Abstract

Ever since Paul Ehrlich proposed the concept of “magic bullet”, the pharmaceutical sector has been on the lookout for that special molecule. However, with the reducing chemical universe and strict Food and Drug Administrator regulations, the drug discovery pipeline for new small molecular entities as potential drug candidates is drying. Further, it has also led to the increase in the research and development costs involved in the development of a novel drug candidate. Therefore, pharmaceutical industry is more absorbed towards the development of peptide-based drug therapies in recent times. At such a critical juncture, the pharmaceutical industry is also open to discovering new avenues for drug repurposing and designing therapies using existing drug molecules. Peptides offer a wide source of novel therapeutic molecules and therapies owing to the distinct probabilities of chemical sequence combinations. Moreover, peptides also provide ample chemistry for the attachment of multiple molecules through simple chemical reactions. Given the biological origin against traditional chemical nature of existing drugs, it also offers avenues for better biocompatibility and a reduced post action toxicity.

Cell penetrating peptides (CPPs) are short peptides which have the ability to pass through the cell membrane while maintaining low levels of toxicity. The uptake of CPPs may be an energy dependent or independent process and does not involve chiral recognition by specific cellular receptors. Since the discovery of the transducing capabilities of the Tat peptide in 1988, many peptides capable of cell penetration have been discovered and designed. They have been utilized for transporting various cargoes: small molecules, nanoparticles, nucleic acids liposomes and proteins inside the cells and thus, show promising application as drug delivery vehicles. CPPs exhibit vast range of physiochemical properties

along with a rich diversity of sequence variation. Such diversity has led to various attempts to classify them on different bases like origin, sequence characteristics, charge, hydrophobicity, pathway of internalization, etc. The CPP database, "CPPsite" has more than 1800 entries for peptides with cell penetrating activity. Majority of these peptides have been derived from various proteins, while the others are either chimeric (formed by fusion of two sequences) or synthetic (rationally designed) sequences.

In the present thesis, the evolution of three distinct peptide series/families with cell penetrative capabilities will be discussed. About fifty peptides were designed and synthesized, after multiple rounds of sequence optimization. After primary screening, three series of peptides were selected on the basis of their design philosophy, efficacy and physico-chemical characteristics. The peptides were biocompatible in human plasma and bovine serum. I also tested the cargo delivering potency of the designed peptides. The characterization of the three series of peptides provides sufficient data for the emergence of a functional design platform for future design of peptides with tailored features and consequential functions. The design platform encompasses different variables of peptide backbone design, electrostatic potential distributions and amino acid sequence optimization. Further, a set of bioinformatics tools were developed during the course of this study to supplement the design platform. The thesis is divided into four working chapters detailing the design and characterization of three peptide series and the design platform developed.