Title: Understanding the role of the novel apelin receptor ligand Apela in the regulation of neuroendocrine function.

Supervisors: Dr Anne-Marie O'Carroll (A.M.OCarroll@bristol.ac.uk)
Dr Stephen Lolait (S.J.Lolait@bristol.ac.uk)

Project Description

The apelin receptor APJ (1) was first identified as an orphan GPCR, with closest identity to the angiotensin II receptor, type AT1a. In the ensuing years, the receptor was deorphanised when its cognate ligand, apelin, was isolated (2). APJ and apelin are highly expressed in the hypothalamo-neurohypophysial system (HNS) that regulates fluid homeostasis, in the hypothalamic-pituitary-adrenal (HPA) axis that controls the response to stress, and in forebrain and lower brainstem regions involved in cardiovascular function, where they have been shown to be critically involved as key mediators of physiological responses to multiple homeostatic perturbations (see ref. 3 for review).

Unlike most other GPCR families, apelin appears to mediate its effects via binding to only one receptor subtype, APJ. Until recently apelin was considered to be the sole endogenous ligand for APJ. However in 2013 a peptide hormone, APELA (or ELABELA), identified in human embryonic stem cells, was described as a novel peptide that was indispensable for heart formation and that mediated its actions via APJ (4). Apela gene expression has since been found in the adult heart and kidney (5). Little is known on the *in vivo* regulation of apela, and its precise function *in vivo* remains to be determined. It appears that apela, like apelin, can exist in a number of differently processed forms and there is some evidence that apela may act both as a protein and as a non-coding RNA (6,7).

Specifically, this project is intended to extend our ongoing work to elucidate the role of the apelinergic pathway in the brain and peripheral tissues. The aims of this proposal are to determine the extent and significance of the involvement of different forms of apela in challenges to HNS (e.g., dehydration), HPA axis (e.g., acute physical and social stressors), and cardiovascular homeostasis in rats that have been administered apela, apelin and APJ-specific lentiviral-based short hairpin RNA (shRNAs). The hypothesis is that apela, mediating its effect through APJ located on hypothalamic neurons, is an important regulator of these homeostatic systems. This is based on our work where we have determined the distribution of apela gene expression in the brain.

The student will be able to develop this project in line with his/her own neuroscience interests. This work should provide important new insights into the functions of APJ and its endogenous ligands, and provide unique information about a potentially new target transmitter system whose pharmacological modulation may prove to have consequences for improvement of the quality of life.

References:

(1) O'Dowd BF *et al.* (1993). A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. Gene 136:355-360.
(2) Tatemoto K *et al.* (1998). Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun 251:471-476.
(3) O'Carroll A-M *et al.* (2013). The apelin receptor APJ: journey from an orphan to a multifaceted regulator of homeostasis. Journal of Endocrinology 219:R13-R35.
(4) Chng SC *et al.* (2013). ELABELA: a hormone essential for heart development signals via the apelin

receptor. Developmental Cell 27:672-680.
(5) Hassan AS *et al.* (2010). Expression of two novel transcripts in the mouse definitive endoderm. Gene Expr Patterns 10:127-134.
(6) Yang P *et al.* (2015). Apelin, Elabela/Toddler, and biased agonists as novel therapeutic agents in the cardiovascular system. Trends Pharmacol Sci 36:560-567.
(7) Li M *et al.* (2015). An Apela RNA-Containing Negative Feedback Loop Regulates p53-Mediated Apoptosis in Embryonic Stem Cells. Cell Stem Cell 16:669-683.

Keywords: endocrinology, molecular biology, neuroscience / neurology