

Perspective: Trapping Moving Targets with Small Molecules

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Summary

Static protein models of active site targets most commonly used for structure-based drug design but this limits opportunities for novel drug development. Using small molecules to target allosteric sites on proteins may be more productive. Highlights the use of nuclear magnetic resonance spectroscopy in the drug discovery and design process.

Introduction

Allosteric inhibitors can target multiple protein conformations giving more chances for success than a single active site inhibitor.

A number of allosteric inhibitors are in advanced clinical development or on the market, e.g. imatinib (Gleevec), non-nucleoside HIV reverse transcriptase inhibitors and herpesvirus C polymerase.

NMR is a powerful technique for detecting conformational changes in proteins and protein complexes on a per-residue basis in multiple time frames and can be used to study small molecule interactions with large (>20kD) proteins.

Key points raised in this review

Two-dimensional heteronuclear single quantum coherence spectroscopy (HSQC) can identify ligand binding residues allowing easy differentiation between competitive and allosteric-site binders.

NMR also detects disruptions in protein complexes by small molecules and the protein chain to which it binds.

Key Background References:

- 1) R. Sprangers, A. Velyvis, L. E. Kay, Solution NMR of supramolecular complexes: providing new insights into function. *Nat. Methods*. 4: 697, 2007
- 2) N. Vajpai et al., Solution conformations and dynamics of ABL kinase-inhibitor complexes determined by NMR substantiate the different binding modes of imatinib/nilotinib and dasatinib. *J. Biol. Chem.* 283: 18292, 2008
- 3) S. A. Showalter et al., Quantitative lid dynamics of MDM2 reveals differential ligand binding modes of the p53-binding cleft. *J. Am. Chem. Soc.* 130: 6472, 2008
- 4) J. L. Best et al., Identification of small-molecule antagonists that inhibit an activator: coactivator interaction. *Proc. Natl. Acad. Sci. U.S.A.* 101: 17622, 2004
- 5) G. M. Verkhivker et al., Complexity and simplicity of ligand-macromolecule interactions: the energy landscape perspective. *Curr. Opin. Struct. Biol.* 12: 197, 2002

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