

## Engineering Bugs for the Discovery of New Drugs Against Neurodegenerative Diseases

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**P**rotein misfolding is a common pathological feature for many human diseases, such as Alzheimer's disease (AD), Parkinson's disease, type II diabetes and others. We will describe the development and application of an integrated and generalizable bacterial platform for facile discovery of macrocyclic rescuers of disease-associated protein misfolding. In this system, large combinatorial libraries of macrocycles are biosynthesized in *Escherichia coli* cells and simultaneously screened for their ability to rescue pathogenic protein misfolding using a genetic assay based on fluorescence-activated cell sorting. We will first describe the effectiveness of this approach through the identification of drug-like, head-to-tail cyclic peptides that modulate the aggregation of the amyloid  $\beta$  peptide (A $\beta$ ) of AD. By using a series of biochemical, biophysical and biological assays using isolated A $\beta$ , primary mammalian neurons and various established AD models in the nematode *Caenorhabditis elegans*, we have found that the selected macrocycles potently inhibit the formation of neurotoxic A $\beta$  aggregates. Further, to showcase the generality of our approach, we will describe the application of the same platform for the identification of misfolding rescuers of mutant Cu/Zn superoxide dismutase 1 (SOD1), a protein whose misfolding and aggregation is associated with inherited forms of amyotrophic lateral sclerosis. Overall, our approach represents a straightforward strategy for the discovery of molecules that rescue the misfolding of polypeptides known to be associated with disease effectively.

### Biography:

Georgios Skretas graduated from the School of Chemical Engineering of the National technical University of Athens (Greece) in 1998 and received his PhD in Chemical Engineering from Princeton University (USA) in 2006. He then moved on to the University of Texas at Austin (USA) to carry out post-doctoral research training under the guidance of Prof. George Georgiou. Since 2009, Dr. Skretas has been the principal investigator of the Laboratory of Enzyme & Synthetic Biotechnology at the Institute of Biology, Medicinal Chemistry & Biotechnology of the National Hellenic Research Foundation (Greece), where he currently holds the rank of Research Associate Professor.