



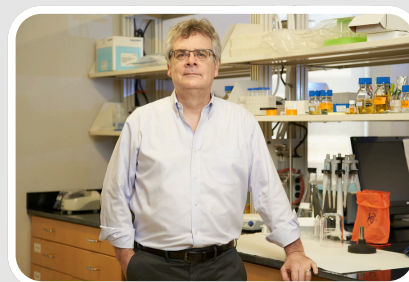
CHEMISTRY & BIOCHEMISTRY SEMINAR SERIES

A disordered life: Entropy in protein structure, stability and function

Abstract:

We have developed variety of NMR and analytical strategies to extract changes in conformational entropy that accompany the binding of a ligand by a protein. We have found that characterization of solution NMR relaxation in methyl-bearing amino acid side chains can be used as a reliable proxy for changes in this previously elusive thermodynamic quantity. Employing over two-dozen protein-ligand interactions, involving a range of ligand types, we have found that conformational entropy can strongly disfavor, strongly favor or sometimes not contribute to the free energy of binding. A possible structural origin for this remarkable variation will be described. Most of the insight into the role of conformational entropy in protein stability and function has been derived from soluble proteins.

We have initiated a study of the side dynamics and attendant conformational entropy in integral membrane proteins prepared in a variety of membrane mimetics. Thus far it has been found that the side chain motion of IMPs is qualitatively distinct from soluble proteins. IMPs appear to retain significant conformational entropy, which helps to stabilize the folded state within the membrane in the absence of the classic hydrophobic effect. In a translational effort, we are using knowledge of changes in conformational entropy to guide affinity optimization of protein drugs (biologics) such as antibodies. A strategy of pre-rigidification to reduce the entropic penalty associated with a local change in side chain motion (entropy), and thereby increase binding affinity, will be illustrated. Finally, time permitting, recent work with the dynamical activation of the E3 ubiquitin ligase Parkin will be described. Supported by the NIH and the Mathers Foundation.



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About the Speaker:

- B.Sc. (Hons) Carleton University, 1979
- M.Sc. Carleton University, 1981
- Ph.D. University of Pennsylvania, 1984
- NSREC Postdoctoral Fellow, National Research of Council of Canada, 1984-1985
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Focus Areas:

Molecular recognition, drug discovery, protein dynamics, NMR spectroscopy, thermodynamics, protein engineering, protein biologics, ubiquitin E3 ligases, parkin, membrane proteins, prostate cancer, Parkinson's disease