

**Soldiers of Science: A Profile****PROFESSOR TEJ PAL SINGH: THE LEGEND OF INDIAN MACROMOLECULAR CRYSTALLOGRAPHY****Md. Imtaiyaz Hassan<sup>1</sup>, Pravindra Kumar<sup>2</sup> and Samudrala Gourinath<sup>3</sup>**<sup>1</sup>*Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India*<sup>2</sup>*Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee 247667, India*<sup>3</sup>*School of Life Sciences, Jawaharlal Nehru University, New Delhi 110067, India*

**Abstract:** Professor Tej Pal Singh, an internationally recognized Indian scientist par excellence, is one of the pioneers of Indian macromolecular crystallography. He is a person of significant and enduring accomplishments as a teacher, scientist, administrator and family man. He has developed various methods to crystallize wide varieties of proteins. He has successfully determined crystal structures of lactoferrin, phospholipase A2, lactoperoxidase, peptidoglycan recognition proteins, disintegrin, zinc- $\alpha$ 2-glycoprotein and several others including various protein-ligand and protein-protein complexes. He has a remarkably high number of structural entries in protein data bank. He received most of the prestigious awards and honors by Indian Government. This article covers most of his research and other achievements which will be a source of inspiration for young scientific community, motivation for peers and joy for his fellow colleagues and friends.

**Keywords:** Macromolecular Crystallography in India; Lactoferrin; Phospholipase A2; Lactoperoxidase; Peptidoglycan recognition proteins; Structural Genomics

**The Scientist at a Glance**

Prof. Tej P. Singh is an eminent scientist and a visionary who has established one of the most successful macromolecular crystallography groups in India. Tej P. Singh is an Indian biophysicist and a scientific leader who has made original and novel contributions in the fields of structure based drug design and protein structure determination using X-ray crystallography (Figure 1). He is a man of great character, a champion of accuracy and a paradigm of philosophical knowledge. He is leading the country in protein structure determination for health care. He has played an active role in the

development of research programmes on drug design in the fields of tuberculosis, inflammation, cancer, epilepsy, gastropathy and arthritis in India. So far he has contributed more than 300 sets of protein structure coordinates to the protein data bank (PDB) and authored over 350 research articles. He has also mentored more than 40 Ph.D. students. Most of his Ph.D. students are leading independent groups in India or abroad, a measure of his success as a mentor.

**The Mentor**

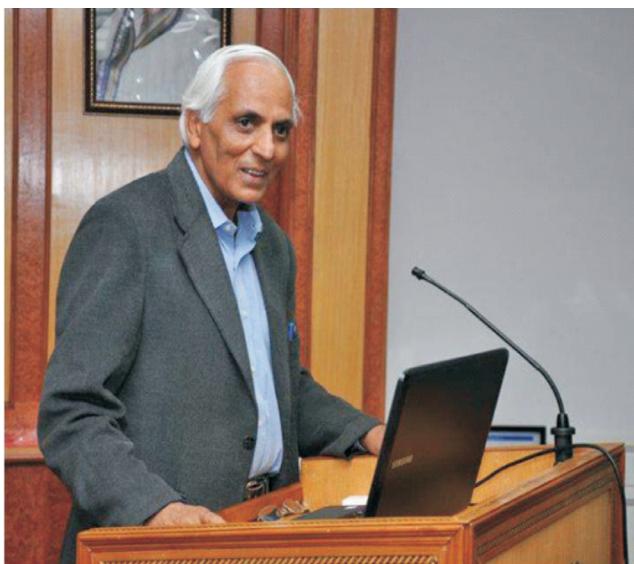
Prof. Tej P. Singh has been a dream mentor and guiding light to his students (Figure 2). He is a person who leads by example and inspires everyone to work hard with dedication and devotion. He always has words of encouragement to lift the morale of students whenever they are struggling with difficult projects. He has inculcated in his students a great deal of scientific temperament by his analytical approach to

Corresponding Author: M. I. Hassan, P. Kumar, S. Gourinath  
E-mail: [mihassan@jmi.ac.in](mailto:mihassan@jmi.ac.in); [kumarfbs@iitr.ernet.in](mailto:kumarfbs@iitr.ernet.in), [sgn9@hotmail.com](mailto:sgn9@hotmail.com)

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**Figure 1:** Professor Singh delivering talk



**Figure 2:** Prof Singh demonstrating peptide model to his students

scientific problems, sharp intelligence, and investigative approach. Prof. Singh's intellectual contribution, along with his magnanimous personality and humble nature, makes him a rare scientist and a leader whose influence and impact will be felt for generations to come. He showed us different ways to approach a research problem and the need to be persistent to accomplish any goal. He made us worthy investigators, more

importantly, he taught us how to work hard and play hard, and how to ski to reduce stress! Finally, he is the most significant person in our life for helping us to complete any research work and giving us an excellent platform, which has helped to shape our career.

