

# UGRL Scholarship Learning Contract

*This document provides the framework for the project to be undertaken by the UGRL Scholar. It provides an outline of the larger research project to which the Scholar will contribute and the detail of that contribution, including timing, duties, outcomes and supervision arrangements.*

*It will be considered by the Faculty/School Scholarship Committee and if a Scholarship is awarded for the project should be signed by the Faculty Academic Lead, the project supervisor and the scholar.*

- 1. Title of Overarching Research Project:** Reconciling the 3D architecture of intracellular membrane compartments with changes in the protein expression in the ageing heart
- 2. Research Project Leader:**
- 3. Scholarship Project Supervisor:** Dr Isuru Jayasinghe
- 4. Working title of Scholarship Project:** Membrane remodelling in the ageing heart
- 5. Period of Scholarship Project Work** (*see note i*): two windows (up to six weeks in duration) over the summers 2016 and 2017; flexible start dates, to be agreed on prior to the commencement of the project
- 6. Summary of the research to which the Scholar will contribute (200 words):**

Muscle cells of the heart are the workhorses that power the movement of blood around the circulation. As a heart begins to fail during cardiac pathology, widespread changes in the fine architecture of the intracellular membrane structures can be observed within these muscle cells. These pathological changes have been linked to the dysfunction of the calcium signalling mechanisms which underpin the mechanical contraction of the ventricles at each heartbeat. Intriguingly, recent experimental work report qualitatively similar changes in mice during healthy ageing. These changes include conspicuous enlargements in the tubular invaginations of the plasma membranes (t-tubules) and proliferation of mitochondria in mice between 75 and 100 weeks of age which coincide with the heart's diminishing capacity to meet the constantly-changing cardiovascular demands throughout the body. Preliminary images show that a number of membrane tethering or membrane remodelling proteins are altered during this healthy ageing process. However a clear mechanistic link between this membrane remodelling and protein expression is currently lacking. Gaining this understanding will involve the characterisation of (a) trends in the structural remodelling, (b) systematic biochemical probing of the underlying protein expression patterns and (c) an in-depth analysis of the changes in calcium signalling that accompany this ageing process.

- 7. Summary of the work to be undertaken by the Scholar (200 words) :**  
(to be used to advertise the Scholarship)

The scholar will have the opportunity to make direct links between the structural remodelling of membrane compartments of cardiac muscle cells, changes in membrane-protein expression and the impaired calcium signalling in mouse hearts during healthy ageing. This will be achieved through three stages of experimentation and analysis:

- (a) 3D reconstruction of intracellular membrane compartments will be performed by applying state-of-the-art image visualisation software to either existing or new high-resolution

microscopy data. These reconstructions will be qualitatively similar [previous reconstructions](#) and will allow the scholar to directly compare cell structures between the young and aged hearts.

- (b) The scholar will apply state-of-the-art quantitative Western Blot technologies to reconcile changes in the protein expression levels observed previously with quantitative super-resolution image data.
- (c) In the final part (year #2), the scholar will have the opportunity to directly observe the loss of cell homeostasis in the ageing muscle cells by imaging the intracellular calcium signals with the novel Airyscan microscopy system.

Taken together, these structural, biochemical and functional observations will allow the scholar to describe the cellular and molecular basis of the gradual loss of cardiac function during healthy ageing at an unprecedented level of detail.

#### **8. Detail of the work to be undertaken by the Scholar (500 words) (see note ii):**

The research work undertaken by the scholar will consist of parallel experimental and analytical components.

Experimental components:

(Year #1) The scholar will master the novel quantitative Western Blot protocols and the calibration standards to measure the expression levels of calcium handling proteins and membrane tethering proteins within mouse hearts aged 10-12 weeks (young adult), 75 weeks and 100 weeks which have already been collected. Laboratory bench space and basic experimental kit for this task are available. Part of the research funds allocated by the scholarship will cover basic consumables for the experiment.

(Year #2) The scholar will follow up the biochemical analysis of calcium handling proteins with high-resolution calcium imaging of live cardiac muscle cells isolated from aged mice. The scholar will receive muscle cells enzymatically-dissociated heart tissue from young and aged mice. These cells will be loaded with fluorescent calcium indicators and imaged for spontaneous calcium signals with the use of the Zeiss Airyscan microscope in the FBS Bioimaging Facility. The remainder of the allocated research funds will cover access charges to the microscope.

