Protein Chemistry Laboratory Major Accomplishments

Since 1995, the Protein Chemistry Laboratory has achieved a number of significant breakthroughs:

- Determination of ETS1 Transcription Factor Binding Kinetics. Our work with the ETS1 transcription factor, using the BIAcore® Biosensor, first defined the complex nature of the binding of this protein to its recognition-site DNA and allowed us to define the C-terminal fragment of the ETS1 protein. The C-terminal fragment exhibited simple binding kinetics, and we defined this fragment's structure during the binding process to its DNA recognition site.

- BIAcore® Studies of HIV NCp7 Binding to Short Oligonucleotides. Surface plasmon resonance spectroscopy (SPR) has been used previously to measure interactions among macromolecules. Our laboratory has pioneered the use of the BIAcore® Biosensor to study the interactions among proteins and nucleic acids. The human immunodeficiency virus (HIV) nucleocapsid (NC) protein is known to bind nucleic acids strongly and non-specifically at low ionic strength and less strongly but more specifically at moderate ionic strength. The use of SPR has led to the definition of nucleic acid sequences that allow high-affinity binding of NCp7, and a patent application has been made (US Patent Application 60/017,128: "Oligonucleotides which specifically bind retroviral capsid proteins"). NCp7 has been shown to bind two short oligonucleotides, utilizing both its zinc finger domains and its N-terminal domain (Fisher RJ et al., J Virol 72:1902-9, 1998).

- Identification of p7:Nucleic Acid Antagonists. The most promising results for p7:nucleic acid agonists have come from the NCI Diversity Set of compounds representative of the NCI chemical holdings. Within an overall hit rate of ~1%, six compounds showed a high degree of structural homology. These compounds and other structurally related compounds were tested in the cell-based anti-HIV assay (J. Mikovits, Laboratory of Antiviral Drug Mechanisms), and the three most potent binders were clearly active, with an anti-HIV potency (EC50) that paralleled the Kd for compound binding to NCp7.