A novel locked nucleic acid oligonucleotide against survivin, EZN-3042, inhibits survivin expression and causes antitumor effects

Puja Sapra, Jennifer Malaby, Mary Mehlig, Maolliang Wang, Baisong Liao, Lee M. Greenberger, Ivan D. Horak

Enzon Pharmaceuticals Inc., 20 Kingsbridge Road, Piscataway, NJ 08854

email: puja.sapra@enzon.com

Therapeutic efficacy

A novel locked nucleic acid oligonucleotide against survivin, EZN-3042, inhibits survivin expression and causes antitumor effects

The effect of EZN-3042 was also evaluated in a carbon tetrachloride (CCl₄)-induced liver regeneration model.

Survivin mRNA level in mouse liver

Survivin mRNA levels in mouse liver were analyzed via qRT-PCR. A representative example in A549 cells is demonstrated below:

Inhibition of survivin expression and cell growth

EZN-3042 demonstrated potent in vitro knockdown of survivin mRNA levels and growth inhibition in several transfected tumor cell lines (A549, Calu-6, DU-145), as measured by qRT PCR and MTS assay, respectively. A representative example in A549 cells is demonstrated below:

Conclusions

1) EZN-3042 displayed potent in vitro knockdown of survivin mRNA and growth inhibition of several human cancer cell lines (IC₅₀ in low nanomolar range).
2) Treatment with EZN-3042 in a single agent or in combination with Taxol® inhibited tumor growth and improved survival in lung cancer xenograft models.
3) In a liver regeneration model, treatment with EZN-3042 resulted in potent and specific knockdown of survivin mRNA.
4) EZN-3042 is a potent and selective LNA–RNA antagonist of survivin in preclinical models and thus merits further evaluation in the clinic.

References