ROLE OF BRAIN-GUT AXIS IN OBESITY INITIATION AND PROGRESSION IN BARDET-BIEDL SYNDROME

IMPACT STATEMENT

Current knowledge of the mechanisms underlying obesity, such as Bardet- Biedl syndrome (BBS), or other syndromic forms of obesity or diet induced obesity in general, is limited. Exploiting a mouse model of a monogenic cause of morbid obesity, Bardet-Biedl syndrome, this thesis aimed at contributing to the understanding of the cellular, molecular and developmental processes required for the maintenance of normal body weight during lifetime.

Investigation of the signalling mechanisms responsible for the onset and development of obesity were performed by scrutinizing the dysregulated pathways in hypothalamus and subsequent study of the vagal afferent signalling in obese condition of Bbs mice.
The research will likely have an immediate and long-term impact on academic communities and clinical researchers. Bardet-Biedl syndrome is a genetic condition with at least 500 diagnosed cases in the UK. Obesity begins in the early childhood that affects 72-92% of BBS patients. It becomes a lifelong debilitation, which very often requires medical intervention. Therefore, this study will have an impact on BBS patients, their clinicians, and subsequently, the National Health and Social services.

Academic community:
The thesis is multi-disciplinary in nature, and the greatest impact will be on the cilia and metabolic fields as it primarily explores obesity in absence of one the Bbs proteins. Cilia are mechanosensory organelle vital for many normal homeostatic functions such as hearing, vision, taste, reproduction and learning and memory. Accumulating evidence suggest the profound role of cilia in development of obesity. However, little is known as to how the defects in ciliary proteins affect the signalling pathways regulating food intake. This study evaluated the altered hypothalamic and vagal plasticity due to dysregulated

energy homeostasis, establishing a link between ciliary proteins, vagal afferent signalling and regulation of food intake.

Bardet-Biedl patients and their clinicians:

BBS proteins when mutated, cause Bardet-Biedl syndrome (BBS) which is a highly debilitating autosomal-recessive genetic condition in which patients present with early-onset blindness, polydactyly, renal disease, learning disabilities, diabetes and obesity. For the clinicians, the knowledge of the underlying aetiology of hyperphagia and obesity in BBS patients is critical for symptomatic treatments. By investigating the role of hypothalamic and vagal afferent signalling in obesity and hyperphagia development in BBS, early intervention programmes may be potentially developed. Finally, although this PhD thesis is an important first step, insights into the sensory role of brain-gut axis (a.k.a vagus nerve and nucleus of the solitary tract) in the development of obesity, provides crucial understanding of neurometabolic physiology and affirms ground work for further study to unravel the dysregulated mechanisms for other common eating disorders.