# Unlocking the molecular mechanisms governing stem cell dormancy

**Supervisory team:**
**Main supervisor:** Dr Bertram Daum (University of Exeter)
**Second supervisor:** Prof Austin Smith (University of Exeter)
Prof Paul Verkade (University of Bristol)

**Collaborators:** Dr Thom Sharp (University of Bristol), Dr James Gilchrist (eBIC, Diamond Light Source in Harwell, Oxfordshire).

**Host institution:** University of Exeter (Streatham)

**Project description:**
Cells in many organisms can enter a deep sleep mode called dormancy. This crucial biological process enables cells to endure harsh conditions by reducing their metabolism to a minimum, and conserving energy during periods of nutrient scarcity or environmental stress. In eukaryotes, dormancy is crucial to developmental stages, e.g. in plant seeds, fungal spores, and mammalian egg cells, and is a typical feature of stem cells. Dormancy is also a key factor in cancer because it enables some cancerous cells to persist during chemotherapy and cause disease relapse years later. One of the most energy-demanding processes is protein biosynthesis, costing actively metabolising cells up to 40% of their chemical energy currency ATP. Upon transitioning into dormancy, cells reduce this energy cost as much as possible, by shifting their protein production factories, the ribosomes, into a “hibernation” mode. However, some ribosomes must remain active to produce essential proteins to keep the dormant cells alive. Despite the importance of ribosome hibernation for dormancy across the tree of life, its molecular mechanisms are poorly understood.

In this interdisciplinary PhD project, you will investigate the mechanism of ribosome hibernation in dormant embryonic mouse stem cells from the cellular to the molecular level. By combining cutting-edge RNA-sequencing, proteomics and confocal microscopy, you will quantify the reduction of ribosome activity in dormant cells, where in those cells residual ribosome activity is maintained, and which essential proteins are still produced. By state-of-the-art cryo-electron tomography, you will solve the structure of the hibernating ribosomes in dormant cells, determine the factors that keep them switched off, and visualise the conformational changes that occur when the ribosomes transition into hibernation. Using modern genetic modification techniques (CRISPR), you will then overexpress or knock out the hibernation factors identified and examine how this affects the cells' ability to become dormant.

This project is the ideal opportunity to work in a truly interdisciplinary, diverse, and inclusive research team. You will work at the interface of three diverse research groups (Daum, Smith, and Verkade) housed at two top UK Universities (Exeter and Bristol) and collaborate with experts across fields, blending biology, imaging, structural biology, and bioinformatics to decipher living systems. You will acquire expertise in cutting-edge research techniques, which will place you at the forefront of research into life’s most fundamental processes. Your work will significantly impact our understanding of stem cell dormancy, and embryo development, and potentially inspire new cancer treatments.

**Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.**