Project Details	
Project Code	NMH27Br Ambler
Title	You snooze, you win: harnessing hibernation biology for organ protection
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Hibernating animals survive with barely-beating hearts and minimal oxygen. What if we could borrow that trick for critically ill patients? We've found that even non-hibernators like rats retain the brain circuitry for torpor — and switching it on halves heart-attack damage (40% smaller infarcts). This PhD asks how. Does protection still work if torpor starts after injury, as in a real heart attack? Are kidneys protected too? And how does the brain trigger these defences? You'll master systems neuroscience, ischaemia-reperfusion models, in-vivo physiology and 'omics — moving a bold idea closer to the clinic.
Description	Ever wondered how animals hibernate? How they tolerate near freezing body temperatures and a barely beating heart?Whether one day we might be able to mimic it in critically ill patients? During hibernation, animals enter torpor — a state of dramatically reduced metabolic rate, heart rate, and body temperature.There is growing interest in mimicking aspects of torpor in humans, with potential applications ranging from improvingtolerance of critical illness through to suspended animation for long-distance space travel. This interest has led to the identification of the neuronal circuit that drives entry into torpor in fasted mice. Using cutting-edge neuroscience techniques,we can selectively activate specific neurons in a region of the mouse hypothalamus called the preoptic area, and doing sotriggers torpor even in fed mice. Even more intriguingly, we have recently shown that species that do not naturally enter torpor retain the neural circuits necessary to do so. In rats — otherwise similar to mice, but which crucially will not enter torpor naturally — we have shown that activating the corresponding preoptic neurons induces a synthetic torpor-like state. Since hibernating animals in torpor are highly tolerant of low oxygen delivery to vital organs, we tested whether hearts taken from rats in synthetic torpor are similarly protected from a lack of oxygen (ischaemia-reperfusion injury). We found that following a 30-minute period of no oxygen, infarct size (the amount of dead heart muscle) is 40% smaller in rats that were in synthetic torpor. This project will investigate the mechanisms by which synthetic torpor confers organ protection, asking: 1. Is the heart still protected if synthetic torpor is induced after ischaemia-reperfusion? This is critical for translational applications such as patients presenting to hospital having a heart attack, where the injury is already underway. 2. Are other organs also protected? Working with Usman Khalid in Cardiff, a consultant transplant surgeon with expertise in rodent renal ischaemia-reperfusion, we will test whether the kidneys are also protected. This has translational relevance across a range of clinical settings, including major surgery and transplantation.

	3. How does the brain engage these peripheral protective mechanisms? This aspect will be shaped by the student's own interests. They might choose to: * Focus on the physiology of synthetic torpor, determining the role of the vagus in both triggering the state and driving the protective cellular responses. * Explore the circuit neuroscience of the preoptic area, asking why mice enter torpor on fasting but rats do not, what the natural role of these circuits are in the rat, and what transmitters and receptors they express — and whether any offer druggable targets to induce synthetic torpor non-invasively. * Define the cellular responses responsible for organ protection, using RNA sequencing and proteomics to map the cellular resilience programmes activated during synthetic torpor, with the aim of identifying peripheral druggable targets. During their studies, the student will gain a broad, cross-disciplinary skill set, including: * Systems neuroscience: chemo- and/or optogenetic manipulation of hypothalamic and brainstem circuits in vivo. * Ischaemia-reperfusion models: in-vivo and ex-vivo cardiac and renal models, including vagotomy and/or renal nerve transection. * In-vivo physiology: telemetered ECG, core temperature and activity recordings, as well as rodent echocardiography under anaesthesia. * Data science and 'omics: single-cell and/or spatial RNA sequencing of neuronal tissue, and proteomic analysis of cardiac and renal tissue. We welcome applicants from either a basic science or clinical background. A strong interest in in-vivo physiology is essential; experience with quantitative or computational analysis would be an advantage for the 'omics-focused route, though full training will be provided. The supervision team brings together clinicical and foundational scientists with expertise inautonomic neuroscience; cardiac, renal and vascular physiology; and in-vivo and ex-vivo models of ischaemia-reperfusion injury. The student will be supported to develop their own research direction, contribute to teaching and supervision of undergraduate and master's students, and present their work at national and international conferences. By the end of the project, they will have built a distinctive, translational skill set spanning circuit neuroscience and organ protection — and moved a genuinely novel idea, that the brain can be recruited to make peripheral organs resilient to injury, closer to the clinic.
Can be completed part time?	Yes
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