APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

Academic Supervisor
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ICH Programme/Section: DBC/Developmental Biology of Birth Defects

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1. Title.

Autologous cell engineering for bladder augmentation: a combined approach of stem cells and tissue engineering for children with end-stage bladder disease

2. Portfolio summary.

Aims:

The overall aim of the project is to deliver functional bladder reconstruction through an autologous cell engineering strategy. We aim to create a continent reservoir using a newly-formed surrogate vascularised host smooth muscle tissue, obtained from a segment of small bowel which has been demucosalised (to remove the absorptive gut epithelium) and re-lined by autologous epithelium (urothelium) generated by propagation in cell culture in vitro. In this way we overcome the difficulty of engineering a functional vascularised smooth muscle tissue.

Background:

Bladder augmentation is used surgically both in children and adults with end-stage bladder disease or urinary incontinence to provide a low-pressure, compliant urine-storage reservoir. In the paediatric population, the need for bladder augmentation is usually due to a congenital anomaly such as Bladder extrophy or posterior urethral valves. Bladder extrophy is a complex and severe congenital anomaly characterized by a defect in the closure of the lower abdominal wall and bladder. The bladder and related structures (bladder mucosa, ureteral orifices, posterior bladder neck, and urethra) are everted through the ventral wall of the abdomen between the umbilicus and symphysis pubis.

Proposed methodology to be adopted:

In order to develop a tissue engineering surgical model, we will focus here on transplanting in vitro-propagated normal and diseased human urothelium onto bowel-derived demucosalised smooth muscle segments in an immunosuppressed pig model. This is an important step before determining if urothelium from diseased bladders will provide a suitable source of epithelium for use in bladder augmentation (using a technique called “composite cystoplasty”). The host laboratory has been already harvesting urothelial cells from human normal and diseased bladder and has successfully cultured them. We have demonstrated that we are able to establish cultures and expand them through several passages to obtain adequate numbers of cells; these cells can then be used to create differentiated cell sheets for the bladder reconstruction.
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Skills to be achieved by the PhD trainee:

(i) Primary cell culture and human cell harvesting from biopsies; (ii) Tissue engineering and natural scaffold preparation
(ii) Histology, immunohistochemistry and immunocytochemistry
(iii) Surgery in large animal pre-clinical model (pig)

Relevance to the area of paediatric surgery:

End stage bladder disease is a devastating condition in which children require major surgery to enlarge their bladder and reduce the risk of developing kidney failure.

Children born with bladder extrophy, which has an incidence of 2.07 per 100,000 live births, require, in up to 70% of cases, bladder augmentation in order to achieve an adequate bladder capacity.

References: