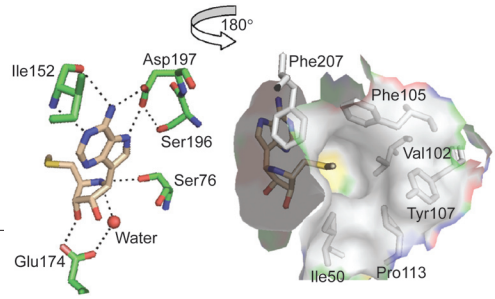
# In this ISSUE

acs chemical biology




## The State of the Transition State

Enzyme inhibitors are extraordinarily useful biological tools and, if the enzyme happens to be involved in a pathological process, valuable potential drug leads as well. Stable transition state analogues are often promising starting points in the design of potent and effective inhibitors, and knowledge about the enzymatic transition state certainly comes in handy during the design process. However, probing enzymatic transition states can be tricky because of their short lifetimes and complicated structural and kinetic properties. Now, Gutierrez *et al.* (p 725 and Point of View p 711) describe a new method for predicting the nature of enzymatic transition states using transition state analogues.

The authors employ a defined set of inhibitors of 5′-methylthioadenosine nucleosidases (MTANs), a family of bacterial enzymes involved in the metabolism of 5′-methylthioadenosine, to characterize the nature of various MTAN transition states. Through the use of inhibitors that mimic either an early dissociative transition state or a late dissociative transition state, comparison of the ratio of their dissociation constants turned out to be a reliable predictor of early and late dissociative MTAN transition states.

## Assays Designed for Success

The recent marriage of cell-based assays and high-throughput screening technologies has fostered aspirations toward an efficient and relevant approach for elucidating complex biological processes and discovering new drugs. Jones and Diamond (p 718) review strategies for the design of cell-based assays with increased chances of success.

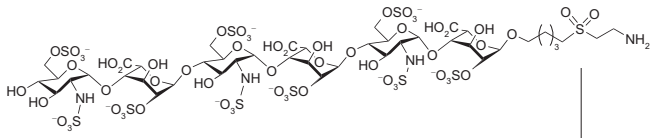
Many cell-based assays employ phenotypic readouts such as cell death or cell proliferation in the identification of lead compounds. Two strategies are suggested for increasing the usefulness of a particular cell-based assay. First, the assay should be designed with an endpoint specific to the disease mechanism. Examples include assays that detect protein aggregation, modulation of gene expression, changes in protein conformation, protein translocation, or the interaction between a protein and its cofactor. Second, careful consideration should be given to the compounds chosen to be screened. The authors suggest using smaller libraries composed of cell-permeable, nontoxic, nonmutagenic, and bioavailable compounds, especially natural products and drugs already approved for use in humans.

## RNA and Small Molecules Chip In

As new cellular roles are ascribed to RNA, these molecules continue to dazzle with an ever-expanding functional repertoire. Encouraged by these discoveries, scientists are engineering synthetic RNA molecules to interact with a plethora of small-molecule ligands. The common *in vitro* selection process allows the detection of RNA that interacts with a specific ligand. Conversely, screening of small molecules in chemical microarrays facilitates the identification of ligands that bind to an RNA molecule of interest. In an elegant approach described in this issue, Childs-Disney *et al.* (p 745) combine these approaches into an integrated platform.

The authors' detection system required a microarray surface that allowed (i) immobilization of the studied ligands, (ii) binding of RNA molecules in native conformation, and (iii) harvesting of interacting RNA for identification. Agarose, a polysaccharide commonly used in nucleic acid biochemistry, satisfied all three criteria. Using the small-molecule microarray platform that they devised, the authors probed the interactions between 4 aminoglycosides and 4096 RNA molecules obtained by randomizing an internal loop.

## Chemokines and Chemical GAGs



The immune system relies on specialized proteins termed chemokines to guide the appropriate subset of white blood cell to sites of injury or infection. Chemokines interact with a heterogeneous group of linear, highly sulfated polysaccharides termed glycosaminoglycans (GAGs), but deciphering the molecular nature of the chemokine–GAG interaction is a significant challenge, in part because of the structural complexity of GAGs. De Paz *et al.* (p 735) now use synthetic GAG mimics in a microarray assay to help determine the GAG-binding profiles of various chemokines.

Using a microarray platform in which GAG mimics are immobilized to the microarray surface, the authors evaluated the binding interactions between 8 chemokines and 12 synthetic heparin-like oligosaccharides. Significant differences in the interactions between specific chemokines and the GAG-like oligosaccharides were readily apparent with this approach, which provided clues to the molecular determinants important in the interactions. Surface plasmon resonance confirmed the microarray results and provided more detailed information about the binding interactions. Further validation came when dendrimers coated with a specific GAG mimic inhibited migration of lymphocytes toward a specific chemokine gradient. In addition, preliminary *in vivo* experiments further supported the idea that, when the molecular details of a specific GAG–chemokine interaction are known, multivalent displays of GAG mimics could be effective modulators of chemokine activity.

**Published online November 16, 2007 • 10.1021/cb7002237 CCC: $37.00**