

Triangulating Fluoxetine into a Novel Macular Degeneration Therapy via Biochemical, in vivo and Big Data Approaches

Ambati, Meenakshi (School: Albemarle High School)

Dry macular degeneration affects nearly 200 million people worldwide. There is no FDA-approved therapy for this disease, which is the leading cause of irreversible blindness among people over 50 years of age. Vision loss in this condition results from degeneration of the retinal pigmented epithelium (RPE). RPE cell death in dry macular degeneration is driven by accumulation of toxic molecules known as Alu RNAs, which are noncoding RNAs in the human genome. Alu RNA induces RPE degeneration by activating a macromolecular protein complex known as the NLRP3-ASC inflammasome. I report that fluoxetine, an FDA-approved drug for treating clinical depression, inhibits activation of the NLRP3-ASC inflammasome in RPE cells and macrophages, two critical cell types in dry macular degeneration. I also demonstrate that fluoxetine, unlike several other anti-depressant drugs, inhibits RPE degeneration in an in vivo model of dry macular degeneration. Finally, I present a Big Data analysis of a health insurance database of 25 million Americans, in which I identified a dramatic reduction in the development of dry macular degeneration among patients with depression who were treated with fluoxetine compared to those treated with other anti-depressants. Collectively, these studies triangulate to link fluoxetine as a potential drug repurposing candidate that could become the first therapy for a major unmet medical need that causes blindness in millions of people in the United States and across the world.