ImmunoTools *special* Award 2015

Cecilia Rocchi, PhD-student

Supervisor: Professor Dr. Rob Coppes

Department of Cell Biology (room 557), University Medical Centre Groningen A.Deusinglaan 1, building 3215, 5th floor (FB30)
9713 AV Groningen, The Netherland

Stem cell based therapy to ameliorate radiation-induced Xerostomia: expansion of human salivary gland stem cells via modulation of signalling pathways

Worldwide around 500.000 new patients are diagnosed every year with head and neck cancer and the majority of them are treated with radiotherapy, either alone or in combination with chemotherapy and/or surgery. Irradiation of the tumors results in the co-irradiation of the healthy salivary gland tissue, which leads to irreversible hyposalivation and subsequently to xerostomia, compromising the patient's quality of life. Nowadays, clinical management of xerostomia is poor and therefore new approaches and treatments are necessary. Due to the fact that radiation induced hyposalivation is caused by the sterilization of the salivary gland stem cells, the autologous transplantation of salivary gland stem/progenitor cells may be an effective way to restore salivary gland secretion function.

In our group, we have recently shown that cells isolated from salivary glands are capable of forming 3D aggregate structures, named salispheres, which increase in size over time in culture and contain proliferating cells. Mouse salisphere derived cells are able to self-renew, differentiate into all salivary gland lineages and are capable of restoring salivary gland function and morphology in irradiated mouse salivary glands. Preliminary data shows that human salisphere derived cells showed similar in-vitro properties as the murine salispheres. These characteristics makes them a promising candidate for an adult stem cell based therapy for people suffering from radiation induced xerostomia. However, translation to the clinic requires characterization, long-term expansion, testing of functionality and long-term genomic stability of human salivary gland stem cells (hSGSC). In our current study we are focusing on the identification and modulation of pathways that are critical for the survival and the regenerative ability of our putative hSGSCs, with the aim of augmenting the regenerative potential of adult human salivary gland stem cells.

Genome wide expression analysis performed in our group on long-term expanded murine salivary gland stem cells identified 13 genes that were enriched >LogFc 4.0 fold in late culture passages, where the stem cell cohort is more homogeneous, compared to early

passages. Four of these 13 genes belonged to the Wnt pathways. Further analysis on our mouse 3D culture system showed that boosting the Wnt pathway enahnce the regenerative ability of our salisphere. In contrast to mouse salivary gland stem cells, in vitro induction of Wnt signalling is not sufficient to ensure extensive human salivary gland stem cell self-renewal. It is likely that human salivary gland stem cells require further stimulation for prolonged culture, and these results, together with the evidence from other adult stem cell populations, indicate that the contribution of the BMP/TGFβ and Notch signalling pathways could be important for the long-term expansion of our salisphere cultures. Modulation of pathways, such as Notch or BMP/TGFβ, may enhance the self-renewal potential of our salivary gland stem/progenitor cells. Therefore, recombinant human proteins from these key pathways from ImmunoTools would be a huge benefit for the optimization of our 3D in vitro long-term culture system, and we apply for the ImmunoTools Special Award 2015 in order to maximise the regenerative potential of our human salivary gland stem cells via pathway modulation, and expedite the journey of these cells towards a cellular therapy for radiation-induced hyposalivation.

ImmunoTools *special* AWARD for **Cecilia Rocchi** includes 15 reagents

recombinant human cytokines: rh Activin A, rh BDNF, rh beta NGF, rh BMP-2, rh BMP-7, rh GDNF, rh Noggin, rh Neuregulin, rh CTGF, rh IGF-I, rh IGF-II, rh EGF, rh VEGF-121, rh SCF, rh SHH DETAILS more AWARDS