Inc., which aims to commercialize the intellectual property associated with their recent discoveries and

introduce to the market new therapeutic agents for the treatment or prevention of AMD, DR, RP, and other progressive, incurable blinding diseases. The Company was recently awarded first place in the Morganthaler-Pavey Startup Competition hosted by the Veale Institute for Entrepreneurship and has additionally partnered with UCI Beall Applied Innovation in the Wayfinder Incubator Program; through this strategic alliance, Luu and Palczewski are serving as co-investigators on a newly awarded Proof of Product grant, which will support the advancement of their pipeline therapies toward clinical trials and eventual commercialization.

More information: Jennings C. Luu et al, Stress resilience-enhancing drugs preserve tissue structure and function in degenerating retina via phosphodiesterase inhibition, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2221045120

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