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Science in the News - AG10 inhibits amyloidogenesis and cellular toxicity of the familial amyloid cardiomyopathy-associated V1221 transthyretin

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Currently in class, we discussed how amyloid fibrils are associated with multiple diseases such as Alzheimer's and Creutzfeldt-Jakob Disease(CJD). The reason amyloid fibrils are formed has to do with the misassembly of partially unfolded proteins. This article focuses on an example of a misfolded protein and a way to stabilize it so disassembly does not happen.

In the study, treatment of cardiac amyloidoses, a disorder caused by deposits of abnormal proteins(amyloids) in the heart tissue, is currently in development. Cardiac amyloidoses are commonly caused by transthyretin (TTR), a transport protein, that becomes toxic from mutations such as the Val122lle and non-mutations such as the WT mutations. Because of the genetic mutations, TTR can become unstable and misfold, causing toxic amyloids to accumulate in the body. A current study of TTR, has led to the development of AG10, a small molecule, that binds and stabilizes, the Val122lle and WT-TTR from dissociating and later cause cardiac amyloidoses.

The development of AG10, started by focusing on the currently developed TTR stabilizers, tafamidis and diflunisal. After analyzing a TTR structure with a WT mutation, and additional data on the current stabilizers, scientists predicted that adding an additional carboxylic acid to the WT-TTR structure would result in a better TTR stabilization. Studies later showed that the new stabilizer, later known as AG10, was a highly effective stabilizer for both the WT and Val122lle mutations, and prevented dissociation of transthyretin. Currently AG10, is in

Phase 2 of clinical trials, but data from Phase 1 has been presented to the public. The presentation discussed how AG10 did not show any discrepancies when treated with healthy volunteers and binded to the misfolded proteins during the clinical trials.

In conclusion, the reason I chose this article is because the professor I am currently researching for developed the AG10 stabilizer and helped me want to pursue a better understanding on how proteins work in the body.

Work Cited

Penchala, Sravan C., et al. "AG10 Inhibits Amyloidogenesis and Cellular Toxicity of the Familial Amyloid Cardiomyopathy-Associated V122I Transthyretin." *PNAS*, National Academy of Sciences, 11 June 2013, www.pnas.org/content/110/24/9992