

**Application of XIAP Antisense to Cancer and Other Proliferative Disorders:
Development of AEG35156/ GEM(R)640.**

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Targeting apoptosis control provides a novel therapeutic approach to the treatment of cancer and other proliferative disorders. We summarize the evidence for apoptosis deregulation in cancer and describe the pivotal role of XIAP, the X-linked Inhibitor-of-APoptosis. XIAP is the predominant inhibitor of caspases 3, 7 and 9 in cells, which suppresses the programmed cell death effector capability of these proteases. Evidence is presented validating XIAP as a cancer target. The inhibition or downregulation of XIAP in cancer cells lowers the apoptotic threshold, thereby inducing cell death and/or enhancing the cytotoxic action of chemotherapeutic agents. We describe the development of AEG35156 (also named GEM(R)640), a second generation antisense compound targeting XIAP, from concept to in vivo preclinical proof-of-principle studies, through formal toxicology, and to a phase 1 clinical trial in cancer patients.