CHIEF SCIENTIST OFFICE

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ETM/325. Mesenchymal Stromal Cells for co-transplantation with pancreatic islets to improve graft function in Type-1 diabetes.

Researchers

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Aim

Mesenchymal Stromal Cells (MSC) are multipotent cells. MSC support regeneration of tissues by e.g. supporting blood vessel formation but also have strong immune-suppressive effects which could stop rejection of transplanted tissues. Islet transplantation may be life-changing treatment for patients with Type-1 Diabetes, stabilising blood glucose control. Multiple grafts are needed due to loss of engraftment, and immune-rejection over time. MSC have great potential to be co-transplanted with islets to improve function. The aim of this study was: To generate and characterise MSC from pancreatic and other sources to GMP-standards; To assess the pro-regenerative and immune-suppressive modes of action of the MSC from different sources; To assess these MSC for their ability to enhance engraftment of pancreatic islets for treatment of Type-1 diabetes in appropriate in vivo models.

Project Outline/Methodology

All work with human tissue was carried out following the appropriate ethical and research governance consent. At SNBTS, MSC were generated in vitro from the waste materials left over from the processing of donated pancreata for islet transplantation (untransplanted fractions or visceral fat). MSC were also generated from liposuction waste, and umbilical cord after collection of cord blood. All MSC were transitioned from research to fully-clinical-grade medium and reagents. The in vitro pro-regenerative and immune-modulating properties of the cells were compared by flow cytometry, low density gene array, cytokine production, migration assays and T cell inhibition assays. At U. of Edinburgh new islet transplant in vivo models were established. These were used to establish human islet transplant to "cure" diabetes in the NSG model. Grafts were then co-formulated with and without MSC to study degree and longevity of engraftment, and resistance to immune rejection.

Key Results

GMP-grade MSC can be generated from pancreatic, adipose and umbilical cord waste material to GMP-standards. MSC generated using our methodology are profoundly immune suppressive and do not need inflammatory challenge to mediate this effect. Pancreatic and umbilical cord MSC have unique, distinct, and previously undescribed regenerative and immune-suppressive phenotypes. A human islet transplant model is established in the NSG system, which can effectively reverse streptozotocin-induced Diabetes. Co-formulation of islets for transplant with MSC (pancreatic or umbilical cord origin) promotes engraftment of islets, improves the graft function in reponse to glucose challenge, and may prolong graft survival as compared to transplants with islets alone.

Conclusions

The study has met all of its aims

What does this study add to the field? Systematic development of MSC from non-bone marrow sources at scale and fully GMP compliant. Completely new understanding of the immune reponse modulation by MSC and role of inflammatory challenge - how tissue source influences this. Development of highly relevant new transplant models.

Implications for Practice or Policy This study paves the way for the implementation of MSC as cellular therapies in Scotland and further afield. The results will now provide the basis for SNBTS establishment of a GMP bank of MSC for clinical use. Additionally, the in vivo transplant models have laid the foundation for advanced mechanism of action and safety studies which will be required to enable first use in man of islets and MSC co-transplants.

Where to next? Banking of MSC from at least 2 different Tissue Sources for use in clincial trials. Applications to research councils and major charities for large grants to underpin bank establishment and final pre-clinical studies. Significant funding that will support banking and first in man use recently awarded (award still awaiting announcement).

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