# PhD studentship

#### Project: Towards engineered T cells for osteosarcoma

* Primary supervisor: **Dr Martin Pule**
* Thesis committee members: **Dr Karin Straathof and Dr Sandra Strauss**

**This is a 4-year studentship funded by the Bone Cancer Trust, which covers tuition fees at the UK rate and a stipend of £18,065 per year. The earliest start date for this studentship is October 2022.**

**Closing date:** 12th September 2022, 17.00 (BST)

# Description

Aim of this project is develop engineered T cells for osteosarcoma. Osteosarcoma is the most common bone cancer in adolescents and young adults (80% of the patients are younger than 25 years old) but nevertheless are rare cancer. Intensification of chemotherapy at diagnosis or relapse has not modified patient outcome and survival of patients with osteosarcoma has not improved in the last four decades.

Here we aim to develop chimeric antigen receptors (CAR) T cells for osteosarcoma. CARs graft the specificity of an antibody onto a T cell. CAR T cell therapy has an established role in the treatment of refractory B cell malignancies. In this setting, CD19 CAR T cell therapy can result in durable remissions in chemo-refractory patients. There is now considerable interest in applying CAR T cell therapy to solid cancers but lack of convenient tumour targets (such as CD19), hostile immune microenvironment and tumour heterogeneity makes application more difficult than in lymphoid malignancies.

Disialoganglioside (GD2) is ex-pressed at high density in certain cancers including osteosarcoma and neuroblastoma while only expressed at low level in peripheral pain fibres and brain parenchyma. We have developed a GD2 CAR which can discriminate high level pathological expression from low level physiological ex-pression. We have tested this CAR in children with relapsed / refractory neuroblastoma (https://pubmed.ncbi.nlm.nih.gov/33239386/). We observed robust, but transient anti-tumour activity. This work demonstrates that GD2 can be safely targeted. Now we need to further engineer the CAR T cells to resist and modulate the hostile tumour microenvironment to convert transient into sustained anti-tumour activity.

Our GD2-CAR will be used as starting point for this project. GD2 is known to be expressed in osteosarcoma. Here, the student will study GD2 expression in osteosarcoma in depth (heterogeneity, density), as well as the osteosarcoma microenvironment. To these ends, the student will assess primary tumour samples using a new method called chip-cytometry which allows multidimension spatial analysis. Using these data, the student will work with our team to design CAR T cells which incorporate genetically encoded “modules” which render the T cells resistant to inhibitory factors within the osteo-sarcoma microenvironment. Finally, using orthotopic PDX and tumour explant models (immune PDX) models and related methodologies, the student will test candidate CAR T cells activity within the pathological microenvironment.

We anticipate that this PhD would be an important step in developing an optimal engineered T cell therapy for refractory osteosarcoma and the data would be used to initiate an experimental clinical study.

This unique project is an excellent opportunity for a junior scientist with an interest in cellular immunotherapy work within one of the largest CAR programmes in the world.

More detailed information about the research project is available on request from m.pule@ucl.ac.uk

# Environment

# The UCL Cancer Institute is a state-of-the-art institute to consolidate cancer research at UCL and promote links with our partner teaching hospitals, in order to support excellence in basic and translational studies. The Institute draws together talented scientists who are working together to translate research discoveries into developing kinder, more effective therapies for cancer patients. It is a Cancer Research UK and Experimental Cancer Medicine Centre, and contains approximately 580 staff, including 120 PhD and MD (Res) students and 40 MSc students. Core facilities within the Institute include: Genomics Facility (gene expression microarrays); Proteomics Facility; Imaging and Cell Sorting (confocal, time-lapsed microscopy, MoFlo FACS); Pathology Suite (laser capture microdissection, tissue arrays); Experimental Imaging (with UCL Institute of Child Health); and Transgenesis. Moreover, UCL Cancer institute forms part of the Cancer Research UK City of London Centre – partnership between UCL, The Francis Crick Institute, King’s College London and Queen mary University to develop biological therapies and translate these into the clinical. Further information on the Cancer Institute can be found at <https://www.ucl.ac.uk/cancer>.

