Project Details	
Project Code	MRC21NMHEx Mosienko
Title	Regulation of stress response by astrocytes
Research Theme	Neuroscience & Mental Health
Summary	Exposure to chronically stressful situations is a major risk factor for clinically diagnosed depression. The brain integrates stress signals through the limbic system, the activation of which ultimately leads to glucocorticoid release. This project will investigate how astrocytes fine-tune processing of stress signals in the limbic system and how glucocorticoids in turn feedback to astrocytes to ensure an appropriate stress response.
Description	Depression is the most common mental health illness affecting 1 in 4 people in the UK. It costs England an estimated £7.5 billion a year spent on services, treatments and lost employment. Exposure to chronically stressful situations is a major risk factor for clinically diagnosed depression. To respond to stress, the brain first integrates signals in the brainstem and the limbic system which includes the prefrontal cortex, amygdala and hippocampus. These in turn activate signalling networks in the hypothalamus and pituitary gland and lead to glucocorticoid release from the adrenal gland into the blood. Glucocorticoids feed back to the limbic system to regulate the strength of the stress response and to restore the system to baseline level after stress. Understanding the cellular and molecular basis of the stress response will lay the foundation for the development of drugs that might prevent extreme stress responses and possess antidepressant properties. Astrocytes are the most abundant type of brain glial cells. They integrate various physiological signals through modulation of synaptic transmission. Our previous collaborative work identified lactate as a novel gliotransmitter released specifically by astrocytes. During periods of increased local brain activity, astrocytes elevate their release of lactate to support a wide range of brain area-dependent functions, including memory (hippocampus and cortex), decision making (amygdala and anterior cingulate cortex) and attention (brainstem). Our ongoing work shows that astrocytic lactate in amygdala also drives the response to acute stress, and hippocampal astrocytic lactate reinforces the acute response to novel stimuli. Building on our current work, this project will investigate limbic astrocyte pathways that regulate responses to chronic stress. Using cutting edge technology including in vivo lactate amperometry, next generation sequencing unique and molecular tools to reduce lactate specifically in astrocytes, this project will address the following main questions: 1) How are lactate levels regulated in the limbic system during chronic stress? 2) Can limiting astrocytic lactate in the limbic system affect responses to chronic stress? 3) What are common astrocyte pathways regulated by chronic stress and glucocorticoids? and 4) What are the underlying genetic determinants of stress resistance in astrocytes? The prospective student will employ transgenic mouse models in combination with brain area-specific viral vector mediated expression of lactate degrading enzymes recently engineered by the Teschemacher lab (Bristol). This will allow modulation of lactate signalling specifically in astrocytes with subsequent characterisation of changes in anxiety- and depression-like behaviour in

	an animal model of chronic mild stress. Behavioural testing will be combined with lactate measurements in behaving animals using in vivo lactate amperometry. To discover astrocyte molecular pathways underlying stress resistance and responsiveness the student will analyse profiling changes in gene expression in astrocytes isolated from animals undergoing chronic mild stress, and perform histology, and calcium and intracellular metabolite live cell imaging experiments. The student will join a well-funded lab and a vibrant Neuroscience community at the University of Exeter and will be supported throughout the PhD by the excellent collaborative team of researchers in Exeter and at the University of Bristol. The project includes an outstanding chance to train in big data analysis and bioinformatics, in vivo physiology and confocal microscopy by a collaborative research team with a successful track-record in genetics, pharmacology and molecular and behavioural neuroscience.
Supervisory Team	
Lead Supervisor	
Name	Dr Valentina Mosienko
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Medical School
Email Address	v.mosienko@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Anja Teschemacher
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	School of Physiology, Pharmacology and Neuroscience
Co-Supervisor 2	
Name	Professor Emma Robinson
Affiliation	Bristol
College/Faculty	Life Sciences
Department/School	School of Physiology, Pharmacology & Neuroscience
Co-Supervisor 3	
Name	Professor Katie Lunnon
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Medical School
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	