3 Fully-Funded PhD Studentships Announced

The Institute of Cancer Therapeutics (ICT) is excited to announce **3 fully-funded PhD studentships**. Two PhD studentships will be the latest recruits to our **Doctoral Training Centre** (DTC), while a third PhD studentship is an exciting opportunity for a medic with a passion for cutting-edge cancer research.

We are now looking for applications from outstanding potential PhD candidates to embark on PhD projects commencing in **October 2022**.

Why study with us?

- Fully-funded PhD studentships at a leading UK research institute focused on cancer drug discovery
- Join a multi-disciplinary research environment, with facilities for cancer drug design and synthesis, *in vitro* pharmacology and molecular biology, and *in vivo* biology
- Join an academic team with a track record of success in translational research, commercialisation, and delivering drug candidates to the clinic.

What do we offer?

Doctoral level training in a unique multidisciplinary environment at the interfaces between medicinal chemistry and pharmacology. Cutting-edge research projects focused on exciting new anticancer prodrugs. Modern facilities. Extensive support: an experienced supervisory team, an independent mentor, a strongly-focused team environment. Each studentship benefits from a full training package in techniques in modern cancer research, e.g. compound synthesis, analysis, *in vitro* screening for pharmacology, molecular biology, cell culture, and drug metabolism (see individual projects overleaf for details).

Who should apply?

Applicants with a passion for cancer drug discovery and/or cancer research.

DTC projects #1 and #2: Candidates should have, or expect to obtain, a first or good upper second class degree (or equivalent) in a relevant chemistry-based subject (see individual projects overleaf) or an appropriate Masters qualification.

PhD Project #3: Candidates are expected to hold a Medical degree (e.g. MBChB, MBBS), completed pre-registration training, and hold/be eligible for full registration with the UK General Medical Council (GMC). Further details overleaf.

Applications are invited from UK citizens. Outstanding EU/international students will require additional funding, but may be eligible for a University bursary, and will be considered - please enquire. The University of Bradford champions equality, diversity and inclusion, and we encourage applications from excellent candidates from all backgrounds. We particularly welcome applications from under-represented groups, e.g students from areas of low higher education participation, low household income or low socioeconomic status, students from black, Asian and minority ethnic backgrounds, mature students, and other groups identified by the Office for Students.

Funding

Studentships cover tuition fees, a tax free stipend (at standard MRC rates) for the duration programme and a research budget. Projects #1 and #2 additionally include a travel fund for each student to guarantee participation in a national and international conference.

How to apply

For further information about research at the Institute of Cancer Therapeutics, please take a look at our website www.bradford.ac.uk/ict/study

Applications should be submitted by email to the main supervisor contact associated with the individual project (see project descriptors overleaf).

You should submit a **CV** (max. 2 pages) and a **covering letter** outlining your background and interest in the project(s). Applicants may indicate that they wish to be considered for more than one of the studentships.

Application deadline: we will continue to accept applications until all places are filled. We will initially consider all applications received by **1 May 2022** for shortlisting and interview.

UNIVERSITY of BRADFORD

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Institute of Cancer Therapeutics

Project #1: Targeting integrin degradation in the lysosome for anti-metastatic drug discovery

Background The integrin family of cell surface proteins allow cells to interact with their surroundings leading to cell survival, migration and invasion. Normally, integrin function is required for the maintenance of body tissue structure, such as wound healing. Changes to the identity, number and activation state of integrins are common in cancer cells; for example, αvβ3 is highly expressed in melanoma and glioblastoma and is associated with disease progression and metastasis. As a result, integrins have been popular targets for anticancer drug discovery but improved strategies are required. An exciting new way of targeting integrins is provided by the recent development of PROTACs, and LYTACs, which remove a target protein from the cell by hijacking the normal cellular processes for protein destruction. This PhD project aims to synthesise integrin targeted protein degraders by linking small molecule integrin antagonists to molecules directed to the lysosome or an E3 ligase.

Aim To develop a new small molecule targeted integrin degrader

Focus Synthesis of integrin-targeted prodrugs and coupling to lysosome or ligase targeting groups. Optimisation of linker and targeting groups. Evaluation of the effect of compounds in cell-based assays of proliferation and integrin function (migration/ invasion). Evaluation of the effect of compounds on integrin protein levels and localisation.

Main skills Chemistry, Medicinal chemistry, Pharmacology

Background required Candidates should have, or expect to obtain, a first or good upper second class degree (or equivalent) in a chemistry-based subject or an appropriate Masters level qualification.

Relevant papers Ahn, G.; et al. Nat. Chem. Biol. 2021, 17, 937. Slack, R. J.; et al. Nat. Rev. Drug Discov. 2022, 21, 60.