# Ideal person specification

**Essential**

* Minimum upper second-class Honours Degree in an associated discipline, or an overseas qualification of an equivalent standard.
* Enthusiasm for cancer, immunotherapy and CAR T cell research
* Knowledge of tumour immunology and molecular biology
* Preliminary knowledge of tumour immunology models
* Experience in cellular immunology research
* Ability to develop understanding of complex problems and apply in-depth knowledge to address them.
* Potential to develop expertise in new areas of the subject.
* Potential for innovation and initiative, and evidence of an ability to work independently.
* Effective communication skills in both written and spoken English.

**Desirable**

* Holding a MSc or MRes Degree in a relevant subject (e.g. Cancer, Immunology, Biomedicine) is highly desirable
* Experience in molecular biology, T cell culture and immunohistochemistry/

Immunofluorescence is desirable

**Students will also need to qualify as UK fee payers and meet UCL general admissions criteria.**

Links:

* Fee Status Information: <https://www.ucl.ac.uk/students/fees-and-funding/pay-your-fees/fee-schedules/student-fee-status>
* Admissions requirements for Cancer Institute PhD <http://www.ucl.ac.uk/prospective-students/graduate/research/degrees/cancer-institute-mphil-phd>

# Duties and responsibilities

**Research**

* To apply highly specialist scientific skills and expertise to lead in the delivery of high quality research and the preparation of high-impact research publications.
* To keep abreast of current developments in this research area.
* To report research progress to the supervisory team, the Cancer Institute, and at scientific conferences and meetings.
* To work with other Scientists within the team as necessary.
* To work safely by adhering to all University policies and practices, including preparing and following laboratory risk assessments, and complying with Health and Safety policies, ethical approval processes and Human Tissue Act guidelines.

**Analytical and Judgement Skills**

* To demonstrate a high-level of technical and analytical skill to resolve highly complex scenarios, requiring analysis, interpretation and expert judgement to find the most appropriate solutions.
* To identify, interpret and integrate information from a wide variety of sources, and critically evaluate the quality and assumptions of these data.
* To show initiative and the ability to make decisions in areas where no previous work has been undertaken.
* To show awareness of your own developmental needs and undertake appropriate training where appropriate.
* To comply with professional codes of conduct.

# Application Procedure

To apply for this studentship, you must:

1. Submit the following **three** documents.
   1. Your full CV including:
      1. The names and contact details of two referees (at least one of which must be an academic reference from your previous educational institution).
      2. And a short summary (<500 words) detailing how your experience and ability matches the project and the person specification.
   2. A single PDF file containing scans of your award certificate and transcripts showing your unit/module marks for all of your degrees, undergraduate and postgraduate. If any of your original documents are not in English you **must** submit an official English translation with them.
   3. An equal opportunities monitoring form.

This form will be separated from your application before it is forwarded to shortlisters. By submitting this form you are giving us consent to use the data contained for quality and monitoring purposes. Data will be anonymised.

These **three** documents must be emailed to [CI.Scholarships@ucl.ac.uk](mailto:CI.Scholarships@ucl.ac.uk) by **12th September 2022 17:00 (BST**). The subject line of your email should contain the studentship code “**Bone Cancer Trust\_22/23\_ your surname**”

1. You must also contact your referees and ask them to submit their references by email to [CI.Scholarships@ucl.ac.uk](mailto:CI.Scholarships@ucl.ac.uk) from a verifiable academic or professional email address. The studentship code above and your surname **must** be in the email subject line.

References must be received from your referees by **12th September 2022 17:00 (BST).** Please ensure that your referees have submitted references for you, as we will not chase missing references. Incomplete applications will not be forwarded to the Shortlisting Panel.

Shortlisting and notification will likely take place **W/C 19th September 2022.**

Queries about the application procedure or recruitment process should be directed to: [ci.scholarships@ucl.ac.uk](mailto:ci.scholarships@ucl.ac.uk)