

## ORAL PRESENTATION O4

### **Structurally conserved helical fold of diverse Bcl-2 family of apoptotic proteins: analysis of experimentally determined Bcl-2 structures**

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The Bcl-2 family of proteins play a vital role in the regulation of an important physiological process of cell death termed apoptosis, critical for cell survival and development, tissue homeostasis and protection against pathogens [1]. Structural and simulation studies have led to a number of key insights on their function and regulation at the molecular level [2,3]. To date, three dimensional structures of sixteen different Bcl-2 family proteins have been determined from various organisms. These solved structures have shown that the overall topology consists of seven to eight helices with very similar arrangement of helices. The common feature observed in this fold is a predominantly hydrophobic central  $\alpha$ -helix surrounded by several amphipathic helices that pack against this helix. Despite a high degree of structural similarity, these family members exhibit poor amino acid sequence identity ranging from 7 to 41%.

As the overall sequence of a protein diverges, the residues which are critical for its viability are expected to be conserved. We have analyzed the 16 experimentally determined structures to identify possible set of residues critical for this helical fold. These structures were derived from diverse organisms such as viruses, *C-elegans*, mouse and human. Structure-based sequence alignment shows that the length of the central hydrophobic helix is relatively conserved as compared to the variations observed in other helices. Though overall similarity is observed in the helical fold, the geometry, described by helix crossing angles and inter-helical distances, varies widely across the family members. This is possibly to compensate for the mutations occurring at the interfaces of the helices. Sequence analyses of the structurally conserved regions have led us to identify a set of core residues which show conservation in their chemical property. These residues are mostly solvent inaccessible and are involved in inter-helical contacts in all or majority of the structures. Thus this group of residues is indispensable for maintaining the helical fold of these diverse Bcl-2 proteins.

#### References:

1. Cory *et al.* *Science* 281:1322 (1998)
2. Fesik *et al.* *Biochim. Biophys. Acta* 1644 :83 (2004)
3. Lama and Sankararamakrishnan *Proteins* 73, 492 (2008)