Stargardt disease Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	LAKKARAJU, APARNA	Mechanisms of cellular clearance in the retinal pigment epithelium	**Research Question:** How is autophagy regulated in the retinal pigment epithelium (RPE) and how can it be therapeutically targeted for age-related macular degeneration (AMD)? **Stage:** In vitro with animals **Methods:** • High-speed live imaging of polarized primary adult RPE monolayers • Gene disruption • Abca4-/- mouse model of Stargardt disease **Drug Development:** This research is not directly aimed at drug development, but rather aims to understand the mechanisms of autophagy in the RPE, which may inform future therapeutic targets for AMD.
WEILL MEDICAL COLL OF CORNELL UNIV	NOCIARI, MARCELO M	Modulation of Lipid Bisretinoids Clearance with Beta-Cyclodextrins	**Research Question:** How do beta cyclodextrins (βCDs) remove toxic lipid bisretinoids (LBs) from retinal pigment epithelium (RPE) cells? **Stage:** In vitro with animals and potentially transitioning to human trials (clinical trials) **Methods:** • Cell cultures • Enucleated eyecups from ABCA4/RDH8 double knockout mice • Intravitreal injection in ABCA4/RDH8 knockout mice • Development of βCD-threaded polyrotaxanes for enhanced delivery **Drug Development:** This research directly targets drug development by investigating βCDs and βCD-threaded polyrotaxanes as potential therapies for Stargardt disease (STGD1), cone-rod dystrophy (CRD), retinitis pigmentosa (RP), and Age-Related Macular Degeneration (AMD). These therapies could potentially be moved to human trials if successful in animal models.
NATIONAL EYE INSTITUTE	HUFNAGEL, ROBERT	Generation of Induced Pluripotent Stem (iPS) Cell Lines from Somatic Cells of Participants with Eye Diseases and from Somatic Cells of Matched Controls	**Research Question:** Not directly applicable (This is a protocol to obtain tissue samples for research on various retinal diseases) **Stage:** In vitro **Methods:** • Skin biopsy and blood collection from human subjects with various retinal diseases **Drug Development:** Not directly applicable (This is a protocol to obtain tissue samples for research on various retinal diseases) **Key Point:** This protocol collects skin and blood samples from patients with various retinal diseases to create patient-specific induced pluripotent stem cells (iPSCs). These iPSCs can then be differentiated into retinal pigment epithelium (RPE) or neural retina cells for further research on the specific diseases. This research aims to improve our understanding of retinal diseases at the cellular and molecular level.
MEDICAL UNIVERSITY OF SOUTH CAROLINA	KOUTALOS, YIANNIS	Transport Processes in Photoreceptors	**Research Question:** How do the different forms of retinal (all-trans retinal, 11-cis retinal, and 11-cis retinol) affect cone photoreceptors and contribute to vision loss in diseases like Age-related Macular Degeneration (AMD)? **Stage:** In vitro with isolated cone photoreceptors from monkey and human donor eyes **Methods:** • Fluorescence imaging of single cone photoreceptors • Measuring oxidative damage and formation of lipofuscin fluorophore precursors

