[S6-3] [10/11/2003(Sat) 10:20-11:05/ Grand Ballroom 103]

Tageting Protein-Protein Interactions-A Fragment Assembly Approach

Kumar Paulvannan

Sunesis Pharmaceuticals, Inc, U.S.A.

I describe here a novel and promising approach to drug discovery that involves the identification and assembly of drug-like fragments to afford lead compounds. This approach is attractive for a number of reasons. First, the productive assembly of two weakly bound fragments, even fragments with independent dissociation constants in the low mM range, can potentially afford ligands with sub-micromolar affinities for their targets. Second, there is a tremendous economy of scale from identifying leads in pieces rather than screening fully elaborated compounds (for example, as occurs in high-throughput screening). Screening even a modest collection of 1,000 fragments could theoretically sample the diversity space of the 10^6 derivatives that could result from the assembly of every combination of two fragments. Sunesis has developed a proprietary technology called covalent tethering that allows the facile screening and detection of drug-like fragments, and we have shown that these fragments can be elaborated into drug-like leads suitable for input into medicinal chemistry programs. The description of the covalent tethering technology will be followed by three working examples, which include the discovery of novel inhibitors of the enzymes thymidylate synthase and caspase-3, as well as the discovery of a small-molecule antagonist of the IL-2/IL-2R□ interaction.

Tethering is a facile technique for fragment discovery. Captured fragments bind via specific, drug-like interactions, and these fragments can be advanced to non-covalent inhibitors using a variety of techniques. Tethering has been used successfully in several target classes, including the inhibition of protein:protein interactions.

Tethering is a service mark of Sunesis Pharmaceuticals, Inc. for its fragment based drug discovery.