### His Academic Background

Tej P. Singh obtained B.Sc. and M.Sc. degrees with first rank from University of Allahabad. He started his research career in 1971 as a graduate student at the Indian Institute of Science, Bangalore under the supervision of Professor M. Vijayan. He obtained his Ph. D degree in the mid 70's working on X-ray crystallographic structure determinations (Bhat *et al.*, 1974). He gave a live structural model of analgesics and their interactions with target (Singh and Vijayan, 1973, 1976). He then joined University of Indore as Lecturer in the Department of Physics.

Thereafter, he was awarded the Alexander von Humboldt Foundation Fellowship with Professor Robert Huber at the Max-Planck Institute for Biochemistry in Munich, Germany and worked there on the structure determination of serine proteases including trypsin and trypsinogen at sub zero temperatures (Walter *et al.*, 1982). Professor Robert Huber later received the Nobel Prize in Chemistry jointly with Johann Deisenhofer and Hartmut Michel (Figure 3).

### The Early Years

Upon returning to India in 1980, he joined as Reader at the Sardar Patel University and set up a centre for X-ray crystallographic research. In 1982, he joined the Institute for Crystallography, Berlin to work on the structure determination of proteinase K and rubisco enzymes, which he subsequently continued in the Department of Biophysics, All India Institute of Medical Sciences after his joining the prestigious institute in 1983. His group crystallized the disordered activation domain of trypsinogen at low temperature (Figure 4). The crystal structure of the transition state analog complex formed covalently between proteinase K and a peptide methoxysuccinyl-Ala-Ala-Pro-Ala-chloromethyl ketone was determined at 2.2 Å resolution and provided a suitable model for enzyme-inhibitor interactions

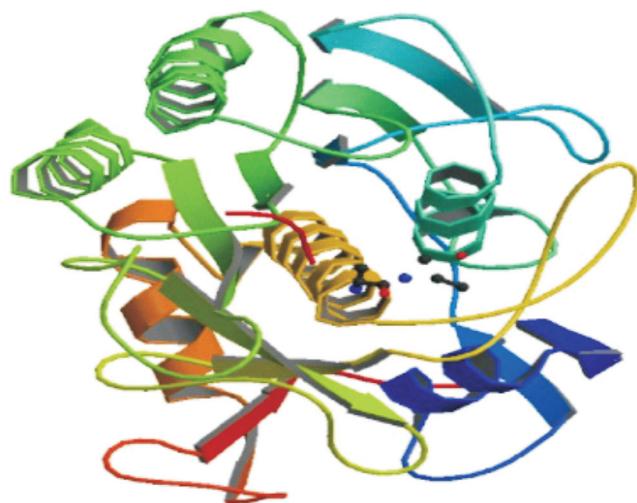
(Wolf *et al.*, 1991), which was further supported by the structure of the complex of proteinase K with a substrate analogue hexapeptide inhibitor (Betzel *et al.*, 1993) (Figure 5). Furthermore, this group produced a high-resolution crystal structure of proteinase K at 0.98 Å showing regions of the main chain and the side chains more clearly,



**Figure 3:** T. P. Singh with Robert Huber at AIIMS



**Figure 4:** Disordered activation domain in trypsinogen at low temperature (PDB id: 1PTN)



**Figure 5:** Structure of the complex of proteinase k with a substrate-analogue hexa-peptide inhibitor (PDB id: 1PEK)

which were not observed earlier (Betzel *et al.*, 2001). Proteinase K isolated from *Tritirachium album* Limber was crystallized with HgCl<sub>2</sub> in excess and this structure provided a model of metal ion induced inhibition at atomic level (Gourinath *et al.*, 2001). Few more structures of modified serine proteinase at high resolution were produced from his lab in 2001 (Sharma *et al.*, 2001b; Singh *et al.*, 2001b).

### The Consolidation – Peptide Design

Almost at the same time, he initiated work on peptide design with dehydro amino acids and proposed design rules for peptides with α-β-dehydro-residues (Patel *et al.*, 1990; Singh *et al.*, 1987; Singh *et al.*, 1989; Singh *et al.*, 1990). He also proposed that if dehydro residues occur consecutively in an amino-acid sequence, the backbone folds into an alternating right- and left-handed alpha-helix (Singh *et al.*, 1990). These results have a direct application in the design of polypeptide sequence for performing specific function (Bhatnagar *et al.*, 1995). Furthermore, he proposed that a tetrapeptide with two consecutive delta Phe residues sequenced with Valines on both ends adopts two overlapping beta-turns of Types II and I' (Dey *et al.*, 1996a). Interestingly, in order to induce predictably unique structures with dehydro-residues at (i + 1) position, they introduced branched beta-carbon dehydro-residues instead of nonbranched beta-carbon residues (Vijayaraghavan *et al.*, 2003).

