APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

Academic Supervisors
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1. Title.
Early correction of abnormal bladder development

2. Portfolio summary.

Overview
Fetal urinary tract abnormalities that disrupt urine flow, such as posterior urethral valves, are common causes of end-stage renal failure in young children(1). This is because mal-development of the bladder perturbs nephrogenesis leading to reduced nephron number during kidney development. ‘Valve’ bladders usually show detrusor hypertrophy and dysfunctional voiding, and these abnormalities may persist despite valve ablation(2). We hypothesise that early strategies which prevent detrusor hypertrophy should improve both long term bladder function and reduce the severity of developmental kidney injury.

Project details
We will use two mouse models of abnormal bladder development:

1) The T(2;11)30H mice (T30H)(3, 4) generated many years ago which has abnormal detrusor smooth muscle development. The genetic defect has just been identified in a PhD project supervised by Professor Winyard and that student is doing complementary work on antenatal gene therapy.

2) Partial surgical obstruction of the urethra in mice, as reported by a previous GOS Urology colleague, which replicates many of the changes seen in valve bladders(5).

The overarching aim of the project is to increase understanding of and find ways to correct abnormal bladder musculature. Objectives towards this aim include:

- Generating a vesicostomy in the T30H mice to facilitate bladder drainage
- Creating surgical partial bladder obstruction in five week old mice(5) and characterising subsequent smooth muscle and matrix changes
- Simulating the effects of T30H using gene therapy in the bladder of surgical obstruction mice in an attempt to block compensatory detrusor hypertrophy

Techniques will include animal husbandry, microsurgery, immunohistochemistry, PCR, Western blotting and gene therapy. Additional experiments may include fetal bladder culture, detrusor muscle culture and analysis of human bladder biopsies (Professor

Significance of this project
This study will equip the appointee with first-rate experimental and analytical skills to take forward into future academic surgical training. It will also increase understanding of aberrant bladder development and should lead to funded studies in larger animals - both supervisors
have worked with fetal sheep and Professor Cuckow is part of a porcine research group at the University of Aarhus. Ultimately, we hope that this area of research will inspire new therapeutic approaches to improve outcome for human conditions such as posterior urethral valves.

References