BCL-2 Inhibitors and Cancer Chemotherapy

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Key observations of Kerr, Wyllie and Currie in the 1970s described the importance of programmed cell death and apoptosis in cancer. Subsequent work by Bob Horvitz and colleagues recognised the critical importance of three genes, CED-3, CED-4 and CED-9, in developmental cell death in the nematode *C. elegans.* This was followed by the identification of the mammalian homologues of these genes and a rapid explosion of our understanding of fundamental mechanisms of apoptosis. Resistance to apoptosis is recognised as one of the hallmarks of cancer. Subsequent studies in numerous laboratories in academia and industry have tried to utilise this knowledge to treat various diseases including cancer. Many avenues have been pursued including stimulation of death receptors with their cognate ligands, such as TRAIL, activation of p53 or caspases, SMAC mimetics and inhibitors of the BCL-2 family of proteins although the magic bullet still seems to allude us. Some of the progress and pitfalls of the development of BCL-2 inhibitors will be discussed.