His group also developed an optimized protocol for synthesis of numerous peptides with potential biological activities (Dey *et al.*, 1996a, b; Makker *et al.*, 2002; Padmanabhan *et al.*, 1992; Padmanabhan and Singh, 1993; Singh and Narula, 1993; Singh *et al.*, 1989; Vijayaraghavan *et al.*, 2001). His group designed a large number of peptides using structure-based rational design for protein targets such as proteinase K (Betzel *et al.*, 1993; Saxena *et al.*, 1996), endothelin receptor, phospholipase A2 (PLA2), cyclo-oxygenase-2 and breast cancer factor, SPX-40. These rules are being exploited to design specific peptide inhibitor which will show tight binding to the substrate.

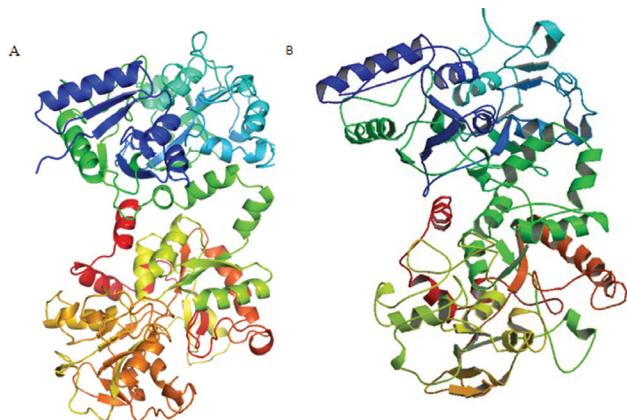
### Milk Protein Structures – his Signature

His group has determined a large number of three-dimensional structures of various milk proteins including lactoferrin (Sharma *et al.*, 1996; Sharma *et al.*, 1999a; Sharma *et al.*, 1997), lactoperoxidase (Sheikh *et al.*, 2009; Singh *et al.*, 2008), peptidoglycan recognition protein and mammary gland protein from several species. Structurally, the lactoferrin molecule is divided into two lobes representing the N-terminal and C-terminal halves of the polypeptide chain, each containing an iron binding site. They provided evidences for proteinase K dividing this protein into two equal halves. In the first step of hydrolysis by proteinase K, the C- and N-lobes, each having a molecular weight of approximately 40 kDa, are generated. In the next step, the lobes are further hydrolyzed into small molecular weight peptides. His group successfully determined the crystal structure of C-lobe of lactoferrin and provided mechanism for iron binding and transport (Sharma *et al.*, 1999b; Singh *et al.*, 1998). They provided details of the proteolytic preparation of C-lobe and interspecies comparisons of its sequence and structure, as well as the scope of its therapeutic applications, as it contains various antimicrobial peptides which are released upon its hydrolysis by proteases (Sharma *et al.*, 2003; Sharma *et al.*, 2013d; Sinha *et al.*, 2013). Crystal structure of a complex of lactoferrin with a lanthanide ion ( $\text{Sm}^{3+}$ ) showed that the protein is capable of sequestering ions of different sizes and charges, though with reduced affinity (Sharma and Singh, 1999). Furthermore, crystal structure of the complex formed between mare

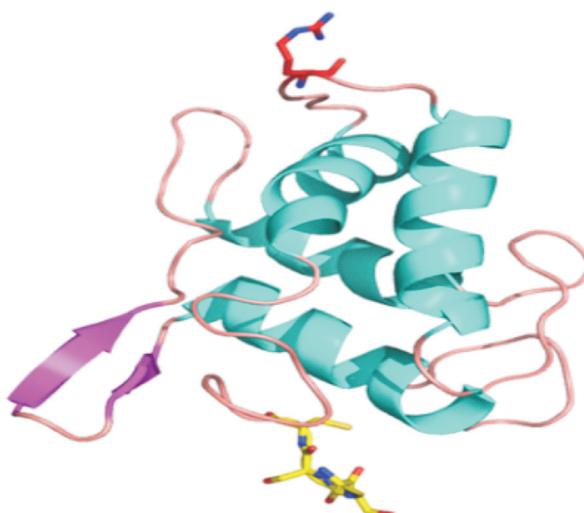
lactoferrin and melanin has provided possible implications in melanin polymerization (Sharma *et al.*, 2001a). Crystal structures of lactoferrin were determined from various species (buffalo, equine, goat and camel) to understand the mechanism of iron binding and release (Karthikeyan *et al.*, 1999; Karthikeyan *et al.*, 2000; Khan *et al.*, 2001a; Kumar *et al.*, 2002a; Kumar *et al.*, 2002b) (Figure 6A). In addition, structural basis of its dual role was determined by carrying out the 3D structures of camel lactoferrin in apo and intermediate form (Khan *et al.*, 2001b) (Figure 6B). Crystal structure of C-lobe of lactoferrin in complex with bacterial outer membrane protein OmpC (Sundara Baalaji *et al.*, 2005), non-steroidal anti-inflammatory drug (Mir *et al.*, 2009; Mir *et al.*, 2010b), and sugar were extensively analyzed and explored further (Mir *et al.*, 2010a).

