OFFICIAL ABSTRACT and CERTIFICATION

Specific Dinucleotide Repeat siRNAs Decrease Proliferation and Viability of Human Ovarian Carcinomas via a DISE-dependent Mechanism

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Trinucleotide repeat disorders manifest as triplet amplifications of specific genetic sequences that exceed a normal range threshold for the affected gene. The most representative example of this class of disorders, Huntington's disease, is characterized by expansion of a CAG repeat in the first exon of the huntingtin gene. Interestingly, Huntington's patients exhibit a dramatic reduction in the incidence rates of nearly all forms of cancer in relation to the general population. Recent evidence suggests that this remarkably low cancer prevalence among the Huntington's population is a consequence of the production of small interfering RNA molecules (siRNA) that selectively target and destroy the products of a subset of genes essential for cell survival, a process referred to as death induced by survival gene elimination (DISE). The current study was conducted to assess the effectiveness of a series of dinucleotide repeat siRNAs to induce DISE in a HeyA8 ovarian cell line. Results indicated that cells transfected with siCU and siUC repeats displayed significantly impaired proliferation and decreased cell survival via live-cell imaging and ATP viability assays, respectively, as compared to scrambled siRNA negative control. Furthermore, survival of cells treated with siCU and siUC were comparable to those transfected with siCAG, a previously validated DISE inducing trinucleotide repeat. Lastly, qPCR data derived from cells transfected with siCU and siUC revealed a 2-8 fold reduction in relative mRNA expression levels for three of four survival genes probed (LPP, CCND1, MYO10) as compared to GAPDH control, suggesting dinucleotide siRNA repeats may be viable cancer therapeutics.

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