Weill Cornell Medicine

Small Molecule Inhibitors of Lipofuscin Toxicity to Prevent Blindness

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Background & Unmet Need

- Lipofuscin is a variable mixture of proteins and lipids that accumulates in lysosomes of many cell types, with age or due to genetic mutations
- Lipofuscin is a universal marker of aging but is also a risk factor in pathologic processes, including the most common forms of macular degeneration
- Ocular lipofuscin accumulates in the retinal pigment epithelium (RPE), where it interferes with the support of the neuroretina
- Retinal lipofuscin is directly linked to RPE cell death in Stargardt disease, but the role in age-related macular degeneration (AMD) is unclear
- Ongoing clinical trials to treat lipofuscin-associated pathologies target the formation of lipofuscin, and therefore do not treat established deposits
- **Unmet Need:** Improved understanding of lipofuscin toxicity is necessary to inform the development of novel therapeutic strategies to prevent blindness

Technology Overview

- **The Technology:** Identification of compounds that protect the retina against lipofuscin toxicity
- **The Discovery:** Lipofuscin promotes retinal degeneration via a light-independent atypical necroptotic cascade
- Lipofuscin was shown to form aggregates in lysosomes, triggering lysosomal membrane permeabilization (LMP) and subsequent atypical necroptosis
- Necrosulfonamide, necrostatin-7, and arimoclomol were all shown to effectively block lipofuscin toxicity, by targeting different steps in the necroptotic cascade
- **PoC Data:** The identified compounds successfully protected against cell death induced by A2E accumulation and LMP induced by the lysosomotropic peptide LLOMe

Inventors:
Marcelo M. Nociari

Patents:
PCT Application Filed

Publications:
Pan et al. *PNAS.* 2021.

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Technology Applications

- Treatment of genetic and age-related causes of macular degeneration (e.g., Stargardt disease, Age-related macular degeneration (AMD))

Technology Advantages

- Protects against further damage to the retina by lipofuscin
- Applicable to multiple causes of blindness
- Arimoclomol is already in clinical trials for separate indications, which may enable an accelerated development pathway for ophthalmic diseases

Supporting Data / Figures

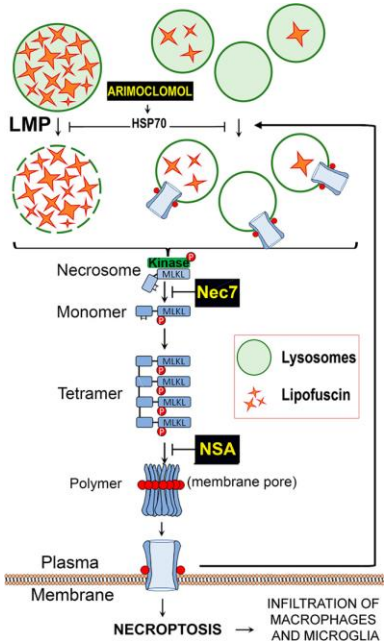

Figure 1: Working model for the light-independent cytotoxicity elicited by the accumulation of lipofuscin. Arimoclomol, necrostatin-7, and necrosulfonamide all were shown to block the necroptotic cascade.

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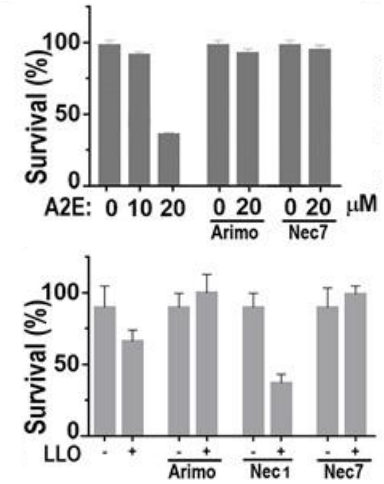

Figure 2: Arimoclomol and necrostatin-7 block atypical necroptosis induced by A2E and LLOMe and therefore promote survival to retinal lipofuscin accumulation in cultured RPE cells.

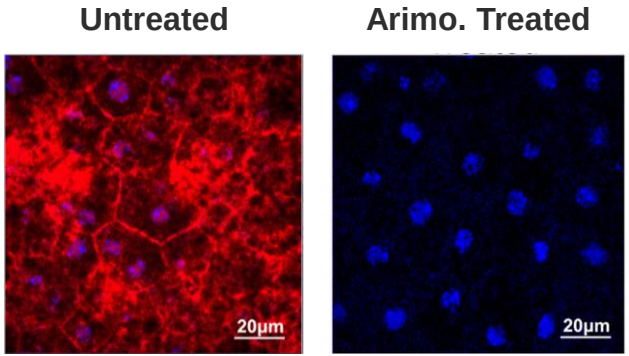

Figure 3: Single intra-ocular injection of arimoclomol reduces necroptosis (red) in the RPE (nucleus blue) of an animal model of Stargardt disease, restoring the healthy appearance of the retina.

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