### Bifunctional Enzymes – the Structural Conquest

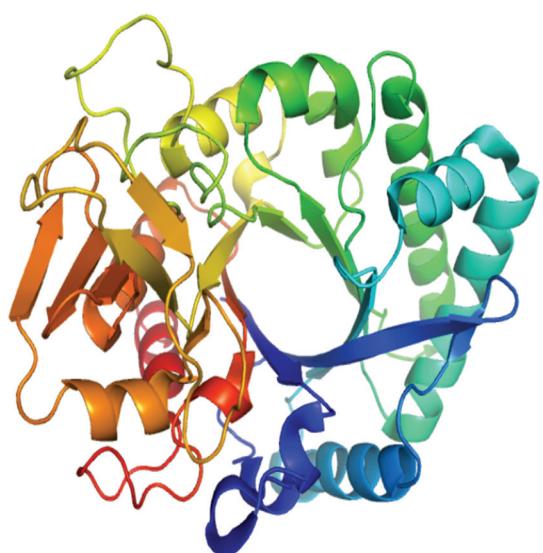
Around the same time, he also initiated work on protease inhibitors from ragi seeds and chick peas. The structural and functional studies of novel bi-functional trypsin/amylase inhibitor from ragi has been reported (Gourinath *et al.*, 2000; Gourinath *et al.*, 1999) (Figure 7) and explained the complex amylase inhibition by inhibitor and its mimicking peptides (Alam *et al.*, 2001). Simultaneously, a novel 40 kDa regulatory protein was identified from goat mammary secretions (Kumar *et al.*, 2001). They determined the crystal structure of a novel regulatory protein (MGP-40) from the mammary gland (Mohanty *et al.*, 2003) (Figure 8). This protein was implicated as a protective signaling factor that determines which cells are to survive the drastic tissue remodeling that occurs during involution. This protein is secreted only during the early phase of involution when the drastic tissue remodeling occurs in the mammary gland. Crystal structure of this protein was determined from sheep, bovine, camel and many other mammalian sources (Ethayathulla *et al.*, 2007; Kumar *et al.*, 2006; Srivastava *et al.*, 2006). His group has first time reported the detailed structural basis of its catalytic mechanism, which was supported by the crystal structure of the complexes of SPG-40 with numerous oligosaccharides of different lengths (Kumar *et al.*, 2007; Srivastava *et al.*, 2007).



**Figure 6:** Structures of (A) Camel apo-lactoferrin (PDB id: 1DTZ) (B) Equine apolactoferrin (PDB id: 1I6B)



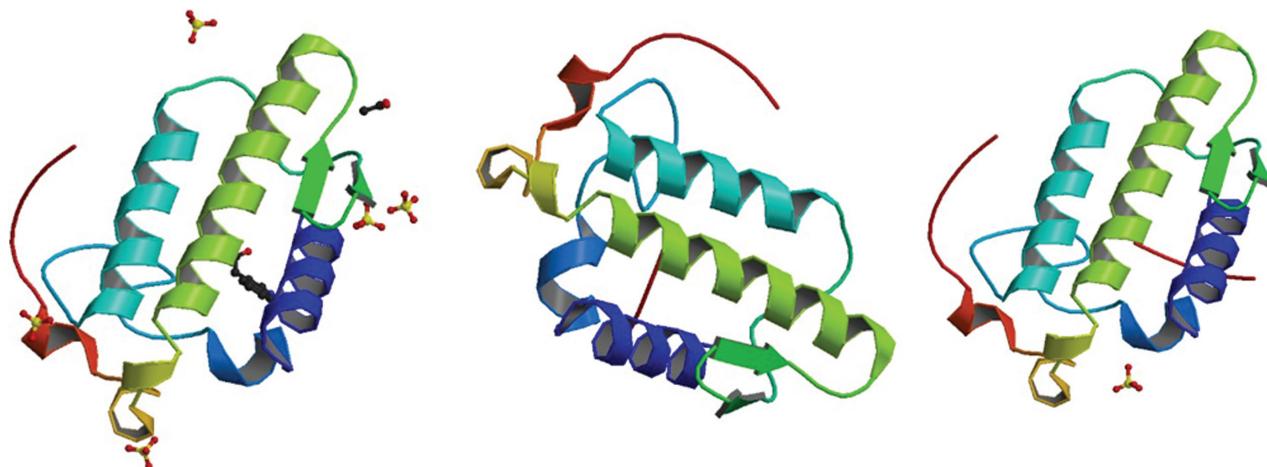
**Figure 7:** Structure of the bifunctional inhibitor ragi (PDB id: 1B1U)



**Figure 8:** Structure of a novel regulatory 40 kDa mammary gland protein (MGP-40) secreted during involution (PDB id: 1LJY)

