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ABSTRACTS SELECTED FOR POSTER PRESENTATIONS

Pancreatic Cancer

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LNA-Modified Oligonucleotides Targeting mRNA of DICER in Pegylated Colloidal Nanoparticles With Linked Abs Against CD44 on Pancreatic Cancer Stem Cells (PCSCs) Induces PCD After Inhibition Of Oncomirs Leading to Downregulation of Antiapoptotic Oncogenes That Interact With Their 3'UTRs and Inhibition of DNA Hypermethylation Leading to Activation of Apoptotic Tumor Suppressor Genes

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Background: Pancreatic Ca is incurable due to chemoresistance caused by cancer stem cells due to overexpression of oncomirs which upregulate oncogenes and hypermethylation in CpG islands which inactivates tumour suppressor genes.

Methods: Pancreatic cancer stem cells (PCSCs) were obtained from patients and injected into xenograft animal models, which were treated with LNA oligonucleotides targeting DICER where the 2'-oxygen is bridged to the 4' position via a methylene linker leading to formation of a rigid bicycle locked into a C3 endo (RNA) sugar conformation encapsulated in PEG colloidal nanoparticles with linked Abs targeting CD44. Microarray, RT-PCR, IHC, flow cytometry, MTT, BrdU, TUNEL, and TEM were used.

Results: There was inhibition of Dicer RNAIII endonuclease which blocked exportin-5 cleavage blocking formation of mature oncogenic miRNA segments. This inhibition of oncomirs led to silencing of oncogenes such as transcription factors, apoptotic inhibitors, chromatin modifiers, growth factors (tyrosine kinases-integral membrane proteins), and signal transducers (cytoplasmic regulators, membrane associated G-proteins, GTPase exchange factors, and serine/threonine kinases). Dicer silencing led to inhibition of angiogenesis, invasion, metastasis, PCSC proliferation by inhibiting stem cell pathways Bmi-1, Notch, SHH, and Wnt. There was inhibition of hypermethylation of CpG islands reactivating apoptotic tumor suppressor genes, inducing irreversible D2 stage of type I PCD/apoptosis which led to a bystander killing effect. BrdU and MTT exhibited inhibition of DNA synthesis and metabolic activity of PCSCs

Conclusions: Silencing of DICER exerted a synergistic apoptotic effect by activation of tumor suppressor genes after demethylation, and inhibition of oncomirs and linked oncogenes leading to eradication of chemoresistant PCSCs.