

PhD studentship (reference number PhD_BIOT1_NIBSC)

A 3-year full-time PhD studentship is available in the Division of Biotherapeutics and Advanced Therapies at the Medicines and Healthcare products Regulatory Agency, in collaboration with the King's College London. The studentship is available to commence immediately.

Title

Investigating the immune-stimulating effects and therapeutic potential of conjugates for antibody-mediated delivery of nucleic acid adjuvants to the tumour microenvironment

Project description

Recent clinical advances in tumour immunotherapy based on immune checkpoint blockade have proven that the ability of the immune system to eradicate tumours can be harnessed in the clinical setting and have reignited an interest in immunotherapeutic approaches. While immune checkpoint blockade with drugs such as ipilimumab is effective in unleashing the cytotoxic effector functions of tumour-infiltrating CTL, many patients have to stop this form of treatment due to adverse events. One of the most frequent adverse responses observed upon ipilimumab treatment is caused by inflammation of tissues such as the gut and represent a direct consequence of systemic tissue-unspecific immune checkpoint blockade. Thus, there is a need for alternative strategies such as tissue-specific targeted approaches that promote cytotoxic effector functions in the tumour and leave healthy tissues unaffected. Such tumour-targeted approaches have the potential to minimise adverse responses and to be suitable for a wider range of patients. The aim of the proposed study is to explore the targeted deposition of nucleic acid (NA) adjuvants in tumour tissue as a novel strategy to promote the effector function of tumour infiltrating cytotoxic effector cells. NA adjuvants are particularly suited for induction of anti-tumour immunity since they are strong inducers of T helper type I responses and cytotoxic effector functions. Furthermore, it has been demonstrated that untargeted deposition of NA adjuvant in the tumour tissue promotes anti-tumour immunity. This has not only been shown in mouse models but is already applied in the clinical setting as exemplified by the treatment of basal cell carcinoma with the Toll-like receptor (TLR)7/8 agonist imiquimod. However, unlike topical application, systemic application of TLR agonists is difficult to manage in a clinical setting due to unspecific widespread innate immune activation, which limits the application of TLR agonists in tumour immunotherapy. The targeted deposition of NA TLR agonists in the tumour tissue represents a strategy that has the potential to allow for efficient local promotion of anti-tumour immunity while at the time avoiding adverse responses on a systemic level.

The proposed project will build on our expertise on NA adjuvants and the generation of biochemical conjugates of NA adjuvants and antibodies. A completed proof of principle study established the benefit of site-specific antibody-NA adjuvant conjugates (unpublished data). However, their efficacy in delivering adjuvant to the tumour, their effects on the tumour microenvironment and their ability to raise anti-tumour immune responses remain important questions which we aim to address in this follow-up study.

Objectives: In this study we will also investigate the functional consequences of altering the antibody isotype and delivering NA adjuvants stimulating different TLR via different routes of administration. The objective is to understand how the biochemical design and

administration route of antibody-adjuvants shape the anti-tumour immune response (potency) and reduce systemic immune activation (safety).

The overall aim of the project is to characterise and compare the immunotherapeutic response of various antibody-adjuvant conjugates differing in the antibody isotype, the adjuvant and the route of administration. A better understanding of the mechanisms underlying the anti-tumour immune response induced by specific antibody-adjuvant conjugates will allow to define the structure-function relationship enabling the design of optimised antibody-adjuvants targeting tumour markers.

The project entails:

1. The cloning, expression and purification of modified antibodies.
2. The generation and purification of antibody-adjuvant conjugates.
3. The characterisation of antibody-adjuvant conjugates in various in vitro assays including cell-based immunoassays.
4. The optimisation of a humanised mouse tumour model for studying the efficacy of antibody-adjuvant conjugates in inducing anti-tumour immunity.
5. The comparison of different antibody-adjuvant conjugates in the humanised mouse tumour model.

Key Responsibilities

- To undertake the research project in line with the project aims
- To communicate effectively, orally and through written media, undertake presentations at scientific meetings, maintain excellent records, prepare reports and manuscripts for publication in peer-reviewed journals.
- To interact regularly and effectively with the supervisors and interact appropriately and effectively with other staff
- To fulfil the requirements of the University PhD programme and to undertake specific training as required by the host institutions

In addition to meeting all the academic, security and residency requirements, you will have:

- an academic background in cellular or molecular biology or immunology.
- knowledge of most relevant immunoassays
- a demonstrated aptitude in a laboratory setting and motivation to undertake research
- a demonstrated interest in the field of study and ability to work accurately and precisely
- demonstrated excellent oral and written communication, and IT skills
- a previous experience in one or more of the key interest areas as an advantage

About MHRA

The Medicines and Healthcare products Regulatory Agency enhances and improves the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research.

About the Group

The Immunotherapy group, within the Division of Biotherapeutics and Advanced Therapies, is a leader in the development of biological reference materials and evaluation of the safety and potency of biotherapeutics. The group also pursues an ambitious research programme into immunotherapeutic cancer medicines.

Awarding institution

[The Comprehensive Cancer Centre at King's College London](#) is the academic arm of one of the leading cancer centres in Europe and brings together world-class clinical services,

research and education for the benefit of cancer patients in south east London and beyond. The School of [Cancer and Pharmaceutical Sciences](#) is situated with the Faculty of Life Sciences & Medicine and is committed to improving patient response through fundamental science discovery.

The student will be supervised by Drs Sandra Diebold (MHRA) and James Arnold (King's College London). The student will be based primarily at MHRA South Mimms campus with a secondment to King's College London during the first, second and third years for additional training and study.

Qualification requirements for King's College London

As a candidate, you will be a motivated individual with a keen interest in undertaking research in the field of vaccines. You will have or expect to achieve a 1st or 2:1 (or international equivalents) in a relevant subject.

Funding

Tuition fees for home students as set out by the university are covered; there is provision for laboratory consumables and travel to conferences and the University; there is a student stipend of £ 18,500 p.a.

English language requirements

English language requirements are found at <https://www.ucl.ac.uk/prospective-students/graduate/english-language-requirements>

Visas and immigration

Applications are open to UK and EU students only, with demonstration of a right to reside in the UK.

To apply

Send (i) your CV including the name and contact details of two academic referees and (ii) a personal statement of no more than 1000 words explaining your interest in this project and aspirations for undertaking a PhD to studentship@nibsc.org by 31 January 2023

Please ensure the studentship reference number is included in the subject line of the email and your personal statement.

If you have a disability defined by the Equality Act 2010 (<https://www.gov.uk/definition-of-disability-under-equality-act-2010>) you may apply under the UK Civil Service Guaranteed Interview Scheme provided that you meet all of the qualifications, skills, requirements and experience defined as essential for the studentship. You must submit the Guaranteed Interview Scheme Declaration form with your application: this can be found at <https://www.gov.uk/government/publications/guaranteed-interview-scheme>. At interview all applicants will be assessed solely on merit.

Any offer of a studentship is conditional upon successful background screening which includes, but is not limited to, checks on identity, qualifications and right to study in the UK.



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