### Initiative into Structure based Drug Design

His team reported the crystal structure of one of the enzyme, PLA2 that catalyses the first step in the production of secondary messenger to the Central Nervous System. This enzyme also carries out the hydrolysis of arachidonic acid from membrane phospholipids which upon downstream processing produces pro-inflammatory eicosanoids (Betzel *et al.*, 1999; Chandra *et al.*, 2001; Chandra *et al.*, 2000; Chandra *et al.*, 1999; Jabeen *et al.*, 2006; Nagpal *et al.*, 1999; Singh *et al.*, 2005a; Singh *et al.*, 2001a; Singh *et al.*, 2005d). Since this enzyme was thought to be a potential target for structure based drug design, therefore, structural studies of the enzyme with small molecules was undertaken to provide a detailed insight into the mechanism of the interaction of the active site residues of the enzyme and the drug molecules (Hariprasad *et al.*, 2010; Jabeen *et al.*, 2005a; Jabeen *et al.*, 2005b; Jabeen *et al.*, 2005c; Jasti *et al.*, 2004) (Figure 9). Among the several synthetics peptides tested against PLA2, the peptide Phe-Leu-Ser-Tyr-Lys (FLSYK) showed the highest inhibition. Crystal structure of protein-peptide complex was obtained (Chandra *et al.*, 2002b). In order to regulate the production of pro-inflammatory compounds, he further designed many specific peptide inhibitor of PLA2 such as Leu-Ala-Ile-Tyr-Ser (Chandra *et al.*, 2002c), Val-Ala-Phe-Arg-Ser (Singh *et al.*, 2003), etc. His group also provided first structural evidence of alpha-tocopherol (alpha-TP) as a possible drug candidate against inflammation, because it specifically and effectively inhibits PLA2, which was supported by the crystal structure of the complex formed between PLA2 and alpha-tocopherol (Chandra *et al.*, 2002a) (Figure 9). Furthermore, they also provided first structural observation of a plant product aristolochic acid showing high affinity for PLA2 that regulates the synthesis of arachidonic acid, an intermediate in the production of prostaglandins (Chandra *et al.*, 2002d). He produced a large number of PLA2 structures complexed with non-steroidal anti-inflammatory drugs (Jabeen *et al.*, 2005d; Singh *et al.*, 2004), indole, 2-carbamoylmethyl-5-propyl-octahydro-indol-7-yl)-acetic acid (Balasubramanya *et al.*, 2005), fatty acid (Singh *et al.*, 2005b), aspirin (Singh *et al.*, 2005c), etc. This



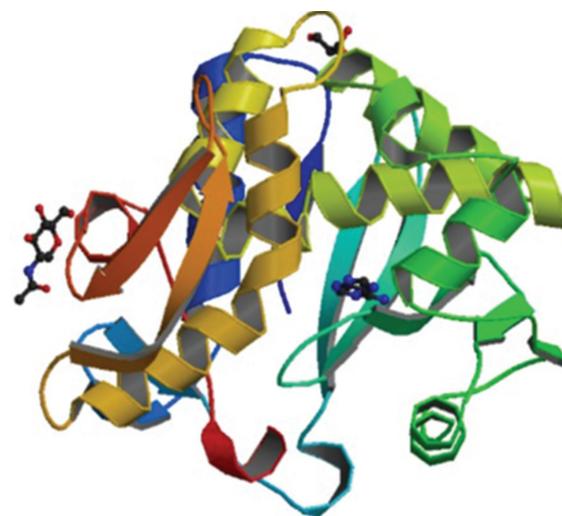
**Figure 9:** Structure of PLA2 and its complexes. Structures are displayed using atomic coordinates of PDB id: 2PYC, 1ZM6 and 2PB8

study is still going on in his lab to produce a potential anti-inflammatory molecule.

Studies on inflammatory pathway was not only limited to PLA2, rather it was extended towards other proteins involved in inflammation such as cyclooxygenase, lipoxygenase, endothelin receptor, endothelin converting enzyme, etc. X-ray crystal structures of the complexes of the COX-1 and COX-2 with the known inhibitors were explored and he synthesized a novel tripeptide inhibitor which showed dissociation constant  $1.90 \times 10^{(-10)}\text{M}$ , the kinetic constant  $K_i$   $4.85 \times 10^{(-9)}\text{M}$  with the  $\text{IC}_{50}$  value of  $1.5 \times 10^{(-8)}\text{M}$  (Somvanshi *et al.*, 2007). Similarly, his group performed ligand binding studies with endothelins and showed that the extracellular region of endothelin is essential for ligand binding and that longer peptides have higher affinity (Saravanan *et al.*, 2007; Saravanan *et al.*, 2004).

