A HIGH THROUGHPUT SCREEN FOR NOVEL PHARMACEUTICALS TO TREAT ALZHEIMER'S DISEASE

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Alzheimer's disease is estimated to affect 10% of people over 65, and nearly 50% of people over 85. As the 'baby boomer' generation ages, and medical advances enable people to live longer, the number of Alzheimer's victims is expected to increase dramatically. Several pharmaceuticals are available to treat Alzheimer's disease. However, these compounds merely target the symptoms of Alzheimer's disease. Since they do not target the underlying molecular causes of Alzheimer's disease (AD), these drugs cannot halt the progression of the disease. Indeed, halting the progression of Alzheimer's disease, and reducing its future incidence will require the development of new kinds of drugs that do not merely ameliorate the symptoms, but which actually prevent (or reverse) the underlying molecular causes of AD.

A range of biochemical and genetic studies indicate that the molecular events that lead to AD stem from problems of protein misfolding and aggregation. In particular, the misfolding and aggregation of the Alzheimer's peptide, A-beta, is known to play a central role in the molecular etiology of AD. While the detailed mechanism of A-beta aggregation and toxicity remain active areas of research, it is already clear that conformational changes (i.e. folding/misfolding) of the A-beta peptide, followed by aggregation into some form of oligomeric complex initiates a cascade of events that ultimately leads to neurodegeneration.

Inhibition of either (i) the conformational changes in A-beta that precede aggregation, or (ii) the aggregation step itself are both attractive targets for the prevention and treatment of AD. However, finding compounds that accomplish this goal without interfering with the folding of other proteins in the cell has been seen as a major challenge. Indeed, this perceived difficulty has discouraged many researchers – both in academic labs and at pharmaceutical companies – from pursuing folding modulators or aggregation inhibitors as AD therapeutics.

To overcome this challenge, we recently developed a high throughput screen that allows us to search through vast collections (libraries) of small organic molecules for compounds that inhibit A-beta misfolding and/or aggregation. Most importantly, our new screen is designed to ensure that generic inhibitors of protein folding will not be isolated. Only compounds that block the “bad” A-beta misfolding and aggregation, but allow the “good” folding of other proteins will be isolated by our screen.

We propose to use this screen to isolate new compounds to treat Alzheimer's disease. Specifically, we propose (i) to apply the new screen in a high throughput format to search vast combinatorial libraries of drug-like compounds for those that inhibit A-beta misfolding and aggregation; (ii) to characterize these ‘hits’ biochemically, thereby elucidating their mechanism of action: and (iii) to demonstrate the efficacy of these compounds as inhibitors of A-Beta toxicity through the use of biological assays in cells and/or model organisms.

Commercial Applications: Because of the widespread prevalence of Alzheimer's disease, and the current unavailability of effective therapeutics, the potential for commercial applications is substantial. These applications fall into two classes:

(i) Technology: Licensing of the high throughput screen to search libraries of drug-like compounds for 'hits'. (Princeton University has applied for patent protection for the method.)

(ii) Specific Compounds: Intellectual property associated with specific compounds isolated by the screen. Such compounds will provide leads and/or drugs for the treatment and/or prevention of Alzheimer's disease.