

SNS01- An eIF5A-based biologic with significant anti-tumoral activity following systemic administration in a murine model of multiple myeloma

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Eukaryotic translation initiation factor 5A (eIF5A) is post-translationally modified to hypusine-eIF5A and is the only known protein to contain hypusine. Recent studies have indicated that unhyposinated eIF5A is strongly pro-apoptotic, initiating both mitochondrial and death receptor mediated apoptosis, whereas hypusine-modified eIF5A has a pro-survival function

SNS01 has two therapeutic components: (1) an RNAi-resistant plasmid with a B-cell-specific (B29) promoter encoding eIF5A^{K50R}, a mutant of eIF5A that cannot be hypusinated; and (2) an siRNA that selectively suppresses endogenous hypusinated eIF5A which promotes growth of cancer cells. SNS01 nanoparticles are formed by complexing these therapeutic nucleic acids with polyethylenimine (PEI), a synthetic cationic polymer that serves as a delivery vehicle. SNS01 induces apoptosis in both IL-6-responsive (KAS-6/1) and IL-6-independent (U266) myeloma cell lines and exhibits anti-tumoral activity when administered systemically to SCID mice bearing subcutaneous human multiple myeloma (KAS-6/1) tumors. Control mice treated with PEI nanoparticles containing a non-expressing plasmid and a non-targeting siRNA had an average tumour volume of 284 mm³ at the time of sacrifice, whereas mice treated with 1.5 mg/kg or 0.75 mg/kg SNS01 exhibited significant tumor regression and had average tumor volumes of 13 mm³ (95 % inhibition; *p = 0.026) and 24.5 mm³ (91 % inhibition; *p = 0.03), respectively. TUNEL-labeling of tumor tissue indicated that tumor regression induced by SNS01 is attributable to apoptosis. Bio-distribution studies have indicated that SNS01 nanoparticles are also taken up by B cells in the bone marrow. Thus SNS01 may be an effective treatment option for multiple myeloma patients.

Biography

John Thompson is Professor of Biology and Associate Vice-president, Research at the University of Waterloo, Chief Scientific Officer for Senesco Technologies Inc and a Fellow of the Royal Society of Canada.

Catherine Taylor is a Senior Research Associate in John Thompson's laboratory.

Richard Dondero is Vice-president, Research and Development at Senesco Technologies Inc.