### Structures of RIP

He also determined the crystal structures of ribosome inactivating proteins (RIP) to understand the mechanism of plant defense (Mishra *et al.*, 2005; Mishra *et al.*, 2004a). Moreover, ribosome-inactivating proteins having antitumor and immunomodulatory properties constitute the active principle of widely used mistletoe therapy (Mishra *et al.*, 2004b) (Figure 10). Recently, his group reported six crystal structures, type 1 RIP from *Momordica balsamina* in complexed states with ribose, guanine, adenine, adenosine

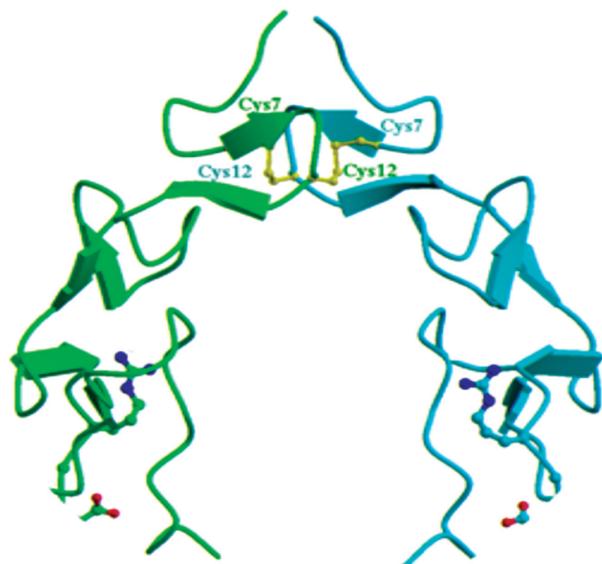


**Figure 10:** Structure of type 1 RIP and adenine (PDB id: 3U6Z)

triphosphate (ATP) and 2'-deoxyadenosine triphosphate (2'-dATP) to understand the mechanism of its action and provided first structural evidence of recognition of mRNA cap structures by a RIP (Kushwaha *et al.*, 2012; Kushwaha *et al.*, 2013).

### Structures of Disintegrin

His group determined crystal structure of heterodimeric disintegrin from *Echis carinatus* venom, which was thought to be a potent antagonist of alpha4 integrins (Tomar *et al.*, 2001). They have also identified features that may be important in the binding of two integrins to a single dimeric disintegrin (Bilgrami *et al.*, 2005) (Figure 11). Furthermore, the crystal structure of

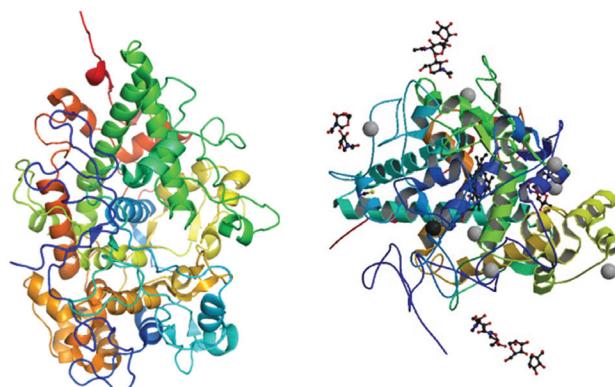


**Figure 11:** Crystal Structure of schistatin, a disintegrin homodimer from saw-scaled viper (PDB id: 1RMR)

a disintegrin homodimer was also determined that seems to be responsible for the clustering of integrin molecules. The homodimer binds to integrins apparently with a higher affinity than the monomers and also plays a role in the signaling pathway (Bilgrami *et al.*, 2004).

### Towards Understanding of Antimicrobial Function

His group also produced crystal structure of lactoperoxidase (LPO), an enzyme with antimicrobial function and involved in innate immune responses, and its complexes to understand the mechanism of catalysis (Kumar *et al.*, 1995; Sheikh *et al.*, 2009; Singh *et al.*, 2008; Singh *et al.*, 2012). LPO is a heme containing enzyme that catalyzes the inactivation of a wide range of microorganisms (Sharma *et al.*, 2013c). He attempted to address this question through the new crystal structures of LPO complexes with SCN<sup>-</sup> ions using goat, bovine, and buffalo LPOs (Sheikh *et al.*, 2009). In the presence of hydrogen peroxide, LPO preferentially converts thiocyanate ion into a toxic hypothiocyanate ion. Samples of bovine lactoperoxidase containing thiocyanate SCN<sup>-</sup>(SCN(-)) and hypothiocyanate OSCN<sup>-</sup>(OSCN(-)) ions were further purified and crystallized to understand the structural basis of inhibition of LPO (Singh *et al.*, 2009a) (Figure 12). They also attempted to understand the binding modes of aromatic ligands to mammalian heme

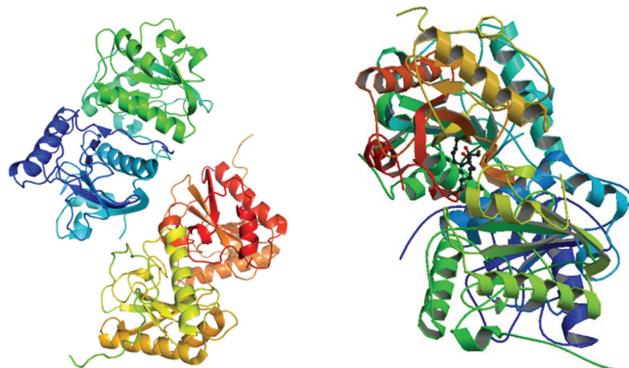


**Figure 12:** Crystal structure of lactoperoxidase (PDB id: 2R5L) and its complex with cyanide (PDB id: 3FAQ)

peroxidases with associated functional implications supported by the structures of LPO complexes with acetylsalicylic acid, salicylhydroxamic acid, benzylhydroxamic acid, inorganic substrates, SCN, I, Br, Cl and tuberculosis prodrug isoniazid (Singh *et al.*, 2010; Singh *et al.*, 2011; Singh *et al.*, 2009b).

