APPLICATION FOR A GOSHCC SURGICAL SCIENTIST PHD STUDENTSHIP

**Academic Supervisor**  
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1. **Title.**  
Exploring cranial mechanotransduction as a novel treatment for craniosynostosis

2. **Portfolio summary.**

**Aims:**  
Understanding the impact of mechanotransduction on cranial suture development and homeostasis at the molecular and cellular level.  
Design new therapeutic strategies for craniosynostosis based on mechanotransduction.

**Background:**  
Craniosynostosis is a birth defect with a prevalence of 1 in 2,500 births. Premature closure of cranial sutures has profound effects on brain development as well as the size and shape of the future head and face. Craniosynostosis, in particular in syndromic forms, is progressive and presents on-going clinical problems in the life of the affected child and adolescent until skeletal maturity.  
There is a growing body of literature on how craniofacial sutures respond to mechanical forces (i.e. loading) both in vivo and in vitro. When dissected calvaria of wild type rat skulls are loaded under tension in an explant culture model, it was found that loaded interfrontal sutures remained open while unloaded sutures in the control group fused. An in vivo study on the premaxillary suture in rats showed similar results. These studies support the hypothesis that calvarial loading impacts on suture patency and can delay suture closure in wild-type animals.

**Proposed methodology to be adopted:**  
Using an existing mouse model for Crouzon syndrome that is characterised by coronal craniosynostosis and displays differences in bone density between individual cranial bones, we intend to employ in vitro and in vivo techniques to investigate the effect of cranial bone loading on cranial bone growth and suture patency in wild-type and mutant mice. For the in vitro studies, calvaria will be dissected from mutant and control mice and grown in culture using protocols currently used in our laboratory. During culture, external force will be applied to the tissue and the effects of mechanotransduction will be investigated using qualitative and quantitative morphological analysis as well as standard gene and protein expression assays. For the in vivo studies, postnatal animals will be subjected to a cyclical loading protocol using equipment developed in collaboration with Dr Moazen at UCL Mechanical Engineering. A Home Office Project License (70/8817) is in place for these experiments. Suture patency will be analysed using microCT analysis as well as standard post-mortem morphological, cellular and molecular analysis.

**Skills to be achieved by the PhD trainee:**  
The PhD candidate will be trained in basic laboratory techniques (molecular biology, cell biology, cell/tissue culture, mouse genetics, embryology, microdissection, etc.) as well as
the foundations of biomedical research including: scientific data generation, collection and analysis.

**Relevance to the area of paediatric surgery:**

Craniosynostosis is caused by the premature fusion of the bones that form the skull, which can have serious, possibly life-threatening results. Traditional approaches to the treatment of this type of craniofacial birth defect employ complex surgical remodelling of the skull including facial deformities, aimed at protecting brain development, visual function and the restoration of a more normal craniofacial appearance. While the surgical correction of the craniofacial deformity and its secondary defects is reliable in many cases, there is a heavy burden of care and ongoing surgical intervention from birth to maturity. The research described in this proposal intends to explore the possibility of cranial bone loading as an alternative or supplementary, less invasive treatment of craniosynostosis.

**References:**