

“MaxSALIVA”: A Nano-Sized Dual-Drug Delivery System for Salivary Gland Radioprotection and Repair in Head and Neck Cancer

Authors : Ziyad S. Haidar

Abstract : Background: Saliva plays a major role in maintaining oral and dental health (consequently, general health and well-being). Where it normally bathes the oral cavity and acts as a clearing agent. This becomes more apparent when the amount and quality of salivare significantly reduced due to medications, salivary gland neoplasms, disorders such as Sjögren’s syndrome, and especially ionizing radiation therapy for tumors of the head and neck, the fifth most common malignancy worldwide, during which the salivary glands are included within the radiation field or zone. Clinically, patients affected by salivary gland dysfunction often opt to terminate their radiotherapy course prematurely because they become malnourished and experience a significant decrease in their quality of life. Accordingly, the development of an alternative treatment to restore or regenerate damaged salivary gland tissue is eagerly awaited. Likewise, the formulation of a radioprotection modality and early damage prevention strategy is also highly desirable. Objectives: To assess the pre-clinical radio-protective effect as well as the reparative/regenerative potential of layer-by-layer self-assembled lipid-polymer-based core-shell nanocapsules designed and fine-tuned in this experimental work for the sequential (ordered) release of dual cytokines, following a single local administration (direct injection) into a murine sub-mandibular salivary gland model of irradiation. Methods: The formulated core-shell nanocapsules were characterized by physical-chemical-mechanically pre-/post-loading with the drugs (in solution and powder formats), followed by optimizing the pharmaco-kinetic profile. Then, nanosuspensions were administered directly into the salivary glands, 24hrs pre-irradiation (PBS, un-loaded nanocapsules, and individual and combined vehicle-free cytokines were injected into the control glands for an in-depth comparative analysis). External irradiation at an elevated dose of 18Gy (revised from our previous 15Gy model) was exposed to the head-and-neck region of C57BL/6 mice. Salivary flow rate (un-stimulated) and salivary protein content/excretion were regularly assessed using an enzyme-linked immunosorbent assay (3-month period). Histological and histomorphometric evaluation and apoptosis/proliferation analysis followed by local versus systemic bio-distribution and immuno-histochemical assays were then performed on all harvested major organs (at the distinct experimental end-points). Results: Monodisperse, stable, and cytocompatible nanocapsules capable of maintaining the bioactivity of the encapsulant within the different compartments with the core and shell and with controlled/customizable pharmaco-kinetics, resulted, as is illustrated in the graphical abstract (Figure) below. The experimental animals demonstrated a significant increase in salivary flow rates when compared to the controls. Herein, salivary protein content was comparable to the pre-irradiation (baseline) level. Histomorphometry further confirmed the biocompatibility and localization of the nanocapsules, in vivo, into the site of injection. Acinar cells showed fewer vacuoles and nuclear aberration in the experimental group, while the amount of mucin was higher in controls. Overall, fewer apoptotic activities were detected by a Terminal deoxynucleotidyl Transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay and proliferative rates were similar to the controls, suggesting an interesting reparative and regenerative potential of irradiation-damaged/-dysfunctional salivary glands. The Figure below exemplifies some of these findings. Conclusions: Biocompatible, reproducible, and customizable self-assembling layer-by-layer core-shell delivery system is formulated and presented. Our findings suggest that localized sequential bioactive delivery of dual cytokines (in specific dose and order) can prevent irradiation-induced damage via reducing apoptosis and also has the potential to promote in situ proliferation of salivary gland cells; maxSALIVA is scalable (Good Manufacturing Practice or GMP production for human clinical trials) and patent-pending.

Keywords : saliva, head and neck cancer, nanotechnology, controlled drug delivery, xerostomia, mucositis, biopolymers, innovation

Conference Title : ICB BBB 2023 : International Conference on Biotechnology, Biomaterials, Bioengineering and Biosciences

Conference Location : Montreal, Canada

Conference Dates : June 15-16, 2023