化學系-余靖教授

一、 學歷

1972-1976	B.S., Chemistry, Fu-Jen Catholic University, Taiwan
1978-1984	Ph.D., Chemistry, Florida State University, Tallahassee, Florida
1984-1985	Postdoctoral fellow, University of California, Davis

二、 經歷

1978-1979	Teaching Assistant, Department of Chemistry, Florida State University, Tallahassee, Florida
1979-1984	Research Assistant, Department of Chemistry, Florida State University, Tallahassee, Florida
1984-1985	Postdoctoral Fellow, Chemistry Department, University of California, Davis, California
1985-1992	Associate Professor, Chemistry Department, National Tsing Hua University, Hsinchu, Taiwan
1992-2003	Professor, Chemistry Department, National Tsing Hua University, Hsinchu, Taiwan
2003-2005	Professor, Department of Chemistry and Biochemistry, University of Arkansas
2005-present	Tsing Hua Chair Professor, National Tsing Hua University

三、 榮譽

1993-1995	Distinguished Research Award, National Science Council, Taiwan (國科會傑出研究獎)
1997-1999	Distinguished Research Award, National Science Council, Taiwan (國科會傑出研究獎)
1998	Guest Editor, Journal of Toxicology-Toxin Reviews
2000	Sun Yat-Sen Scholar Award (中山學術獎)
2001-2003	Distinguished Research Award, National Science Council, Taiwan (國科會傑出研究獎)
2005-2008	Fellow of National Science Council Award, Taiwan (國科會特約研究獎)
2011-2014	Fellow of National Science Council Award, Taiwan (國科會特約研究獎)

四、 研究領域

1. Biomolecular NMR
2. Protein-protein interaction
3. Drug design

五、 研究興趣與成果

Snake Venom Proteins

Snake venoms are a mixture of many pharmacologically important principles, the most important of them are the cardiotoxins and the neurotoxins. Neurotoxins block nerve transmission by binding to the acetylcholine receptor. Cardiotoxins on the other hand possess a wide array of interesting biological activities such as lysis of erythrocytes, contracture of muscle cells, selective lysis of tumor cells and inhibition of key enzymes such as Na^+-K^+-Atpase and protein kinase C. My research group has solved the three-dimensional structures of a short neurotoxin and four cardiotoxin analogues isolated from the Taiwan Cobra using multidimensional NMR techniques. Our concerted efforts working on these toxins have paid dividends and currently, we have an in depth view of the structure-function relationship in these toxins. Recently, we studied the backbone dynamics of one of the cardiotoxin analogue, CTX II, from the Taiwan Cobra using multidimensional NMR techniques. This study for the first time suggested the existence of specific cell surface receptors for cardiotoxins. In addition, we recently elucidated the three-dimensional structure of the CTX-dATP complex. This study provided the basic mechanism underlying the inhibitory effects of CTXs on enzymes such as protein kinase C and Na+ - K^+ ATPase.

My research group has profound interest in understanding the molecular mechanisms involved in the protein folding reaction. Using the quenched-flow hydrogen-deuterium exchange technique in conjunction with multi-dimensional NMR techniques, we successfully traced the structural events in the kinetic refolding pathway of cardiotoxin analogue III (CTX III) from the Taiwan cobra. Recently, we also studied the disulfide bond refolding pathway of CTX III. In addition, we have successfully used the native state hydrogen-deuterium exchange technique together with multi dimensional NMR techniques to probe the structural forces responsible for the extraordinary conformational stability of cardiotoxins. This study has provided a detailed picture of the relative contribution of each amino acid towards the structural stability of the protein.

Fibroblast Growth Factors

Acidic Fibroblast growth factors (FGFs) are 17 kDa, all β-sheet proteins which regulate key cellular processes such as mitogenesis, angiogenesis and morphogenesis. FGFs are intricately involved in the wound healing process. We have cloned and expressed the wild type and various mutants of the acidic fibroblast growth factor (FGF-1) from the human and newt sources. Using triple resonance NMR experiments, we solved the structure of the newt FGF-1 to high resolution. In addition, employing a variety of biophysical techniques including multidimensional NMR methods, we had for the first time demonstrated that oligomerization induced by heparin is not a prerequisite for the cell proliferation activities of FGF-1. Very recently we compared the backbone dynamics of the human FGF-1 in its free and ligand forms using ^{1}H-^{15}N inverse detection methods. The results of the study provided strong clues on the receptor binding sites on the protein. Additionally, we were also successful in the identification and characterization of an equilibrium intermediate state in the unfolding pathway of human FGF-1.

There are two types of cell surface receptors high-affinity and low affinity receptors. The low affinity receptors are heparin and heparan sulfate-containing proeglycans. The high-affinity receptors are composed of an extracellular ligand-binding domain that contains three immunoglobulin (Ig)-like domains (D_1,D_2 and D_3), a single transmembrane helix and a cytoplasmic domain that contains protein tyrosine kinase activity. We are now in the process of cloning and expressing the D_2-D_3 (the FGF binding domain) domain of the receptor. We intend to study the solution structure of the D_2-D_3 using three-dimensional NMR techniques. Subsequently, the solution structure of the D_2-D_3/hFGF-1 complex would be determined. This exercise would provide useful information on the molecular forces operating at the FGF/receptor interface. These studies are also likely to yield useful clues for the design of drugs that block the receptor/FGF-1 interaction and consequently inhibit the mitogenic activity of growth factor. hFGF-1 owing to its mitogenic activity strongly participates in tumour growth and development. Hence design of drugs that inhibit the mitogenic activity of hFGF-1 is a rational mode of blocking the tumour growth. The Structure- Activity Relationship by NMR (SAR by NMR) technique is being effectively used to identify ligands which bind strongly to hFGF-1 and inhibit its mitogenic activity. The SAR by NMR technique allows the screening of hundreds of drugs against aFGF based on the chemical shift perturbation observed in the ^{1}H-^{15}N HSQC spectra upon addition of the ligand/drug.

S100 family Protein Interact with RAGE Domain:

S100A family proteins (S100A1, S100A2, S100A4, S100A6, S100A6, S100A7 S100A8, S100A9, S10011, S100A13) are interacted with RAGE-doamin (RAGE-V, RAGE C! and RAGE-C2). After the protein-protein interaction, the signal transduction cascade will introduce and cause a series disease such as diabetics, and cancer happen. By study the complex 3D structure of the protein-protein complexes, we could find out the mechanistic point of views how to cause and prevent the diseases.