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MS-based Structural Proteomics for Drug Development and Design

Status	Current
Competition	Development of New Technologies Competition
Sector	Development of New Technologies
Genome Centre	Genome British Columbia
Project Leader	Christoph Borchers

Project Description

Proteins play a key role in important biological processes, and as such, are key targets for newly-developed drugs. The three-dimensional model of a protein can be analyzed to find promising sites for potential drug binding, a process called “rational drug design”. Determining the structure of a single protein typically takes months or even years using currently available techniques such as x-ray crystallography or nuclear magnetic resonance. The challenges these technologies face include the length of time required and that some key families of proteins (notably membrane receptors, which are often drug targets) may not be amenable to these types of analyses. Also, these techniques provide information about the most stable form of a protein, while the biologically active protein may take on a different shape while it interacts with other molecules as part of a biological process.

The sequencing of both the human genome and the genomes of several key pathogens has accelerated the pace at which potential protein drug targets are discovered. A recent study has estimated that 29% of proteins involved in binding to other proteins (“protein-protein interactions”) contain potential binding sites for small-molecule drugs. Since current screening processes do not easily detect these sites, this represents a vast, untapped resource of potential drug targets.

In order to speed up the drug design process and to take advantage of the possibilities presented by protein-protein interactions, this project will make use of techniques currently employed in the analysis of large numbers of proteins in a cell, tissue, or organism (“proteomics”). Specifically, emerging cross-linking techniques using formaldehyde and newly synthesized reagents will be employed to preserve biologically-active protein-protein interactions in living cells or in solution for subsequent analysis by mass spectrometry (MS). MS is an extremely sensitive and specific technique for determining chemical structures, and can provide comprehensive structural information about protein-protein interactions when used in combined with these cross-linking reagents. Understanding these interactions can help assist in the development of potential lead drug candidates. Developing algorithms and software for the interpretation of the MS data in order to determine 3D structural models will be a major part of the project. We will utilize the solid foundation of existing modeling, prediction, calculation and database methods in order to achieve our goals. Our approach will be validated by the analysis

of protein-protein interactions involved in a model system that is involved in the yeast cell cycle: the anaphase-promoting complex (APC). These tools and protocols will allow for the compilation of interaction data from 5 to 10 samples per day, and for analysis of three dimensional structures of protein families that are not easily studied by conventional techniques.

These tools will be adaptable to a variety of platforms, and should be of great value both to academic researchers seeking to understand the nature of biologically important proteins and to the pharmaceutical industry in the search for new therapeutics.