### Structural Basis of Molecular Recognition

The mammalian peptidoglycan recognition protein-S (PGRP-S) binds to peptidoglycans (PGNs), which are essential components of the cell wall of bacteria. His group produced first crystal structure of the secretory PGRP-S, which revealed that the protein exists in the form of two independent dimers, each of which has two fully accessible binding sites, one for binding to PGNs and one for the binding to non-PGN molecules (Sharma *et al.*, 2008). Furthermore, he provided the structural basis of recognition of pathogen-associated molecular patterns and inhibition of pro-inflammatory cytokines by camel PGRP (Sharma *et al.*, 2011a) (Figure 13). Multi-ligand



**Figure 13:** Crystal structure of PGRP (PDB id: 2R90) and its complex with myristic acid (PDB id: 3USX)

specificity of pathogen-associated molecular pattern-binding site in peptidoglycan recognition protein was also identified and analyzed (Sharma *et al.*, 2011b). Crystal structures of the complexes of CPGRP-S with LPS, LTA and PGN also showed that their glycan moieties were also held in subsite S-I indicating that heparin disaccharide also represents an important element for the recognition by CPGRP-S (Sharma *et al.*, 2012a). Finally, they provided structural basis for the recognition of N-acetylglucosamine and N-acetylmuramic acid (Sharma *et al.*, 2012b), lipopolysaccharide and stearic acid (Sharma *et al.*, 2013a), and other fatty acids (Sharma *et al.*, 2013b).

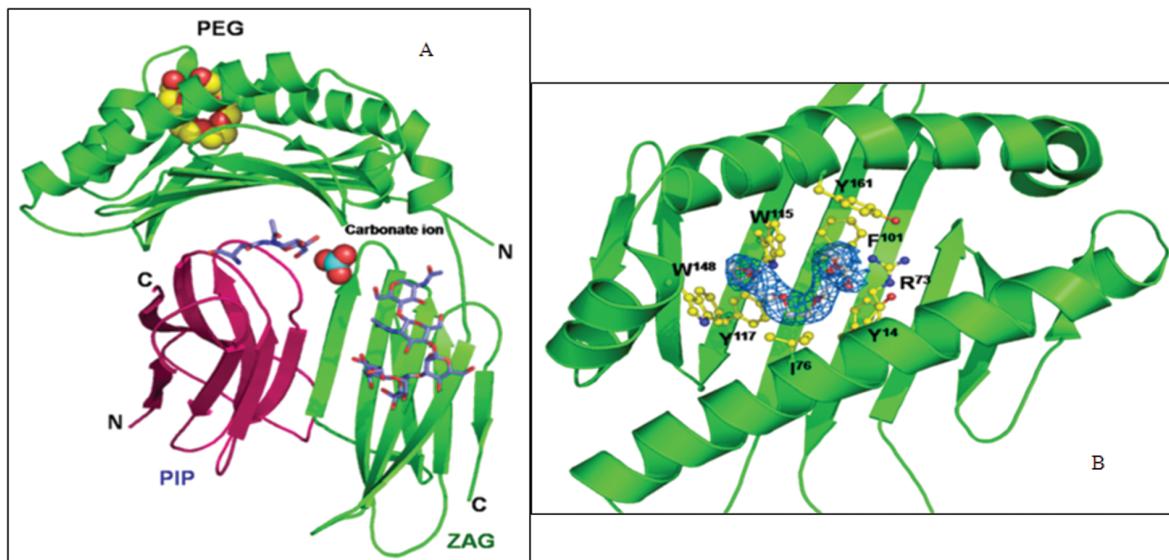
### Diverse Research Continues—Clinical Proteomics

In 2006, his group started a new project on clinical proteomics which produced many excellent publications with very high citation. They identified and characterized various biomarkers from clinical samples including saliva, tear, semen, synovial fluid, peritoneal fluid, cerebrospinal fluid, pleural fluid etc. Work on human seminal fluid identified prostate specific antigen as a potential biomarker for prostate cancer, which was further considered as a therapeutic target for structure based rational drug design (Hassan *et al.*, 2007a; Hassan *et al.*, 2007b; Hassan *et al.*, 2007c). A complex between zinc alpha2-glycoprotein (ZAG) and prolactin-inducible protein (PIP) was first time reported

