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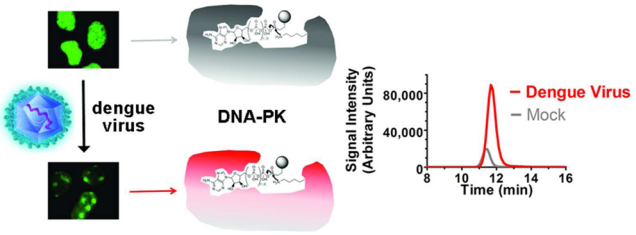
PROFILING DENGUE VIRUS

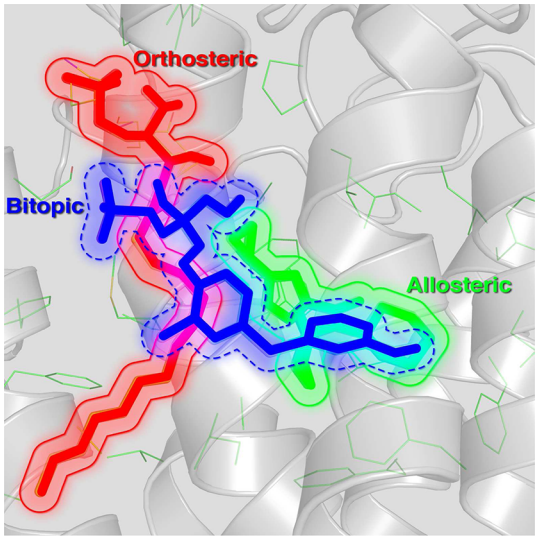
It is estimated that as many as 100 million people are infected with Dengue virus every year. With no treatment or vaccine available, development of methods to help understand the mechanisms and processes that accompany infection is a critical step toward devising strategies for prevention and treatment. To this end, Vetter *et al.* (DOI: 10.1021/cb300420z) now report a chemoproteomic approach for characterizing changes in protein function within the first hour of infection by Dengue virus.



A key element of their approach is the use of two strategically designed small molecule ATP mimics that bind in the ATP-binding site of kinases and then undergo a reaction in which a biotin becomes covalently attached to the kinase. The biotin-linked kinase can be purified and then quantified using mass spectrometry methods. Using this approach, the authors found that the enzyme DNA-dependent protein kinase exhibited increased activity specifically in the cell nucleus within 60 min of infection. The results highlight the utility of chemoproteomic profiling for characterizing changes in protein activity and location in response to external stimuli.

BITOPIC LIGANDS FOR BIASING LIGAND BINDING

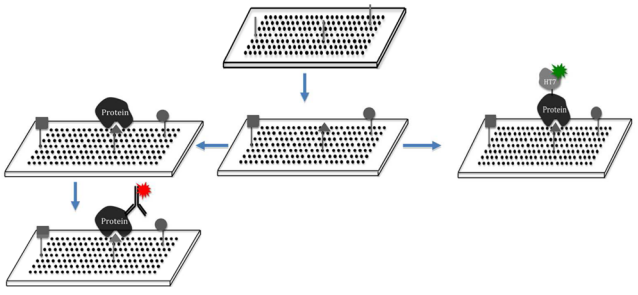
Sphingosine 1-phosphate (S1P) is a lipid-based signaling molecule with important roles in the trafficking of white blood cells and the development of blood vessel walls. S1P binds to a family of five G protein-coupled receptors on the cell surface, called $S1P_{1-5}$, which are similar in structure and sequence but play varied roles in biology. Toward developing small molecule tools capable of interrogating specific S1P receptors, Jo *et al.* (DOI: 10.1021/cb300392z) report the characterization of selective allosteric and bitopic ligands for the medically relevant receptor $S1P_3$.



The receptor–ligand interactions were analyzed using a combination of protein mutagenesis, ligand binding competition assays, and molecular modeling experiments. The dicyclohexyl amide CYM-5541 was determined to be a selective allosteric $S1P_3$ agonist, and it bound to a region distinct from that of S1P. The diaryl thioether SPM-242 was found to be a bitopic antagonist and bound to both the S1P site and the CYM-5541 site. These selective ligands are valuable probes for exploring the specific role of $S1P_3$ in biology and are exciting starting points for development of $S1P_3$ modulators with potential therapeutic applications.

HALOTAG FOR HIGHLY SENSITIVE SMALL MOLECULE SCREENING

Small molecule microarrays, in which small molecules are covalently attached to a glass slide and screened for protein binding, are a valuable screening platform. Compounds that bind anywhere on a protein of interest, regardless of whether they alter protein function, can be identified with this technology. This offers a high-throughput method for discovery of small molecules that bind traditionally "undruggable" targets, but the technology has been limited by low sensitivity. Now, Noblin *et al.* (DOI: 10.1021/cb300453k) describe the application of the HaloTag protein labeling method to increase the scope and utility of small molecule microarrays.



In the HaloTag system, the protein of interest is fused to a small protein that can be selectivity labeled with a fluorophore. Using this methodology, the authors screened 20,000 compounds and discovered several selective ligands for protein tyrosine phosphatase 1B. This approach requires 10 times less protein and is amenable to multiplexing, greatly expanding the potential of small molecule microarrays for ligand discovery.

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