Identification of Fluoxetine as a Direct NLRP3 Inhibitor to Treat Atrophic Macular Degeneration: Molecular Modeling, Mechanism, Morphometry, and Meta-analysis (Year 2)

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Atrophic macular degeneration (AMD) affects 200 million people worldwide. There is no FDA-approved therapy for this disease, the leading cause of irreversible blindness among people over 50. Vision loss in AMD results from retinal pigmented epithelium (RPE) degeneration. RPE cell death is driven by accumulation of Alu RNAs (noncoding transcripts of a human retrotransposon), amyloid beta (Abeta), and iron. Alu RNA, Abeta, and iron induce RPE degeneration by activating the NLRP3-ASC inflammasome. In new data, I report that fluoxetine, an FDA-approved anti-depressant, binds NLRP3 in silico, in vitro, and in cells. In new data, I also report that fluoxetine inhibits NLRP3 ATPase activity. In an extension of last year's work which focused solely on Alu RNA, I provide new data that fluoxetine blocks RPE degeneration induced by Abeta and iron in vivo. In a substantive expansion of last year's work in which I studied a single health insurance database comprising 25 million people, I present new data by analyzing three health insurance databases comprising more than 130 million Americans, which identify a reduced hazard of developing AMD among patients with depression who were treated with fluoxetine. In addition, new analysis from a random-effect meta-analysis model employing propensity score matching and confounder adjustment demonstrates a pooled risk reduction of 17% for fluoxetine users. A prediction interval estimates that a future clinical trial has a greater than 95% probability of identifying a protective effect of fluoxetine against AMD. Collectively, these interdisciplinary studies provide strong support for testing fluoxetine as a potential drug repurposing candidate for AMD, which causes blindness in millions of people in the United States and across the world.

Awards Won:

Second Award of $2,000

Embark China: Third Award

Serving Society Through Science: First Award of $1000