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Centre for Research in Molecular Modeling
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Joint Seminar Series of the
CENTRE FOR RESEARCH IN MOLECULAR MODELING
and the DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

March 12th, 2010, 2:30 pm - Concordia University SP-S110

Optimizing ligand-protein interactions via SILCS:
Site Identification by Ligand Competitive Saturation

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Fragment-based methods for drug optimization have great potential; however, time, expense and sensitivity considerations associated with NMR and x-ray crystallographic based methods limit their applicability. As an alternative we have developed a computational approach, SILCS: Site Identification by Ligand Competitive Saturation, that uses explicit solvent all-atom molecular dynamics to identify binding sites on protein surfaces for functional groups. Information from the SILCS approach may then be combined with structural information on an inhibitor-protein complex to facilitate modification of the ligand to improve its binding affinity. An overview of SILCS and its application to inhibitor-ligand optimization will be presented.

Alexander D. MacKerell, Jr. is the Grollman-Glick Professor of Pharmaceutical Sciences in the Department of Pharmaceutical Sciences of the University of Maryland. He is also the Director of the University's Computer-Aided Drug Design Center. He obtained a Ph.D from the Rutgers University, New Brunswick, in 1985 under the supervision of Prof. Pietruszko. Before his professorship at the University of Maryland in 1993, he was awarded numerous postdoctoral fellowships (NIH, NSF and Karlinska) during which he worked under the supervion of Prof. Rigler at the Karlinska institute, Sweden, and later with Prof. Karplus at Harvard University. In 2006, Dr. MacKerell was named the Maryland Chemist of the Year by the ACS Maryland Section for "his numerous scientific achievements, including pioneering research on the aldehyde dehydrogenase enzyme system, biophysical studies, including time-resolved fluorescence, chemical relaxation and MD simulations of ribonuclease T1, developing methodology in the area of empirical force fields and MD simulations, structure-activity relationships of DNA and RNA and the application of computational methods to drug discovery." (Quoted from http://mdchem.org/cc/cc-06-Dec.pdf)