

2nd International Summit on **Integrative Biology**

August 04-05, 2014 Hilton-Chicago/Northbrook, Chicago, USA

Computer-aided discovery of novel non-peptide inhibitors against A β aggregation for the treatment of Alzheimer's disease

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A non-peptide inhibitor that provides metabolically stable, orally active, and capable of crossing the blood-brain barrier has been a popular option for treating Alzheimer's disease (AD). To identify novel non-peptide inhibitors against A β aggregation, a structure-based pharmacophore model (SBPM) was developed using the representative docked conformation of the recently discovered peptide inhibitor PGKLVYA in the potential binding site on the A β (17-42) protofibril surface. The best SBPM, consisting of 2 hydrophobic, 1 hydrogen bond donor, and 1 positive ionizable features, was further validated using ligand pharmacophore mapping studies and then used as the 3D query in virtual screening to identify potential hits from the National Cancer Institute database. These hits were subsequently filtered by toxicity prediction and molecular docking, and their binding stabilities and affinities were validated by 20-ns molecular dynamics simulations and molecular mechanics Poisson-Boltzmann surface area analysis, respectively. Finally, 2 hits (NSC35984 and NSC102747) were identified as potential leads, which exhibited higher binding stability and affinity towards A β compared with PGKVYA. Our results also showed that these 2 hits can be easily synthesized and have structural novelty, indicating that they are promising candidates for treating AD.

Biography

Hsuan-Liang Liu received his BS and PhD degree in the field of Chemical Engineering in 1991 and 1998 from National Taiwan University and Iowa State University, respectively. Prof. Liu's research fields are computational biology, bioinformatics, proteomics, and genetic & protein engineering. He is currently a distinguished Professor in the Department of Chemical Engineering and Biotechnology of National Taipei University. He joined the member of the Taiwan Institute of Chemical Engineering and received the Young Research Fellow Award in 2004. To date, he has published more than 120 SCI papers with high quality.

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