Analytical component:

This component will be carried out in between experimental procedures of the planned study. The scholar will be supplied with high-resolution confocal image volumes of the membrane structures (t-tubules and mitochondria) of mouse tissue sections from hearts aged 10-12 weeks, 75 weeks and 100 weeks. Training will be provided on state-of-the-art image analysis software (e.g. [Python Microscopy Environment](#), ImageJ and Amira) to scientifically reconstruct the 3D structure of these membrane compartments in order to visualise the true nature of the cellular level remodelling which place in the ageing heart. Some tasks may require elementary training in programming languages such as Python, which will be provided by the supervisor with no expectation of prior programming experience. A workstation equipped with the necessary software tools is already in operation within the laboratory and the scholar will receive unrestricted access to this machine over the duration of the project.

#### **9. Detail of the Leadership development to be undertaken as part of the project (see note iii)**

A specific focus of the supervision will be the development and refinement of the scholar's leadership skills. During the project periods, they will be given the opportunity to participate in the weekly research group meetings to informally present their own research findings and to learn and critique about the research work of others in the group. This, along with weekly one-on-one meetings with IJ will be the scholar's primary opportunity for receiving feedback. Secondly, they will be invited to the Cellular Cardiology group meetings which are attended by

the postgraduate and postdoctoral members. This will be an opportunity to present the ongoing work through a formal presentation (e.g. powerpoint) to a supportive academic audience. Thirdly, the scholar will be given the opportunity to attend and present at a research conference such as the Northern Cardiovascular Research Group Meeting which is well attended by leaders in this discipline in the UK. By the end of the project period, the scholar will be invited to compile the research findings (in collaboration with other members of IJ's group or individually) into a journal article to be submitted to a leading peer-reviewed journal in the field. IJ will guide the process of article writing, revising, data presentation and statistical analysis to ensure that the findings are published in a journal of suitable impact. Research findings of notable impact will be further publicised by guiding the scholar to make a press/media statement via the UoL Press Office. The scholar will also be provided with a webpage under IJ's group webpage within or linked to the FBS domain where he/she can develop an online portal and/or research blog to facilitate public engagement on the impact and relevance of this project to Britain's ageing population.

#### **10. Outputs expected of the Scholar (200 words) including the final report (see note iv)**

##### **Summer 1:**

- By the end of the first window of secondment, the scholar will be expected to complete three sets of three-dimensional reconstructions of membranes in mice aged 10 week, 75 weeks and 100 weeks. The data for this have already been acquired, therefore the analysis will purely be done on a PC in time allocated in between 'wet-lab' experiments
- Become comfortable with Western Blotting protocol and complete basic blots of three key proteins on heart tissue material from the above age windows.
- Become comfortable with using the Zeiss Airyscan system in the Bioimaging Facility and acquire a up to a few image sets of calcium (with calcium indicator Fluo-4) in young mouse heart cells (which will be enzymatically isolated by group members on a weekly basis).

##### **Summer 2:**

- Complete the three-dimensional reconstruction of the mitochondrial networks in young and aged mouse heart muscle cells (to be performed in between laboratory experiments)
- Complete Western Blotting of two more key proteins on the above heart tissue
- Complete a draft of a manuscript incorporating the three-dimensional reconstructions, Western Blotting data and high resolution calcium data to be submitted to a peer-reviewed journal

#### **11. Details of supervision arrangements (see note v)**

The project will primarily be supervised by IJ who will provide the fundamental skills of microscopy image acquisition and detailed image analysis and 3D reconstruction software that is currently used at the elite level of biomedical imaging. The scholar will also receive formal training on small animal handling and husbandry through the CBS and state-of-the-art Airyscan microscopy usage through the FBS Bioimaging facility. The experimental training on tissue histology, immunofluorescence staining, super-resolution microscopy, quantitative Western Blotting and enzymatic cell isolation for calcium imaging will be provided jointly by IJ and IJ's PDRA who will be recruited before June 2016. In addition to the basic training, IJ will personally guide the leadership development plan for the candidate (outlined above in section 9) over the course of the project. During the scheduled 6-week windows of the project work, IJ will facilitate the compilation of the reports which summarise the research findings and a reflective account of the leadership development.

