Rational Drug Design

Bcl-2 Family Proteins and Cancer

1. Bcl-2-family proteins play central roles in cell death regulation
2. Alterations in their expression and function contribute to the pathogenesis and progression of cancer

**BCL-2 (B-CELL LYMPHOMA-2)**

1. The BCL-2 (B-cell lymphoma-2) gene was discovered at the (Brooks, et al., 1999b; Capuano et al., 1996) chromosome translocation breakpoint in B-cell follicular lymphomas (Liu et al., 2004).
2. Translocation placed Bcl-2 under the control of the immunoglobulin heavy chain gene promoter and enhancer- excessive transcription of Bcl-2
3. Introduced a new paradigm for carcinogenesis
   i) unlike previous oncogenes, instead of promoting cell proliferation, overexpression of Bcl-2 inhibits cell death

**How does bcl-2 inhibit apoptosis?**

1. Through protein-protein interactions, Bcl-2 inhibits pro-apoptotic family members

**Mechanisms for bcl-2 family**

**Antagonism**

1. Bcl-2 anti-sense oligonucleotides
   I. Result in degradation of Bcl-2 mRNA
      Oblimersen (Genta)
2. Small molecule inhibitors (BH3-mimetics)
   I. Bind to hydrophobic BH3-binding pocket and release proapoptotic
      Protein ABT-737 (Abbott) (Costantini et al., 2000; Degli-Esposti and Dive, 2003; O’Neill et al., 2004).