Contact: Dr Helen Sheldrake (e-mail: h.sheldrake@bradford.ac.uk). Academic profile link

Project #2: Development of a tumour-targeted theranostic for breast cancer with enhanced therapeutic index

Background Paclitaxel is used for the treatment of metastatic breast cancer, but consistently causes dose-limiting toxicities. Membrane-type matrix metalloproteinases (MT-MMPs) are functionally active at high levels in breast tumours, have negligible activity in normal tissue, and selectively cleaves specific peptide sequences. In preliminary studies, we demonstrated in vivo proof-of-concept for an MT1-MMP-activated paclitaxel prodrug, ICT3205, and a nanoparticle-conjugated theranostic MMP prodrug of a colchicine-derivative. Building on these studies, this project is focused on synthesis and evaluation of a targeted NP -based paclitaxel theranostic that will exhibit enhanced tumour-targeting, optimised drug loading and aqueous solubility.

Aim To develop a new non-toxic targeted prodrug therapy for breast cancer

Focus Synthesis and optimisation of nanoparticle-conjugated taxane prodrug. Fine-tuning of MT-MMP peptide sequence selectivity, and chemical modifications to enhance aqueous solubility. Evaluation of prodrug stability in normal tissues, prodrug activation in tumour tissues; MMP cleavage; assessment of aqueous solubility; nanoparticle characterisation. Pilot pharmacokinetics study in mice for most promising compound

Main skills Medicinal chemistry; peptide chemistry; compound analysis; pharmacological assays; drug metabolism

Background required Candidates should have, or expect to obtain, a first or good upper second class degree (or equivalent) in a chemistry-based subject or an appropriate Masters level qualification

Relevant papers Wu, W. et al. Nanotheranostics, **2019**, 3, 299-310 (link). Mohanty, S. et al. Molecular Cancer Therapeutics, **2017**, 16, 1909-1921 (link). Ansari, C. et al. Small, **2014**, 10, 566-575 (link). Atkinson, J.M et al. Cancer Research, **2010**, 70, 6902-6912 (link).

Contact: Prof Robert Falconer (e-mail: r.a.falconer1@bradford.ac.uk). Academic profile link

Project #3: Investigation of prostate cancer stem cell targeting therapeutics with clinical potential

Background Prostate cancer (PCa) patients with aggressive disease are associated with <30% 5-year survival rates. This reflects the limited efficacy of current treatment options for metastatic castrate resistant prostate cancer (CRPC) (e.g. docetaxel), and highlights the unmet clinical need for new therapeutic strategies to prevent/treat CRPC. Previous work has demonstrated that aldehyde dehydrogenases (ALDHs) function to mediate cell differentiation and prostate cancer stem cell (PCSC) expansion and contribute to both chemo- and radiotherapy resistance. We have shown that targeting specific ALDH isoforms with small molecule inhibitors reduces PCa cell viability with potential to sensitise PCa cells to standard of care drugs. Emerging evidence indicates that hypoxic fractions play host to CSCs and this project seeks to explore how (i) hypoxia in the PCa microenvironment impacts on ALDH-expressing PCSC behaviour and (ii) ALDH-targeting inhibitors and prodrugs can be employed with existing therapies as a new treatment approach for aggressive PCa.

Aim To evaluate ALDH-targeting therapeutics as a new strategy to treat prostate cancer stem cells.

Focus Analysis of ALDH expression in drug-resistant PCa cell lines and PCSCs isolated from clinical samples. Evaluation of novel small molecules targeting ALDH for therapeutic intervention. Evaluation of PCSC-targeting agents in combination with standard of care drugs including androgen receptor antagonists or chemotherapy.

Main skills Cell culture techniques including 2D/3D model development and the identification and isolation of PCSCs. Evaluation of ALDH expression using PCR, WB and IHC. Use of colorimetric, clonogenic/apoptotic assays to assess drug efficacy.

Background required Applicants are expected to be fully committed to bench and clinical work, and ideally, also have knowledge/experience or interest in urological oncology. Candidates are expected to hold a Medical degree (MBChB, MBBS etc), completed pre-registration training, and hold or be eligible for full registration with the UK General Medical Council (GMC). An honorary clinical contract will be sought with the Bradford Teaching Hospitals NHS Foundation Trust at the appropriate level depending on the applicant's experience. The successful applicant will participate in clinical activities and be supported to develop and maintain clinical competencies while whilst undergoing laboratory work for the PhD. The ratio of laboratory/clinical work will be agreed with laboratory and clinical supervisors.

Relevant papers Ibrahim AIM et al., J Med Chem. **2022** Mar 10;65(5):3833-3848 (link). Ibrahim AIM et al., Molecules. **2021** Sep 23;26(19):5770 (link). doi: 10.3390/molecules26195770. PMID: 34641313; PMCID: PMC8510124. Quattrini L et al., Biomedicines. **2020** Dec 4;8(12):E569 (link). Ibrahim AIM et al., J Cancer Metastasis Treat **2018**;4:1-17 (link)

Contact: Prof Klaus Pors (e-mail: k.pors1@bradford.ac.uk). Academic profile link