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"maxSALIVA-II"- Advancing a Nano-Sized Dual-Drug Delivery System for Salivary Gland Radioprotection, Regeneration and Repair in a Head and Neck Cancer Pre-Clinical Murine Model

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Background: Saliva plays a major role in maintaining oral, dental, general health and well-being, where it normally bathes the oral cavity acting as a clearing agent. This becomes more apparent when the amount and quality of saliva is 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 5th most common malignancy worldwide, during which the salivary glands are included within the radiation field/zone. Clinically, patients affected by salivary gland dysfunction often opt to terminate their radiotherapy course prematurely as they become malnourished and experience a significant decrease in their QoL. Accordingly, the formulation of a radio-protection/-prevention modality and development of an alternative Rx to restore damaged salivary gland tissue is eagerly awaited and highly desirable.

Objectives: Assess the pre-clinical radio-protective effect and reparative/regenerative potential of layer- by-layer self-assembled lipid-polymer-based core-shell nanocapsules designed and fine-tuned 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 physico-chemico-mechanically pre-/post-loading with the drugs, followed by optimizing the pharmaco-kinetic profile. Then, nanosuspensions were administered directly into the salivary glands, 24hrs pre-irradiation (PBS, un- loaded nanocapsules, 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 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- months period). Histological and histomorphometrical 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 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 less vacuoles and nuclear aberration in the experimental group while the amount of mucin was higher in controls. Overall, less 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.

Recent publications

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2. Olate, Sergio & Ravelo S, Víctor & Alister, Juan & Netto, Henrique & Haidar, Ziyad & Sacco, Roberto. (2023). Early Treatment of Unilateral Condylar Hyperplasia in Adolescents: Preliminary Results. Journal of Clinical Medicine. 12. 3408. 10.3390/jcm12103408.
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Biography

Ziyad S. Haidar is a Professor of Biomaterials and BioEngineering and Scientific Director of Facultad de Odontología, Universidad de los Andes, Santiago de Chile. Concurrently, Prof. Dr. Haidar is the Founder/Head of the Biomaterials, Pharmaceutical Delivery and Cranio-Maxillo-Facial Tissue Engineering Laboratory (BioMAT'X Chile - HAIDAR LAB), at the Centro de Investigación e Innovación Biomédica (CiiB) and is a Faculty member in the Doctoral Program (BioMedicine) at Facultad de Medicina, Universidad de los Andes , Santiago de Chile. Also serves as Visiting Professor at MaxilloFacial Surgery Division of Universidad de la Frontera-Temuco. Haidar holds a PhD in BioEngineering from McGill University, Montréal-Canada with post-doctoral residency at the Montréal Shriners Hospital (Orthopedics), McGill University Health Center, Montréal-Canada. Before moving to Chile, he served as an Associate Professor of Bioceramics/Chair of Excellence in BioEngineering at Université de Limoges-France and was an Assistant Professor at Department of Pharmaceutics and Pharmaceutical Chemistry (cross-appointment/Department of BioEngineering), University of Utah-USA. Haidar served between 2010 and 2012 as Adjunct Professor of Head&Neck Surgery and the Scientific Director of the Research Center at Inha University Hospital, Seoul-South Korea. Haidar is an international speaker with >125 publications, conference proceedings, text-books, theses and patents and is an editorial board member of several national/international scientific journals and periodicals. He is a member of the International Bone and Mineral Society, Society for Biomaterials, Canadian Biomaterial Society as well as the Canadian and Lebanese Societies of Plastic Surgeons, to name a few.

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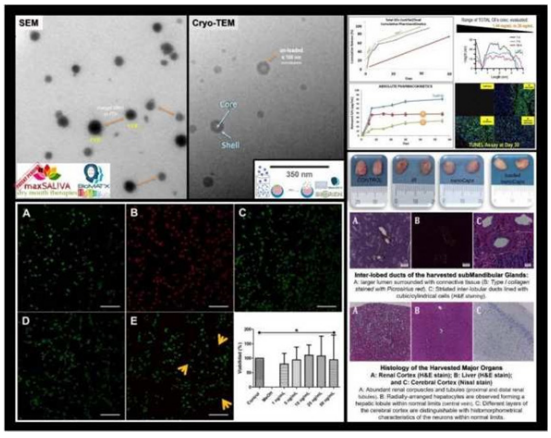

Figure: Graphical Abstract illustrating some of the physical, chemical, pharmacokinetic, cellular and biological (histomorphometrical) prperties of the formulated core-shell nanocapsules, unloaded and loaded with the drugs.