

# Preclinical Characterization of AEG35156/GEM640, a Second-Generation Antisense Oligonucleotide Targeting X-Linked Inhibitor of Apoptosis

Eric C. LaCasse,<sup>1</sup> Gabriele G. Cherton-Horvat,<sup>1</sup> Kimberley E. Hewitt,<sup>1</sup> Lori J. Jerome,<sup>1</sup> Stephen J. Morris,<sup>1</sup> Ekambar R. Kandimalla,<sup>2</sup> DongYu,<sup>2</sup> Hui Wang,<sup>3</sup> Wei Wang,<sup>3</sup> Ruiwen Zhang,<sup>3</sup> Sudhir Agrawal,<sup>2</sup> John W. Gillard,<sup>1</sup> and Jon P. Durkin<sup>1</sup>

**Clin Cancer Res 2006;12(17) September 1, 2006**

## Abstract

**Purpose:** Cancer cells can use X-linked inhibitor of apoptosis (XIAP) to evade apoptotic cues, including chemotherapy. The antitumor potential of AEG35156, a novel second-generation antisense oligonucleotide directed toward XIAP, was assessed in human cancer models when given as a single agent and in combination with clinically relevant chemotherapeutics. Experimental Design: AEG35156 was characterized for its ability to cause dose-dependent reductions of XIAP mRNA and protein in vitro and in vivo, to sensitize cancer cell lines to death stimuli, and to exhibit antitumor activity in multiple human cancer xenograft models as a single agent or in combination with chemotherapy.

**Results:** AEG35156 reduced XIAP mRNA levels with an EC<sub>50</sub> of 8 to 32 nmol/L and decreased XIAP protein levels by >80%. Loss of XIAP protein correlated with increased sensitization to tumor necrosis factor  $\alpha$  related apoptosis-inducing ligand (TRAIL)  $\alpha$  mediated apoptosis in Panc-1 pancreatic carcinoma cells. AEG35156 exhibited potent antitumor activity relative to control oligonucleotides in three human cancer xenograft models (prostate, colon, and lung) and was capable of inducing complete tumor regression when combined with taxanes. Antitumor effects of AEG35156 correlated with suppression of tumor XIAP levels.

**Conclusions:** AEG35156 reduces XIAP levels and sensitizes tumors to chemotherapy. AEG35156 is presently under clinical assessment in multiple phase I trials in cancer patients as a single agent and in combination with docetaxel in solid tumors or cytarabine/idarubicin in leukemia.

---

Authors' Affiliations: <sup>1</sup>Aegera Therapeutics, Inc., Montreal, Quebec, Canada; <sup>2</sup>Idera Pharmaceuticals, Inc., Cambridge, Massachusetts; and <sup>3</sup>Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, Alabama