**12. Resources required for the Scholar to undertake the project (see note vi):**

The project work will primarily involve the use of custom-written software packages (primarily open-source) which will require a medium- to high-performance PC (£700 in estimated value). The scholar will also be given the opportunity to present the work via either an oral or poster presentation at the 2017 Northern Cardiovascular Research Group Meeting expected to be held in Manchester (conference registration, travel and accommodation expected to cost £300). The experimental work will involve microscope time on the Zeiss Airyscan in the FBS Bioimaging facility (£450 at £22.50/hr for 20 hr) to perform high resolution calcium imaging in muscle cells from aged hearts.

(to be completed if a Scholarship is awarded)

**Project Leaders – please tick to confirm the following:**

Consideration of Health and Safety context and appropriate risk assessment and risk management exercises have been completed ✓

Relevant ethical clearance has been sought ✓

Scholar and project leader are aware that any additional expenses or equipment costs are the responsibility of project leader to plan for and approve (if approved, students must provide receipts)


✓

Signature of Scholar

\_\_\_\_\_

Date: \_\_\_/\_\_\_/\_\_\_

Signature of Project Leader

\_\_\_\_\_  \_\_\_\_\_

Date: \_23/\_11/\_15

## Notes

- i. Scholars are expected to work the equivalent of six weeks full-time over the summer following their first and second year, they need not be continuous weeks but the dates are to be agreed between project supervisor and student. Any changes to the dates in the Learning Contract to be updated and signed by the supervisor and the scholar.
- ii. The work is normally assumed to be campus-based unless otherwise agreed, and where this is the case allocated office space and equipment (eg in spaces allocated to PG students) is expected to be available during office hours for the period of the project

The majority of the work must not take place in term time, but exceptionally an early start when exams and assessments are complete may be appropriate, but please note the dates of the induction programme that all scholars are expected to attend. If there is an event or output falling during term time it would be useful for the scholar to contribute to, please ensure time demands are light and does not conflict with programme study.

- iii. **Leadership development:** The project work undertaken by the Scholar is required to develop both research and leadership skills. All Scholars receive leadership training before they start their project and expect to be able to practice and develop those skills as part of their Scholarship Project. Projects should therefore include a specific strand of work which enables the Scholar to practice and develop leadership skills in some aspect of the project, eg data collection, analysis and presentation; dissemination event organisation; experimental design; project management; client feedback; market research design and evaluation. The University's Leadership and Management Standard informs the leadership development to be provided by the Scholarship scheme and details are provided in Annex 2c on page 13.
- iv. **Outcomes:** Describe the intended project outcomes, these may be broken down for summer year 1 and summer year 2, or one long-term goal over the two years. Outcomes must be realistic and clear, and depending on the nature of the project outcomes might include reports, events, media, artefacts, experiments etc). A clear statement of timeframes for work to be completed and reported on is essential so that the responsibility of the Scholar is clear.

**Reports:** Please indicate the reporting expectations. It is expected that this should include at least a first report at the end of summer 1 covering both the project work and the development of the appropriate leadership skills and a final report at the end of the second period of research which should be a reflective and summative report of the whole project covering both the project work and the development of the appropriate leadership skills. Both reports (each of between 1000 and 2500 words depending on the nature of the project) should be scheduled to be completed within the periods of project work and not left for completion during term time.

- v. The minimum requirement for UGRL Scholarship supervision is a formal meeting between scholar and project supervisor at the start, middle and end of each period of project work. The Scholar will provide a record of each of these meetings, to include a review of progress and a action points, to be confirmed in writing by the project supervisor
- vi. Funding is available to cover any essential costs directly associated with project work the Scholar will be undertaking. This is not a grant, it is available where necessary to ensure the Scholar has the resources they need to undertake their project. It might, for example, cover additional equipment needed by the Scholar, travel and accommodation costs to attend a conference to inform the project work or to present its outcomes. Any equipment purchased remains the property of the School and must be retained for the benefit of future

scholars. Any funds not used in this way are returned to the Alumni Office at the end of the Scholarship.