British Society for Paediatric Endocrinology & Diabetes Research Award Report
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Adrenal rescue of Familial Glucocorticoid Deficiency using donor specific reprogrammed cells in mice

Background:

Familial glucocorticoid deficiency (FGD), otherwise known as hereditary unresponsiveness to ACTH, is a rare autosomal recessive disease characterized by glucocorticoid deficiency in the absence of mineralocorticoid deficiency. Mutations of the ACTH receptor, also known as the melanocortin-2-receptor (MC2R), account for approximately 25% of FGD cases. A further 20% is caused by mutations in MRAP (melanocortin-2 receptor accessory protein). MRAP encodes a small single transmembrane domain protein, which is essential in the trafficking as well as function of the MC2R at the cell surface. We recently generated a new mouse model of FGD by knocking out *Mrap* (Novoselova et al. FASEB J, 2018). We found that the vast majority of *Mrap*-knockout (KO) mice died at birth but could be rescued by administration of corticosterone to pregnant dams. Surviving *Mrap*-KO mice developed isolated glucocorticoid deficiency with normal mineralocorticoid and catecholamine production, perfectly recapitulating the FGD human phenotype. This is the first mouse model of FGD with isolated GC deficiency. For this reason, it would be the perfect model to study novel treatment modalities aimed at restoring normal adrenal function and rescue the phenotype of adrenal insufficiency (AI).

The generation of functional steroidogenic cells to restore adrenal function, provides an attractive approach to cure AI, whilst maintaining the complex feedback regulation of the hypothalamo-pituitary-adrenal axis. Dr Guasti (co-PI, QMUL) reported the generation of human induced steroidogenic cells (hiSCs) from fibroblasts, blood-, and urine-derived cells (Ruiz-Babot et al. Cell Rep 2018). Using stem cells that have been reprogrammed to be adrenal cells, we seek to restore adrenal function in these mice and show that this technique can be adopted to treat patients with AI.

Benefit to applicants:

The grant provided a great opportunity to explore cell-based therapies in adrenal disease and to generate proof-of-concept data that such cells can restore adrenal function in an animal model of FGD. hiSCs have been shown to be viable when transplanted into the mouse kidney capsule and intra-adrenal area. The award has directly led to a new collaboration with Boston Children's hospital where work on optimising hiSC to rescue the Mrap-KO mouse is ongoing and we hope to be able to update the Society in the next year. The award has helped our career development. I was awarded a Wellcome and EU grant (all on Mraps) after the BSPED award. We have also identified a novel cell marker which would allow us to isolate adrenocortical progenitor cells for the generation of organoids which has led to one BBSRC grant award and another submitted (Guasti). The award has directly contributed to my promotion to Reader in Molecular Endocrinology and Metabolism in 2020. As a clinician scientist, my ultimate aim to be able to bring bench-side knowledge to the bedside. We have acknowledged the award in a recent publication (Buonocore F et al. JES 2021) and in a submitted manuscript.

Benefit to endocrinology:

To date the diagnosis of adrenal insufficiency (AI) in childhood means a lifetime of glucocorticoid replacement. The inability to recapitulate normal physiology, adrenal responsiveness to stress and illness means that patients with AI have been shown to have increased morbidity and mortality despite being on steroid replacement. The ability to restore adrenal function as a form of cure would transform treatment of AI. After taking years to generate FGD mouse models and time developing reprogramming techniques, we are now in the perfect position to test the possibility of adrenal stem cell treatment in this unique FGD mouse model. We are hopeful that this project will provide data that will underpin future prospective cell based therapies towards curing adrenal insufficiency in children and adults.