

## Method for Rapid Identification of Synthetic Bivalent Ligands that Bind Target Molecules

**Background:** Protein kinases comprise the largest gene family in humans and their deregulation is implicated in numerous human diseases, including cancer. New approaches for the discovery of selective inhibitors of protein kinases have the potential to provide useful therapeutic leads in drug design. It has been extremely difficult, however, to develop specific kinase inhibitors since most inhibitors target the ATP binding site. A previous strategy for increasing selectivity and affinity of protein kinase inhibitors has been the development of bisubstrate inhibitors. A drawback of the bisubstrate design approach is that it necessarily relies on structural information as well as prior knowledge of a specific peptide substrate for the targeted kinases, and such information is not known for many kinases of biological or pharmacological relevance.

### Applications:

- *Identification of highly potent and highly selective protein kinase inhibitors when only minimal structural or substrate information is known for a given target*
- *Aids in development of small-molecule conjugates for development of drugs, reagents for probing biological pathways, microarrays, and labeling reagents for imaging*

### Advantages:

- *Does not require prior knowledge of structural information or prior identification of specific protein kinase substrates/binding proteins*
- *Method can be more broadly developed for targeting different classes of therapeutic targets with known small molecule ligands*

**The Technology:** University of Arizona scientists are developing a new fragment-based bivalent ligand selection methodology that allows for the discovery of protein surface-targeted cyclic peptides which are steered by an active site binding small-molecule ligand. This new bivalent selection approach specifically involves a new tethering strategy that allows for the selection of cyclic peptides, from a library, directed by ATP-competitive small molecules targeted to a protein kinase target. The successful selection and validation of high affinity and highly selective bivalent compounds comprising cyclic peptides attached to small molecules without prior structural knowledge distinguishes this technology from previous approaches.

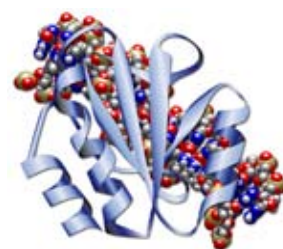
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**Stage of Development:** Active-site directed bivalent selection strategy has been demonstrated against targeted kinase. Potent bivalent inhibitor discovered and proven to be a highly selective inhibitor for the targeted kinase.

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