

TARGETTING THE PROSTAGLANDINS RECEPTORS (EP1-4) AS NOVEL THERAPEUTIC TREATMENT TO CRANIOPHARYNGIOMA

Background: Adamantinomatous craniopharyngioma (ACPs) are intracranial tumours in children. They arise from the pituitary gland and lead to severe endocrine dysfunction. These tumours are locally invasive, often affect surrounding vital structures such as the hypothalamus, visual-pathways and have high recurrence rate. The treatment of ACPs is limited to surgery combine with radiotherapy, which are associated with high morbidity and significant disabling adverse effects. The disease and/or treatment-related consequences are in themselves life-threatening (hypothalamic morbid obesity, temperature instability, blindness, hormone deficiencies), or life-reducing (strokes, visual impairment, Type-2 diabetes mellitus). **There is an urgent need for identifying alternative targeted therapies to current surgical treatment.**

Preliminary data: Several lines of evidence indicate that prostaglandins acting through their receptors EP1-4 signaling plays an important role in ACP tumorigenesis (Figure1 preliminary data): (i) ACP with mutated β -catenin up-regulate cyclooxygenase 2 (Cox2) Figure 1 A which is the main enzyme that catalyses production of prostaglandins (ii) elevation of prostaglandins PGE2, PGE3 and PGD1 are significantly increased in both human and murine ACPs Figure 1 B (iii) PGE2, PGE3 and PGD1 have been shown to accelerate tumour progression in colon, breast and prostate cancer through prostaglandin receptor EP1&4 mediated action (iv) β -catenin-mediated ACPs tumours up-regulate and express two EP receptors EP1 and EP4 both in mouse and in human tumours. These data suggests that blocking of EP1 and EP4 receptors highly up-regulated in human ACPs could inhibit tumour progression and could act as therapeutic agent to treat ACPs. Molecular markers such as Ki67 (proliferation), Sox2 and Sox9 (stem/progenitor), PECAM, endomusin (tumour angiogenesis) will be carefully analysed to assess the role of EP1&4 receptors in ACP progression (Note that these genetic crosses have already started in my laboratory and that all transgenic lines are available to us). 2) We identified EP1 and EP4 receptors to be expressed both in murine and human ACP. Using ACP-cell culture we will assess the effect *in vitro* of antagonists for EP1 (ONO-8713) and EP4 (ONO-AE2-227) (gift from ONO Pharmaceuticals, Co LTD Japan, used successfully before). Concomitantly we will treat the ACP-mouse model with ONO-8713 or ONO-AE227 compound supplemented diets (400 ppm as described in other studies and compare tumour progression as described above). In parallel, we will assess if selective EP 1&4 antagonist are effective in human ACPs. To this end we will generate primary cell cultures of human ACP. We will supplement cultures with blocking PGE receptors EP1 &4 specific antagonists ONO-8713 and ONO-AE227 (5-10 nmol/L). **By performing these studies we will identify for the first time a novel mechanisms of EP receptors ACP progression an a novel therapeutical treatment for ACPs.**

Benefit to applicant I have been awarded the Early Career Fellowship from Barts & The London Medical School to start my independent research on paediatric endocrinology focusing on identification of key genes involved in development of the hypothalamic-pituitary axis and tumorigenesis. The award of this grant will allow me to fund the above project and will be key to generate sufficient preliminary data to be used for a research grant from a main research council. We have obtained preliminary data indicating that prostaglandins negatively affect ACP progression. We are now doing more experiments looking at the effects of blocking the receptors in tissue culture. Using ACP- cell culture we have assessed the effect *in vitro* of antagonists for EP1 (ONO-8713) and EP4 (ONO-AE2-227) on ACPs and in culture cells it shows a protective effect. In vivo we have generated pilot study that indicates that increase prostaglandin accelerates tumour progression. We have generated enough preliminary data to be able to apply for a larger grant to complete the

project. We have also studied the expression of prostaglandins and receptors in ACPs and would like to extend the study to a larger cohort to see if these molecules act as a biomarker.

Benefit to department/institution The Centre of Endocrinology at the William Harvey Research Institute has a team of paediatric endocrinologist led by Professor Leo Dunkel. Moreover, there are further 6 principal investigators focusing paediatric endocrinology with large range of research areas such as adrenal development, genetic of adrenal glands, genetic imprinting and neonatal endocrinology, delay puberty, genetics of growth and pituitary tumours. The award of the grant has allowed me to bring in some precious transgenic lines to study the effect of prostaglandins in pituitary development and disease. It has allowed me to put in place techniques such as in situ hybridisation, mouse embryology and mouse genetics. Our preliminary data has unravelled a new role for the prostaglandins and the receptors in the progression of pituitary tumours.

Benefits to Endocrinology: Although still preliminary, the project is ongoing identifying the molecular mechanism of the prostaglandin receptor antagonist in progression of ACP. If proven beneficial further murine test will be done. This research could have the potential to clearly improve clinical efficiency by providing much needed alternative treatments for ACP patients, ultimately preventing multiple recurrences of the tumour requiring multiple surgeries. Outcomes: we have not yet produced enough data to be able to publish the results. But we expect one publication and we will acknowledge BSPED for the funding.