Title: Design and Discovery of Small Molecular PPI Modulators

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Abstract

1. Understanding the nature of ligand-target interaction
In the development of the first synthetic thrombin inhibitor in clinic, Argatrovan, I noticed a closest packing nature of ligand atoms in the pocket of target protein through the determination of X-ray structures with thrombin and trypsin. Ligand atom positions will be described by the closest packing particles with contact distances of covalent bond atoms or that of non-bonded atoms.
2. Development of a novel drug design software
We developed a novel software, CPADD (Closest Packing Approach for de novo Drug Design) according to the closest packing principle and succeeded in the finding of possible ligand atom positions. Then we extracted ligand molecule structures focusing on the position of ring structures. We use "filtering by assumed binding mechanisms" instead of "score" to rank promising structures.
3. "MUST tool" is real space protein 3d-models
In PPI (protein-protein interaction) targets, there is no catalytic site and drug target sites have to be determined by drug designers. Our experience shows that real space 3d-models are inevitable tools. We developed a machine to produce light solidified polymer models. These models are useful to study and find binding mechanisms and to get guidelines for hit to lead structure optimization.
4. Applications
We have succeeded in finding inhibitors in 18 targets continuously without any failure; 9 of them are enzymes and other 9 are PPI targets. Most of the cases, we obtained experimental, molecular level proofs by X-ray, NMR, SPR and other physicochemical methods.
1) Two methods, CPADD and newly developed SBSG (Structure Based Scaffold Generation) succeeded in finding inhibitors against VEGF, Notch1, IL-6, IgE and other 5 PPI targets. 2) In the case of VEGF, an orally administered compound with MW=490 showed *in vivo* efficacy similar to Avastin, an anti-VEGF antibody. 3) We also obtained acceptable hits for undisclosed PPI targets in collaboration with pharmaceutical companies including Ajinomoto Pharmaceuticals Co. Ltd, Takeda Pharmaceutical Co. Ltd and RaQualia Pharma Inc.
The present system was named as INTENDD (INTerprotein Engine for New Drug Design). We welcome proposals for research collaboration.

Biography

Dr. Takao Matsuzaki, Ph.D. is an Independent Drug Design Advisor and head of Drug Design Lab. of Interprotein Corp. He got his B Sc(1968), M Sc (1970) and Ph.D.(1989) in pharmaceutical sciences from the University of Tokyo. And he received Incentive Award in 1991 from Pharmaceutical Society of Japan. He was a Research Fellow at Mitsubishi Chemical Corp.(1970-2006).