UCL
GREAT ORMOND STREET
INSTITUTE OF CHILD HEALTH

Great Ormond Street Hospital Charity

APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

Academic Supervisor
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Clinical Supervisor
Name: Professor Paolo De Coppi
GOSH department: Paediatric Surgery

1. Title.

Oesophagus tissue engineering in large animals as preclinical model for the treatment of oesophageal atresia

2. Portfolio summary.

Aims:

This study aims at the reconstruction of the stratified epithelium of a tissue engineered (TE) oesophagus using epithelial stem/progenitor cells, necessary to guaranty long tem repair of the epithelial barrier of the gastro-intestinal tract.

The specific objectives are:

1. To reconstitute within a bioreactor ex vivo a fully functional, pluristriatified squamous epithelium on a decellularised oesophageal scaffold which has been previously repopulated with muscle cells.
2. To test the functionality of the whole TE oesophagus in vivo by transplantation of the reconstructed oesophagus into large animals as preclinical models.

Background:
Oesophageal atresia (OA) is a congenital condition characterised by interruption of the continuity of the oesophagus, which ends in a blind-ended pouch instead of normally connecting the throat to the stomach. The incidence is about 3 per 10,000 births and different types of anatomic anomalies characterise OA patients. In the case of 'long-gap' OA, primary anastomosis is not feasible. The therapeutic options for those patients are limited to surgical procedures aiming at oesophageal replacement (e.g. gastric pull-up, where the stomach or the intestine are moved from the abdomen to the thorax to fill the gap). These procedures are often associated with a high rate of post –operative complications and mainly with a poor quality of life. However, regenerative medicine and in particular tissue engineering could represent a therapeutic alternative to these patients as it might provide valid organ-like substitute that could replace the missing portion of the organ.

Proposed methodology to be adopted:

- Acellular oesophageal scaffolds from piglet will be obtained according to a protocol

developed in the laboratory of Prof De Coppi [1]. Cell culture conditions will be optimized to sustain the cells growth of oesophageal progenitor/stem cells over the extra-cellular-matrix (ECM) of pig acellular scaffolds and test their stratification capacity.
-We will perform co-seeding within a bioreactor of human epithelial cells over the lining surface of acellular pig scaffolds previously repopulated with muscle progenitor cells. The recellularised construct will be maintained in bioreactors specifically developed to allow cell seeding and tissue maturation;

-Finally, the TE constructs repopulated with both muscular and continuum epithelial-barrier layers in the lumen will be transplanted orthotopically in a large animal model. These experiments are considered part of the pre-clinical experimentation of a novel approach for oesophageal atresia, which means that if successful, this approach will open the pathway to a phase I/IIa clinical trial.

Skills to be achieved by the PhD trainee:

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

Relevance to the area of paediatric surgery:

The current treatments of OA have reduced mortality in the paediatric age, have however increased morbidity, including cancer, in patients that otherwise would have a normal life expectancy. Therefore, patients with the longest gap between the residual oesophagus and the stomach represent a major challenge in paediatric surgery.

References:

1. Pedersen R.N., Calzolari E., Husby S., Garne E., EUROCAT Working group. (2012) Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 97:227–232.
2. Langer R., and Vacanti J.P. (1993). Tissue Engineering. Science. 260: 920-926.
3. Seery J.P. (2002). Stem cells of the oesophageal epithelium. Journal of Cell Science. 115: 1783-1789.
4. Tan J.Y., Chua C.K., Leong K.F., Chian K.S., Leong W.S., and Tan L.P. (2012). Esophageal tissue engineering: An in-depth review on scaffold design. Biotechnology and Bioengineering. 109(1): 1-15.
5. Totonelli G., Maghsoudlou P., Fishman J.M., Orlando G., Ansari T., Sibbons P., Birchall M.A., Pierro A., Eaton S., and De Coppi P. (2012). Esophageal tissue engineering: A new approach for esophageal replacement. Worl J Gastroenterol. 18(47): 6900-6907.