			Drug Development: This research indirectly informs drug development for retinal diseases by providing a better understanding of the mechanisms of damage caused by different retinal forms. This knowledge can be used to evaluate the potential risks and benefits of various treatment approaches. **Key Point:** This study focuses on cone photoreceptors and their susceptibility to damage from different retinal forms. By comparing the effects of all-trans retinal, 11-cis retinal, and 11-cis retinol, the researchers aim to understand how these molecules contribute to macular degeneration and vision loss. The findings can inform the development of safer and more effective therapies for retinal diseases.
MEDICAL UNIVERSITY OF SOUTH CAROLINA	KOUTALOS, YIANNIS	Transport Processes in Photoreceptors	**Research Question:** Does 11-cis retinal damage human rod photoreceptors and contribute to vision loss in diseases like Age-Related Macular Degeneration (AMD) and Stargardt disease? **Stage:** In vitro with isolated rod photoreceptors from human donor eyes (with comparison to mouse rods) **Methods:** • Fluorescence imaging of single photoreceptors • Measuring oxidative damage and formation of lipofuscin precursors • Microspectrophotometry to measure rhodopsin levels **Drug Development:** This research indirectly informs drug development for retinal diseases by providing a better understanding of the potential toxicity of 11-cis retinal and its role in rhodopsin regeneration. This knowledge can be used to evaluate the potential risks and benefits of therapies that manipulate 11-cis retinal levels. **Key Point:** This study investigates the effects of 11-cis retinal on human rod photoreceptors. By comparing the effects of sequestering or increasing 11-cis retinal, the researchers aim to understand how this molecule might contribute to vision loss in retinal diseases. The findings can inform the development of safer and more effective therapies by providing insights into the risks and benefits of manipulating 11-cis retinal levels for treatment
DIVISION OF BASIC SCIENCES - NCI	AMBUDKAR, SURESH	Biochemical Analysis of Multidrug Resistance-linked Transport Proteins	**Research Question:** This research focuses on P-glycoprotein (Pgp), a protein involved in multidrug resistance (MDR) of cancer cells. The study has several aims: 1. Understand the mechanism of ATP hydrolysis and drug transport by Pgp. 2. Develop non-toxic inhibitors of Pgp to reverse MDR. 3. Determine the 3D structure of human Pgp. 4. Investigate the role of Pgp in cancer stem cells. 5. Identify genes associated with MDR in cancer patients. **Stage:** In vitro and animal studies (with some human tissue studies) **Methods:** • Protein purification and functional assays of Pgp mutants • Screening of natural products and other compounds for Pgp inhibition • Crystallization trials for obtaining 3D structure of human Pgp • Analysis of gene expression in cancer cells and patient samples **Drug Development:** This research directly targets drug development by aiming to identify new therapeutic strategies to overcome MDR in cancer patients. The project investigates natural products and other compounds that can inhibit Pgp, potentially improving the efficacy of chemotherapy. **Key Points:** • The study focuses on Pgp, a protein that pumps anticancer drugs out of cancer cells, reducing their effectiveness. • Researchers are looking for ways to inhibit Pgp to improve chemotherapy outcomes.

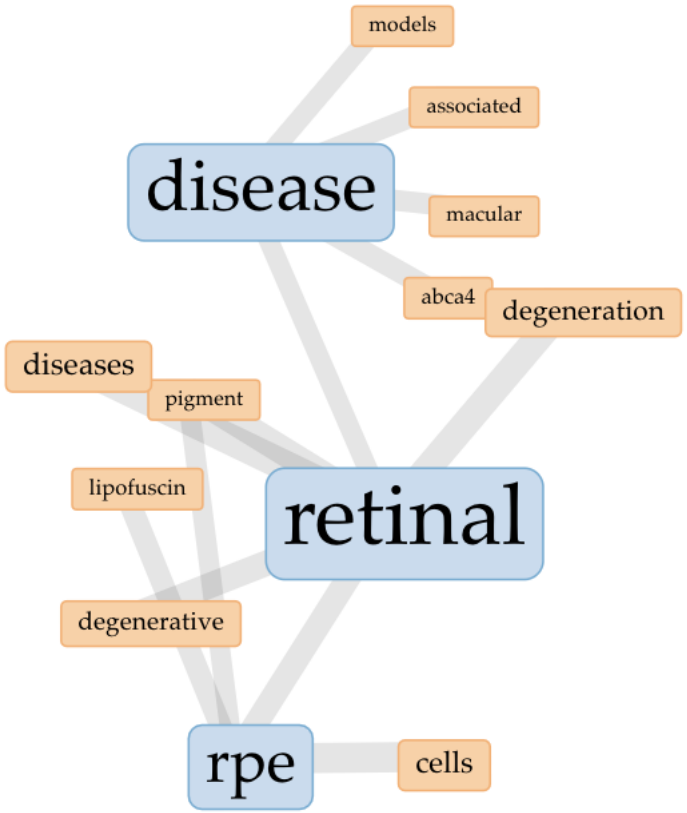
			• The project involves various approaches, including protein biochemistry, inhibitor screening, structural biology, and gene expression analysis. • This research holds promise for developing new drugs to overcome MDR and improve cancer treatment.
UNIVERSITY OF PENNSYLVANIA	CIDECIYAN, ARTUR V	Visual cycle in human photoreceptor and RPE disease	**Research Question:** • How does lipofuscin accumulate and clear in the retinal pigment epithelium (RPE) of patients with ABCA4 disease? • Can lipofuscin accumulation be used as a marker for early detection and treatment of ABCA4 disease? • Can specific compounds modify the accumulation and clearance of lipofuscin in ABCA4 patients? **Stage:** In vivo (human subjects) **Methods:** • Quantitative ophthalmic techniques (unspecified) to measure lipofuscin accumulation and clearance over time • Development of a clinical outcome measure based on lipofuscin microtopography • Pilot studies with compounds targeting lipofuscin accumulation/clearance **Drug Development:** This research directly targets drug development for ABCA4 disease by: • Investigating lipofuscin accumulation as a potential therapeutic target. • Testing pilot studies with compounds that may modify lipofuscin levels. **Key Points:** • This study focuses on understanding lipofuscin accumulation and clearance in ABCA4 disease patients. • Researchers aim to develop a method to measure lipofuscin as a marker for early detection and treatment. • The project tests potential therapeutic compounds that may affect lipofuscin levels in pilot studies. • This research may inform the development of new therapies for ABCA4 disease and potentially other retinal diseases with similar pathologies.
COLUMBIA UNIVERSITY HEALTH SCIENCES	SPARROW, JANET RUTHE	Quantitative Fundus Autofluorescence in Retinal Disorders	**Research Question:** This research investigates the role of lipofuscin, a cellular byproduct, in various retinal diseases using a technique called quantitative fundus autofluorescence (qAF). • Specific Aim 1: Does lipofuscin accumulation in the retina make eyes more susceptible to the toxic effects of hydroxychloroquine (HCQ)? Can qAF levels be used as an early marker for HCQ toxicity? • Specific Aim 2: Why do female carriers of choroideremia have lower levels of lipofuscin as measured by qAF? • Specific Aim 3: Is there a link between loss of the ellipsoid zone (a retinal layer) observed in spectral-domain optical coherence tomography (SD-OCT) images and changes in qAF in patients with central serous chorioretinopathy? • Specific Aim 4: In patients with ABCA4 mutations, why is the distribution of elevated qAF not uniform across the retina? How can multimodal imaging techniques help us understand this? **Stage:** In vivo (human subjects) **Methods:** • Quantitative fundus autofluorescence (qAF) to measure lipofuscin levels

			• Spectral-domain optical coherence tomography (SD-OCT) imaging (Aim 3) • Multimodal imaging techniques (Aim 4, unspecified) **Drug Development:** This research does not directly target drug development. However, it investigates qAF as a potential tool for: • Early detection of HCQ toxicity (Aim 1) • Diagnosis and monitoring of retinal diseases (all Aims) **Key Points:** • This study explores the use of qAF to assess lipofuscin levels and their connection to various retinal diseases. • The researchers aim to establish qAF as a tool for early detection of HCQ toxicity and diagnosis/monitoring of other retinal conditions. • By understanding how lipofuscin accumulation relates to different retinal diseases, this research may inform future therapeutic strategies.

