TREATMENT FOR AGE-RELATED MACULAR DEGENERATION (AMD) BY TARGETING CHOLESTEROL TRANSPORT IN MACROPHAGES

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Technology Description

Researchers in Prof. Rajendra Apte's laboratory developed novel methods for treating macular degeneration and other eye diseases by targeting a cholesterol transport pathway involved in the formation of new blood vessels. Age-related macular degeneration (AMD) is a leading cause of blindness and is characterized by choroidal neovascularization (CNV), the development of abnormal blood vessels under the retina. Current therapies for AMD have limited efficacy and require frequent eye injections. This new technology is designed to prevent CNV through a new mechanism - targeting a cholesterol transport protein (ABCA1) pathway in macrophages.

As macrophages age, their ability to transport and remove cholesterol build-up is impaired, potentially causing CNV. Their cholesterol transport function can be restored through a variety of mechanisms: miR-33 inhibitors (miR-33 normally downregulates ABCA1); cholesteryl ester transfer protein (CETP) inhibitors (CETP normally influences macrophage cholesterol efflux); or by activating ABCA1 in cultured macrophages and treating the patient with those cultured cells. In addition to AMD, these therapies could be used to treat other ocular diseases associated with neovascularization (e.g., diabetic retinopathy and retinopathy of prematurity). A particular benefit of this treatment is that some of these therapeutic agents can be delivered via eye drops, reducing the risk of systemic side effects while potentially preventing or reversing AMD progression and blindness.

Stage of Research

- *In vitro* – The inventors demonstrated that agents which restore ABCA1 levels could improve the ability of macrophages to remove cholesterol, thereby slowing the formation of new blood vessels.
- *In vivo* – The inventors reversed macular degeneration in the eyes of old mice using agents that restore cholesterol removal (miR-33 inhibitors and Liver X Receptor agonists).

Applications

- **Therapeutic for Age-Related Macular Degeneration (AMD)** – protect against blindness using any of the following drug formats:
  - single-stranded RNA inhibitor of miR33
  - small molecule inhibitor of cholesteryl ester transfer protein (CETP)
  - upregulation and/or increased activity of the ABC transporter expression/activity of macrophages

Key Advantages

- **First-in-class treatment –** novel pathway
- **Local drug delivery** – potential for delivery of agents via eye drops, lowering the risk of systemic side effects and off-target complications

Publications

- Sene, A., Khan, A. A., Cox, D., Nakamura, R. E., Santeford, A., Kim, B. M., ... & Chowers, I. (2013). Impaired cholesterol efflux in senescent macrophages promotes age-related macular degeneration. *Cell metabolism*, 17(4), 549-561.
- Cholesterol buildup links atherosclerosis and macular degeneration, Washington University in St. Louis News, Apr. 2, 2013.

Patents

- Inhibition of choroidal neovascularization (U.S. Patent Nos. 9121019, 9254285, 9399045)

Website

- Apte Lab