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Transmucosal delivery of peptides and siRNAs with a novel lipidic pharmaceutical formulation

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Abstract

Peptides and siRNAs are likely to be part of future therapeutic arsenals for neurological and oncological diseases. However, effective delivery of these agents represents a major obstacle to their development as pharmaceutical products.

We have developed a non-toxic water-in-oil microemulsion technology, called Aonys®, for the delivery of such agents through buccal and/or rectal mucosa. The mechanism of delivery can be summarized as follows: i) Aonys®-formulated active ingredient is deposited on buccal or rectal mucosa; ii) absorption of the active ingredient through mucosa and combination with apolipoproteins ; iii) secretion into the lymphatic system ; iv) systemic circulation of the active ingredient incorporated into VHDL/HDL lipoproteins ; v) cellular uptake via the SR-B1 type lipoprotein receptor. Recent applications of this technology will be described.

Peptide 42 (P42) directly interacts with the N17 domain of polyQ-huntingtin implicated in neurodegenerative Huntington's disease (HD) and inhibits aggregate formation. We evaluated the therapeutic effect of P42 in the R6/2 mice, a model of HD. Pre-symptomatic treatment of 2-11 week-old animals *via* buccal and rectal mucosa was performed daily with P42-Aonys® or an empty vector. Several HD-behavioural associated defects (rotarod and foot-clasping time), body weight, and brain section markers were analysed. The data globally show the protective effect of P42 as a presymptomatic treatment.

A cDNA construction encoding a mutated (oncogenic) human Cyclin D1 (hCCND1) was transfected in mouse fibroblasts and these cells were transplanted in the flank of nude mice. After tumors reached 0.2 cm diameter, different siRNAs targeting hCCND1 mRNA, scrambled siRNAs, or the empty vector were administered every day for 3 weeks via the rectal mucosa using Aonys®. While tumor size increased regularly with time in control animals (empty vector or scrambled siRNA), the increase was strongly reduced in animals receiving hCCND1-specific siRNAs. Interestingly, after 3 weeks, tumor size increased in animals in which the hCCND1-siRNA treatment was changed to empty vector or scrambled siRNA, and regressed in animals in which the empty vector or scrambled siRNA treatment was changed to hCCND1 siRNA. These data were confirmed by western blot analysis of CCND1 protein in the tumors.

These data support the use of Aonys® technology for the in vivo systemic delivery of peptides and non modified siRNAs.