

| Project Details |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Project Code    | CMD27Br Mosienko                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Title           | Cardiac glia: gatekeepers of the stressed heart?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Research Theme  | Cardiometabolic Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Project Type    | Wet lab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Summary         | <p>The heart is controlled by the peripheral nervous system, whose nerves are supported by "helper" cells called glia, as astrocytes support neurons in the brain. Long overlooked, cardiac glia are now emerging as active players in heart function. Stress is a major cause of dangerous heart rhythms, cardiometabolic disease and heart failure, yet whether glia protect the heart or contribute to disease remains unknown. The student will address this question while gaining interdisciplinary training in in vivo cardiovascular research, live-cell and metabolic imaging, genetic tools and data analysis, opening a new area of neuro-cardiac biology and a potential treatment target.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Description     | <p>In the brain, astrocytes are active partners of neurons buffering ions, releasing metabolites and signalling molecules (lactate, ATP, glutamate) at "tripartite synapses", and switching to a reactive state under stress that reshapes circuit function. The heart has its own glia, increasingly recognised as active participants in cardiac control and implicated in both sympathetic and parasympathetic neurotransmission. Autonomic control of the heart runs through intrinsic cardiac ganglia, where satellite glial cells and cardiac "nexus" glia ensheath autonomic neurons and contact pacemaker cells, buffering ions, handling neurotransmitters and releasing neurotrophic factors to set heart rate, rhythm and conduction (Kikel-Coury 2021; Kanemaru 2023). Stress is a major, modifiable cause of arrhythmia and heart failure, acting largely through autonomic imbalance. Yet, whether cardiac glia sense stress, and whether their response protects the heart or drives arrhythmia, is unknown. Because one of the fundamental roles of glial cells in the brain is metabolic support of neuronal function, we hypothesise that stress reprogrammes the metabolic signalling of cardiac glia, determining the heart's adaptive versus maladaptive response.</p> <p>Central question: do cardiac glia, through their metabolic and signalling state, determine how the heart responds to stress? The project uniquely combines in vivo cardiac physiology and autonomic phenotyping (Mastitskaya, Bristol), the neurobiology of stress and astrocyte metabolism (Mosienko, Bristol), glial biology and chemogenetics (Khakh, Cardiff), and cardiac-glial metabolism, signalling and metabolite biosensors (Theparambil, Lancaster). The student will address three focused aims.</p> <p>Aim 1: Does stress make cardiac glia reactive and metabolically altered? The student will characterise satellite/nexus (astrocyte-like) glia in intrinsic cardiac ganglia following acute and chronic stress across three dimensions.</p> <ul style="list-style-type: none"> <li>- Localisation: whole-heart tissue clearing with light-sheet/confocal imaging, co-stained for glial and neuronal markers, to map where nexus/satellite glia sit relative to autonomic neurons and the pacemaker regions.</li> <li>- Reactivity and stress-sensing: glial markers and morphology (GFAP, S100<math>\beta</math>), a focused inflammatory panel (RNAscope/qPCR), and</li> </ul> |

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|                             | <p>glucocorticoid-receptor (GR) nuclear translocation by IHC across a stress time-course in glia versus neurons testing whether glia are primary sensors of stress.</p> <ul style="list-style-type: none"> <li>- Metabolism: mitochondrial respiration and glycolysis by Seahorse extracellular-flux analysis of ganglia-rich heart-tissue punches, together with real-time lactate and ATP/adenosine release from living ganglia using genetically encoded biosensors. Existing human datasets (Kanemaru 2023) provide cross-species context. Expected outcome: the first anatomical, reactive and metabolic signature of stress-responsive cardiac glia.</li> </ul> <p>Aim 2: Does stress-induced glial change disturb autonomic control and heart rhythm?</p> <p>In the same cohorts, in vivo ECG biotelemetry (heart-rate variability, autonomic challenges, arrhythmia burden) and longitudinal echocardiography would allow to link the stress-induced glial signatures to autonomic function and remodelling. A terminal isolated atrial/sinoatrial-node preparation would allow to test for arrhythmia susceptibility and direct pharmacological interrogation of glia-pacemaker signalling.</p> <p>Expected outcome: a causal chain from stress to glial change and autonomic dysregulation and arrhythmia vulnerability.</p> <p>Aim 3: Can modulating cardiac glial metabolism prevent stress-induced dysfunction?</p> <p>First, in the inherently cardiac-specific isolated atrial preparation from Aim 2, the student will block glial metabolism pharmacologically using the selective metabolic inhibitor L-<math>\alpha</math>-amino adipate (L-AAA) of astrocyte-like cells (nexus glia) and modulators of glial lactate/ATP release while recording pacemaking, conduction and arrhythmia inducibility. This established, inexpensive pharmacology provides the primary causal test. If effective, and where suitable mouse lines are available, targeted chemo-/genetic manipulation of glia (glial-specific CreERT2 <math>\times</math> floxed effector) will confirm the mechanism in vivo in stressed versus unstressed mice by telemetry and echocardiography.</p> <p>Expected outcome: causal evidence that cardiac glial metabolism sets the heart's electrical stability under stress, a candidate druggable target. The student gains a rare integrated skill set spanning from in vivo cardiovascular surgery and telemetry with a Home Office licence (Bristol) and tissue clearing and glial chemogenetics (Cardiff) to Seahorse metabolic-flux and metabolite-biosensor imaging (Bristol and Lancaster) and coding for physiological data (R/Python, year 1, Bristol). Ownership is built in: after Aim 1 the student chooses which metabolic pathway (e.g. lactate vs purinergic) and glial population (satellite vs nexus) to pursue, selects the manipulation strategy, and (as an optional stretch) can extend the strongest finding to recovery after myocardial infarction. By defining the heart's own glia as metabolic gatekeepers of its response to stress, this feasible, tool-driven project opens a new area of neuro-cardiac biology and nominates cardiac glial metabolism as a target against stress-related arrhythmia and heart failure.</p> |
| Can be completed part time? | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| Supervisory Team  |                                            |
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| Lead Supervisor   |                                            |
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| Co-Supervisor 2   |                                            |
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