

Translational trials with mesenchymal stem/stromal cell therapy for the regeneration of radiation-induced salivary gland hypofunction and xerostomia

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Xerostomia and salivary gland hypofunction are among the most common long-term side effects of radiation for head and neck cancers (HNC). As no satisfactory treatments for these side effects exist, there is a great need for new remedies for HNC survivors. Emerging evidence suggests that mesenchymal stem/stromal (MSCs) cells have the potential to restore radiation-induced lesions.

The purpose of this PhD was to

1. To investigate the long-term safety of injecting autologous adipose-derived MSCs (AT-MSCs) into the submandibular glands of previous OPSCC patients in a Phase 1/2 RCT (MESRIX-I).
2. To develop and investigate the safety and early efficacy of a clinically applicable “off-the-shelf” therapy comprising injections of allogeneic cryostored unmatched AT-MSCs into the submandibular and parotid glands of previous OPSCC patients in a first-in-human, open-label, single-center, phase 1 trial with repeated measurements days 0, 1, 5, 30, and 4 months (MESRIX-II)
3. To explore the actions of AT-MSCs in the human salivary glands xerostomia by quantitative proteomics of whole human saliva.
4. To design a large randomized controlled trial to investigate allogeneic AT-MSCs (MESRIX-III).

In study 1, long-term safety data were collected from all 30 treated patients. Injections of autologous AT-MSCs into the submandibular glands appeared safe as no differences in the number of serious adverse events (SAEs) were found between the two groups for two years follow-up, and complaints of xerostomia decreased [-10.1 (-18.1 to -2.2); $p = 0.013$]. In study 2, ten patients were injected in all four major glands with no treatment-related SAEs and clinically relevant increase in unstimulated whole saliva flow rate 0.06 mL (95% CI: 0.03 to 0.09 ; $p=.0009$) and decrease in xerostomia symptoms was detected 22.6 units (95% CI: 11.7 to 33.6 ; $p=.0004$). In study 3, AT-MSCs were found to change the expression of 99 proteins but did not restore the salivary proteome after four months. Notably, evidence indicates that several of the most upregulated proteins have pleiotropic effects that may be involved in tissue regeneration, angiogenesis, cell growth regulation, and immune system function.

In conclusion, this thesis provides novel results on the safety of intraglandular injections of AT-
MSCs in the major glands of previous HNC patients.