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# Therapeutic potential of T-Oligo and its mechanism of action

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On telomere disruption, exposure of single stranded telomere 3' overhang triggers DNA damage pathways resulting in cell senescence and apoptosis. T-oligo, an oligonucleotide homologous to the 3' overhang, mimics telomere exposure inducing p53/p73 associated damage responses in malignant cells. NSCLC tumors in nude mice treated with T-oligo by intratumoral injections (60 nmoles) for 6 weeks exhibited a 5.6 and 4.3 fold reduction in size respectively. β-galactosidase examination exhibited strong staining for senescence in H358 and SW1573 tumors. Angiogenesis and vasculogenesis staining in H358 and SW1573 displayed 2.2 fold and 3 fold reduction, respectively. Additionally, IV T-oligo reduced melanoma tumors by 3.7 suggesting that T-oligo maybe a molecularly targeted cancer therapy. To increase the stability of negatively charged T-oligo, it was complexed with increasing concentration of a nano-sized cationic α-helical polypeptide and transfected into H358 lung cancer and AN melanoma cells, it inhibited cell growth in a dose responsive manner from 3.3-6.6 and 4.5-8.3 fold respectively *in vitro*. Ongoing *in vivo* studies indicate that this peptide enhances the antitumor efficacy of T-oligo. Immunoblots of TRF 1 and 2, proteins associated with the protective telomere T-loop structure, showed 1.7 fold downregulation of TRF1 and 2.6 fold upregulation of TRF-2 after treatment with T-oligo. Tankyrase-1 aids in increasing telomere length and we found a combination of T-oligo and XAV939, a tankyrase inhibitor had minimal effect on TRF1 but reduced upregulation in TRF-2 suggesting that T-oligo may only stabilize part of the free shelterin complex and tankyrase-1 maybe involved in T-oligo mediated signaling.

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