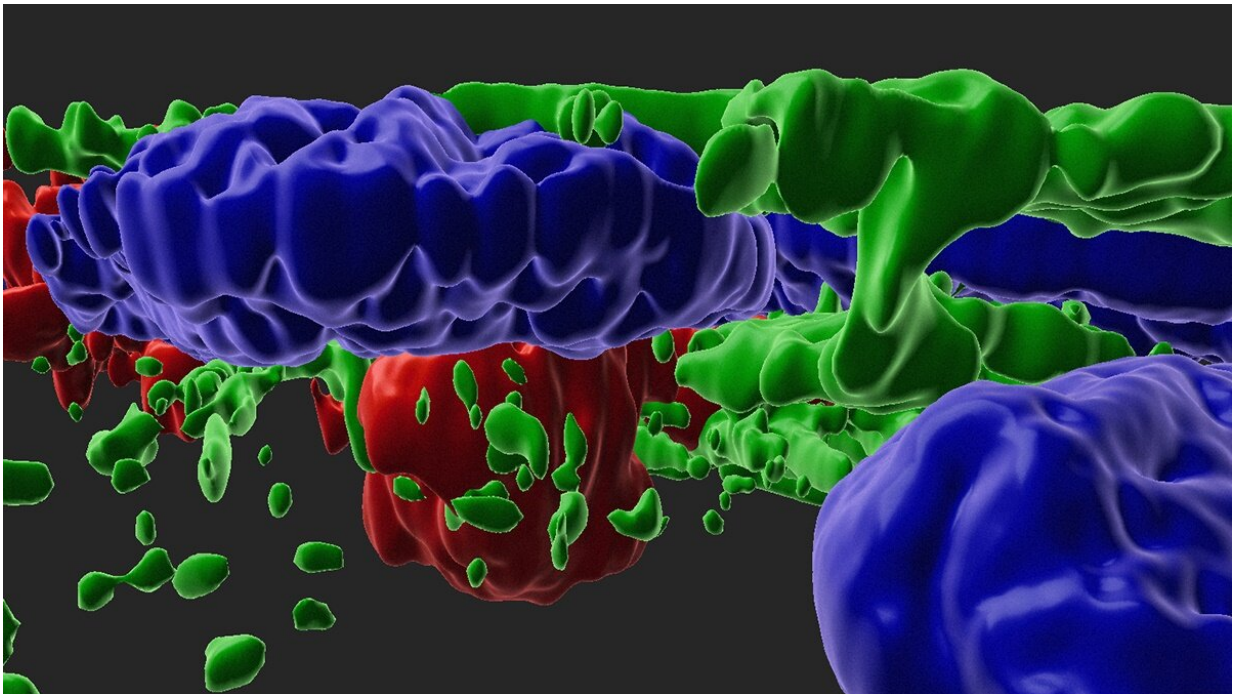# Researchers identify potential AMD drugs with stem-cell based research tool

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A 3D view of complement-activated RPE cells (green—cytoskeleton, blue—nucleus) with drusen/APOE (red) deposits. Credit: Ruchi Sharma and Davide Ortolan (NEI)

Using a stem-cell-derived model, researchers have identified two drug candidates that may slow dry age-related macular degeneration (AMD), a leading cause of blindness for which no treatment exists. The scientists, from the National Eye Institute (NEI), part of the National Institutes of

Health, published their findings today in *Nature Communications.*

"This stem-cell-derived model of dry AMD is a game-changer. Scientists have struggled to unravel this incredibly complex disease, and this model could prove to be invaluable for understanding the causes of AMD and discovering new therapies," said Michael F. Chiang M.D., director of the NEI.

This is among the first studies to show that it's possible to develop a dish-based model that replicates the characteristics (phenotype) of a complex disease, as opposed to a disease caused by a single mutation. The causes of AMD involve a yet-to-be-understood combination of genetic factors, aging, and behavior-related risk factors such as smoking and diet.

The researchers used the model to screen drugs to see if they may slow or halt disease progression. Two drugs prevented the model from developing key phenotypes: the accumulation of drusen, lipid-rich deposits in the retina, and the atrophy, or shrinkage, of retinal pigment epithelium (RPE) cells. RPE is a layer of tissue that nourishes the retina's light-sensing photoreceptors. In AMD, RPE cells shrink and die. Loss of RPE leads to the death of photoreceptors and in turn, to loss of vision.

Led by Kapil Bharti, Ph.D., who directs the NEI Ocular and Stem Cell Translational Research Section, and Ruchi Sharma, Ph.D., a staff scientist in the lab and lead author of the paper, the investigators developed the model using stem cell-derived mature RPE cells. Bharti's group initially developed the cells using skin fibroblasts or blood samples donated from AMD patients. In Bharti's laboratory, the fibroblasts or blood cells were programmed to become induced pluripotent stem cells (iPSC), and then programmed again to become RPE cells.

Importantly, the findings shed light on how genetic variants affect AMD

development.

Previous genetic studies had shown that some AMD patients have variants in genes responsible for regulating the alternate complement pathway, a key part of the immune system. However, it was unclear how the genetic variants led to disease.

One hypothesis was that patients with such variants lacked the ability to regulate the alternate complement pathway once it had become activated, resulting in the formation of anaphylatoxins, a type of protein that mediates inflammation, among other biological functions.

To test this hypothesis, the researchers exposed 10 iPSC-derived RPE cell lines involving different genetic variants to anaphylatoxins from human serum. They predicted that such a stress challenge would act as a surrogate for age-induced increases in alternate complement pathway that had been observed in the eyes of patients with AMD.

iPSC-derived RPE exposed to activated human serum developed key disease phenotypes: the formation of drusen, and RPE atrophy, which is associated with advanced disease stages. While signs of disease progression occurred among all 10 types of iPSC-derived RPE cells used in the study, they were worse in the iPSC-derived RPE from patients with high-risk variants in the alternate complement pathway, compared to those with low-risk variants, which gave the researchers a way to discern specific effects of genotype on disease characteristics.

Using the model, they screened more than 1,200 drugs from a library of pharmacological agents that had been tested for a range of other conditions.

The screen flagged two drugs for their ability to inhibit RPE atrophy and drusen formation: A protease inhibitor called aminocaproic acid, which

likely directly blocks the complement pathway outside cells and a second agent (L745), which stops complement induced inflammation inside the cell indirectly via inactivation of the dopamine pathway.

Of the two, L745 looks most promising and biologically interesting, according to Bharti. The drug was developed by Merck & Co. and was originally tested for treating schizophrenia.

As an extension of the current work, Bharti lab helped generate iPSCs from participants in a large NEI supported clinical study known as AREDS2.

"We grew 65 iPSC-derived RPE lines and they are now being shared with the research community to create models for AMD research," Bharti said. "This paper provides a framework to develop such models and thus has broad implications for the AMD research community."

The AREDS2 iPSC-derived RPE cells are available through a repository managed by the New York Stem Cell Foundation.

  More information: Ruchi Sharma et al, Epithelial phenotype restoring drugs suppress macular degeneration phenotypes in an iPSC model, *Nature Communications* (2021). DOI: 10.1038/s41467-021-27488-x

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