UNIVERSITY OF FLORIDA	HAUSWIRTH, WILLIAM W	Retinal Gene Delivery by Adeno-Associated Virus	**Research Question:** Can gene therapy using AAV vectors rescue, restore, or delay vision loss in animal models of retinal degeneration (RD)?
			Stage: In vivo with animals (mice and rats)
			Methods:
			• AAV vectors delivering various genes:
			  ○ Gene replacement for specific mutations (e.g., rd10 model)
			  ○ X-linked Inhibitor of Apoptosis (XIAP)
			  ○ Ciliary Neurotrophic Factor (CNTF) or CNTFalpha
			• Evaluating the effects of gene therapy on retinal structure and function
			• Measuring the duration of therapeutic effect and optimal age window for treatment
			Drug Development: This research directly targets drug development for retinal dystrophy (RD) by:
			• Testing the efficacy and safety of AAV gene therapy in various RD models.
			• Identifying potentially effective genes for therapeutic intervention.
			Key Points:
			• The study investigates AAV gene therapy as a potential treatment for different types of RD.
			• Researchers deliver various genes using AAV vectors to see if they can improve retinal function and structure in animal models.
			• The project focuses on gene replacement, cell survival factors (XIAP, CNTF), and exploring the effective treatment window.
			• This research holds promise for developing AAV-based gene therapies for human RDs.

ALKEUS PHARMACEUTICALS, INC.	WASHINGTON, ILYAS	Phase 1 Safety and Pharmacokinetics of ALK001 in people over 60	**Research Question:** Is D3-vitamin A, a form of vitamin A enriched with deuterium, safe for people over 60 years old? **Stage:** In vivo (human subjects) **Methods:** • Open-label clinical trial (participants know they are receiving the investigational drug) • One-month duration with one week of D3-vitamin A dosing (1.5 or 3 mg/day) • Monitoring safety through standard blood and urine tests • Measuring D3-vitamin A levels in blood plasma

			Drug Development: This research directly targets drug development for dry age-related macular degeneration (dry-AMD) and Stargardt's disease by: • Evaluating the safety of D3-vitamin A as a potential treatment. • This is a phase I clinical trial focusing on safety before moving to larger efficacy trials. **Key Points:** • This study investigates the safety of D3-vitamin A, a modified form of vitamin A, in older adults. • Researchers assess if D3-vitamin A can be taken up by the body and if it causes any side effects. • The ultimate goal is to see if D3-vitamin A can slow vision loss in dry-AMD and Stargardt's disease, but this study only focuses on safety. • If D3-vitamin A is safe, future studies will test its effectiveness for these diseases.
UNIVERSITY OF CALIFORNIA, SAN DIEGO	ZHANG, KANG	ELOVL4 and Retinal Disease	**Research Question:** • What is the function of the ELOVL4 protein, and how do mutations in this gene cause Stargardt-like macular degeneration (STGD3)? • How does ELOVL4 function relate to retinal development and pathology? • Does ELOVL4 dysfunction contribute to abnormal accumulation of lipofuscin in the retinal pigment epithelium (RPE)? **Stage:** In vitro and in vivo with animals **Methods:** • Biochemical analysis of ELOVL4 function (Aim 1) • Fatty acid composition analysis in cells and animal models (Aim 1 & 2) • Generation and analysis of ELOVL4 transgenic, knockin, and knockout mice (Aim 2 & 3) • Examining RPE function in ELOVL4 mutant mice (Aim 3) **Drug Development:** This research indirectly informs drug development for Stargardt-like macular degeneration and potentially age-related macular degeneration (AMD) by: • Increasing understanding of the underlying mechanisms of these diseases. • Identifying a new pathway potentially involved in macular degeneration (ELOVL4 and fatty acid biosynthesis). • Shedding light on lipofuscin formation, which may be a target for future therapies. **Key Points:** • This study investigates the role of ELOVL4, a protein involved in fatty acid metabolism, in Stargardt-like macular degeneration. • Researchers explore how ELOVL4 functions and how mutations in this gene lead to retinal degeneration in mice. • The findings may provide new targets for therapeutic intervention in Stargardt-like macular degeneration and potentially AMD. • By understanding the role of ELOVL4, this research may open doors for developing new treatment strategies.



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