Continence Project

Regenerative Medicine for Faecal Incontinence: A Microparticle Based Approach

Funded by Medical Research Council

Principal Investigator: Dr Richard Day
Co-Investigator: Dr Anton Emmanuel, Dr Francesco Saverio Tedesco, Dr Bernice Wright, Dr Nina Parmar

Description of Research

Incontinence is a debilitating condition with devastating social, economic and psychological consequences. A common cause is damage sustained during childbirth to the muscles that normally provide control of bowel movements. Current medical and surgical treatments are often inadequate. Emerging treatments involving the use of a patient's own muscle cells offer the possibility of restoring function to the damaged muscle, but improved methods for delivering the cells to ensure they survive and regenerate tissue are needed [1].

The aim of our current research is to demonstrate, through proof of principle, that muscle cells attached to the surface of a unique type of degradable polymer microparticle are more effective at restoring injured muscle compared with conventional methods of muscle cell delivery. The novelty of this approach is the combined use of the microparticles for cell expansion in vitro and targeted delivery into the damaged sphincter muscle.

To achieve this we are taking an interdisciplinary approach involving biologists, clinicians, engineers and materials scientists. The experimental work includes investigating the optimal conditions for attachment of muscle cells to the microparticles; delivery of the cellularized microparticles to pre-clinical models of muscle injury; measurement of integration of the transplanted cells at the injury site; and ability of the transplanted cells to restore muscle contractility.

In parallel to our experimental studies we are establishing women's views on innovative cell-based therapies like the one we are proposing, which will help us to design a therapeutic system best suited to the user's needs.

The outcome from the present study will provide timely, key information for the future development of cell-based therapeutic systems for the treatment of incontinence. The experimental outputs will be used to design future clinical trials investigating the safety and effectiveness of the treatment in faecally incontinent patients.

Both the polymer microparticles and cell types being investigated are already being developed independently for other clinical uses, making transfer of findings from this project to the clinic for faecal incontinence much faster. If successful, the therapeutic system will have tremendous economic benefits to the UK NHS, as well as delivering social, economic and psychological benefits to patients.

Methodologies

The project aims to demonstrate proof of principle for an innovative therapeutic system for functional restoration of injured muscle using a combination of cell therapy and a novel degradable cell microcarrier device.

The novelty of this approach is the use of TIPS microparticles for cell expansion and delivery, utilising their advantageous features and avoiding the need for proteolytic cell detachment prior to delivery [2].

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Key Results

Development of:

TIPS microparticle technology being used in the project is well established and the manufacturing process is simple, efficient, and robust.

Our pre-clinical data demonstrate TIPS microparticles are ideal for culturing cells in vitro [3,4].

As part of a separate Wellcome Trust Translation Award we have established a scalable GMP-ready manufacturing process for TIPS microparticles, together with validated methodology for evaluating particle conformity as a qualified product to meet regulatory requirements. A first-in-man clinical safety study of unloaded TIPS microparticles for the treatment of perianal fistulas is due to begin shortly.

The microparticles are also being investigated for a range of other uses providing synergy with the proposed project. This includes pre-clinical investigations exploring their use as a cell delivery device for ocular and cardiovascular disease; delivery of active pharmaceutical ingredients; and a bioprocessing tool for cell expansion and differentiation.

We have recently relocated part of our laboratory to the Stevenage Bioscience Catalyst Incubator Site, where our focus is on establishing an optimized manufacturing process for the TIPS microparticle platform technology in terms of pilot line scale-up, quality control, and consideration of GMP and regulatory requirements.

Links to Published Papers

[1] Parmar, N., Kumar, L., Emmanuel, A., Day, R. (2014). Regenerative medicine therapies for obstetric trauma-induced fecal incontinence. Regenerative Medicine 9(6), 831-40. doi: 10.2217/rme.14.56

[2] Blaker, J. J., Knowles, J. C., Day, R. M. (2008). Novel fabrication techniques to produce microspheres by thermally induced phase separation for tissue engineering and drug delivery. Acta Biomater. 4(2), 264-272. doi:10.1016/j.actbio.2007.09.011

[3] Ahmadi, R., Mordan, N., Forbes, A., Day, R. M. (2011). Enhanced attachment, growth and migration of smooth muscle cells on microcarriers produced using thermally induced phase separation. Acta Biomater 7(4), 1542-1549. doi: 10.1016/j.actbio.2010.12.022.

[4] Parmar, N., Ahmadi, R., Day, R.M. (2015) A novel method for differentiation of human mesenchymal stem cells into smooth muscle-like cells on clinically deliverable TIPS microparticles. Tissue Engineering Part C. 21(4):404-12. doi: 10.1089/ten.TEC.2014.0431

Link to Website

http://www.ucl.ac.uk/day-lab