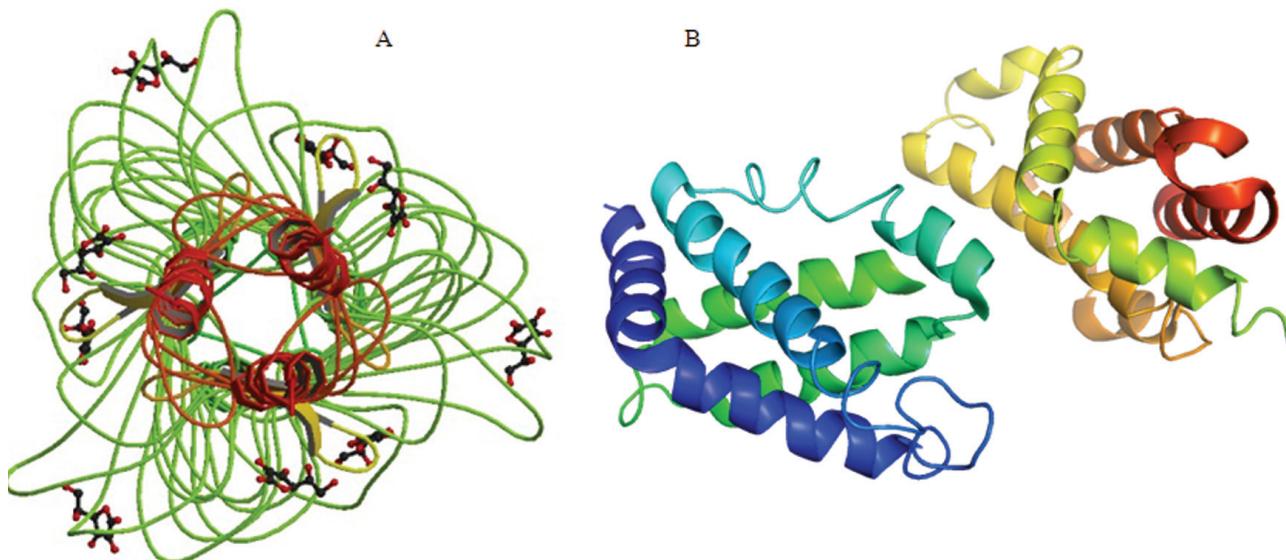
(Hassan *et al.*, 2008b), which was followed by successful crystal structure determination providing an insight for ZAG being a class I MHC molecule (Hassan *et al.*, 2008a; Hassan *et al.*, 2008c, 2009) (Figure 14A and B). Heparin-binding proteins (HBPs) are essential constituents of human seminal fluid, which bind to sperm lipids containing the phosphorylcholine group and mediate the fertilization process. His group also produced many significant publications on the interactions of HBPs and its role in fertility (Kumar *et al.*, 2008a; Kumar *et al.*, 2009a; Kumar *et al.*, 2008b; Kumar *et al.*, 2009b; Kumar *et al.*, 2012).

### Lending a Helping Hand

He has also been supporting other Indian laboratories in solving the crystal structure of novel proteins. The crystal structures of native hyaluronate lyases and its two complexes with ascorbic acid and lactose have been determined (Figure 15A). The structures of complexes show that three molecules each of ascorbic acid and lactose bind to protein at the sugar binding groove in the triple-stranded beta-helix domain. Both ascorbic acid and lactose molecules occupy almost identical subsites in the long saccharide binding groove (Mishra *et al.*, 2009). A 14 kDa truncated fragment of alpha-subunit of phycoerythrin was also identified from cyanobacteria and subsequently its crystal structure was determined (Soni *et al.*, 2010) (Figure 15B).



**Figure 14:** Structure of (A) ZAG-PIP complex. (B) Ligand binding groove of ZAG. PDB id 3ES6 was used for display of the structures



**Figure 15:** Structure of (A) hyaluronate lyase and its complexes with ascorbic acid and lactose (PDB id: 3EKA). (B) C-phycoerythrin (PDB id: 3MWN)

### Other Services and Achievements

He has been serving as Chairman of a committee for implementing a major DST initiative to improve the infrastructural support in the north-eastern region of the country, and as Member of the Board of Governors of IIT Kharagpur. He served INSA as a Vice President from 2007 to 2009. He received the Professor GN Ramachandran 60th Birthday Commemoration INSA Medal (2006), JC Bose Memorial Award, Indian Science Congress (2006) and Professor GN Ramachandran CSIR Gold Medal for Excellence in Biological Sciences and Technology (2006). He was elected as a Fellow of the Indian Academy of Sciences, Bangalore, National Academy of Sciences (India), Allahabad and the Academy of Sciences for the Developing World. He has been awarded various national and international awards over the years, for instance, the Jawaharlal Nehru Birth Centenary Lecture Award of INSA (2011), Annual Award of the Instrumentation Society of India (2011), CSIR Foundation Day Lecture award (2010), Goyal Prize in Life Sciences (2007), etc. We always feel proud for being his Ph.D. student.

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