ImmunoTools *special* Award 2014

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Development of a cell therapy for xerostomia, via the phenotypic characterisation of adult human salivary gland stem cells

Radiotherapy treatment for head and neck cancers often leads to immediate and irreversible damage to the salivary glands (SGs), due to co-irradiation. The dramatic resultant loss in saliva production (hyposalivation) and the accompanying life-long clinical sequelae, (speaking & eating difficulties, dental caries and sleeplessness; together termed xerostomia) results in loss of quality of life for the patient. Current treatment options provide transient relief at best form these symptoms. We have previously shown that salispheres, proliferating floating cultures of cells, can be isolated from the mouse SG. These cells, when transplanted into the SG in a clinically-relevant mouse model of hyposalivation, are capable of rescuing saliva production within 90 days following transplantation. Salisphere cells engraft into the recipient SG, and display morphologies of fully differentiated, functional SG cells, for example acinar and ductal cells. Additionally, murine salispheres show properties of a stem/progenitor cell containing population of cells, for example the ability to self-renew *in vitro*, mutli-lineage differentiation, and expression of several well-established stem cell marker proteins (CD24, CD29, c-Kit). Indeed, rescue of saliva production was achieved with transplantation of as few as 100 c-kit-expressing cells into the SG, in comparison with 50,000 non-selected salisphere cells. These data demonstrate thus that a salisphere-based therapy for hyposalivation is feasible, and furthermore that selection of the most potent cell type is critical for the development of an efficacious cell therapy. In order to translate this cellular therapy for xerostomia into the clinic, we have adjusted our salisphere isolation protocol for the isolation of human salispheres for healthy biopsies of human SG. Human salispheres display similar in vitro properties are murine salispheres, and encouragingly contain sub-populations of cells expressing stem cell marker proteins (CD133, c-Kit, CD24, CD29). Through the employment of an immunedeficient mouse model, the NOD/SCIDIL2Rg$^{-/-}$ mouse, we are in the process of characterising the exciting regeneration potential of human salispheres cells as a cellular therapy for Xerostomia. A significant part of this research will be centred around

the identification of cell surface marker proteins that can be used to select cells within the human salisphere cohort with the greatest regenerative potential, mirroring the work published with c-Kit expression in mouse salispheres. Unfortunately, c-Kit^{+} cells have proven extremely rare and difficult to culture, when isolated from human salisphere cultures, and thus we are searching for a new candidate marker protein, representing the cell sub- population with the most regenerative potential, in order to develop an efficacious therapy for hyposalivation. We are therefore applying for the ImmunoTools Special Award in 2014, to enable us test sub-populations of human salisphere cells for their regenerative potential, following selection via flow-associated cell sorting. Evidence from other adult stem cell populations would also suggest that stimulation of various signalling pathways, for example the hedgehog, Wnt and Notch signalling pathways, may also enhance the regenerative potential of our salisphere cultures, therefore we also apply for this ImmunoTools Special Award in order to investigate the potential of boosting the potency of our putative SG stem cells via signalling pathway stimulation.

ImmunoTools *special* AWARD for **Sarah Pringle** includes 24 reagents

FITC - conjugated anti-human CD11a, CD18, CD24, CD29, CD41a, CD47, CD54, CD56, CD105, HLA-ABC, HLA-DP, HLA-DR, Annexin V,

PE - conjugated anti-human CD11b,

APC - conjugated anti-human CD56, CD61, CD63,

recombinant human cytokines: rh Activin A, rh CTGF, rh IGF-I, IGF-II, rh Myostatin, rh SCF, rh SHH

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