PhD studentship (reference number PhD_Vaccines_MHRA)

A 3-year full-time PhD studentship is available in the Division of Vaccines, Medicines and Healthcare products regulatory agency, in collaboration with the University College London (UCL). The studentship is anticipated to commence in 2023.

Title
Mucosal delivery of a universal protein subunit and mRNA vaccines against Group B streptococci

Project description
Group B streptococci (GBS) is an important pathogen that affects newborn and infants. It can cause life-threatening bacteraemia and meningitis. The main route of infection in infants is from GBS-colonised mothers through the rectovaginal tract during pregnancy or at birth. Currently, there are several vaccines in development which are intended to be administered to pregnant women to protect the baby during and after birth. The lead candidate is a hexavalent capsular polysaccharide (CPS) conjugate vaccine being developed. However, there are 10 GBS serotypes (Ia, Ib, II, III, IV, V, VI VII VIII and IX) that have been recognised as causing GBS diseases around the world, and although the hexavalent vaccine covers the majority of the prevalent disease-causing serotypes (Ia, Ib, II, III, IV and V) it doesn't cover all of them. Serotypes VI-IX have specifically started to become more prevalent in Asia causing up to 8% of the invasive disease cases reported. Additionally, CPS based vaccines are unable to satisfactorily prevent colonisation by GBS as they do not induce substantial immunity at mucosal surfaces, and hence do not contribute to herd immunity. Alternatively, highly conserved GBS protein-based vaccines can provide universal coverage, and some have been shown to be safe and immunogenic in a phase I clinical trial. We hypothesise that administering highly conserved immunogenic GBS protein vaccine candidates through the mucosa (specifically sublingually and intranasally) will induce a strong mucosal and systemic immune response capable of preventing GBS diseases while also blocking GBS colonisation. To this end, we have identified several protein vaccine candidates that are implicated in facilitating GBS colonisation. The proteins selected for this study include surface-exposed fibronectin-binding proteins, FbsC and BspA, that facilitate binding to epithelial cells and the secreted protein EsxA. These are highly conserved proteins that were successfully expressed in our laboratory and proven immunogenic in preliminary studies and in the literature.

The recent success of mRNA vaccines against COVID-19 shows that there is an alternative way to elicit robust immune responses and offer accelerated research and development timelines. mRNA-based vaccines can also provide a plug-and-play opportunity for multiple antigens and enable a quicker response to emerging disease or strain outbreaks. Furthermore, they are easily scalable and can provide greater efficiency. When these properties are coupled with increasing interest in LMIC settings to adopt these technologies for future manufacturing (https://www.afro.who.int/news/towards-africas-first-mrna-vaccine-technology-transfer-hub), especially in Africa where GBS is a pressing concern, they present an attractive option for a novel GBS vaccine. In addition, although theoretically there should be no barriers to applying this technology to bacterial disease, there is limited research on its application against bacterial infection. However, like other injectable vaccines, mRNA vaccines require trained personnel for administration, which can lead to needle

contamination issues in less developed countries, and it is not known if they can elicit mucosal immunity to prevent colonisation.

With this research project, we propose to investigate and evaluate the potential of developing novel GBS vaccines for mucosal delivery, using both recombinant proteins and mRNA approaches. We will utilise sublingual and intranasal routes that were proven successful in our lab for other protein and CPS conjugate antigens. In our group, we have successfully developed mouse models for the study of mucosal delivery using the oral, intranasal, and sublingual routes. These models can be easily adapted for the delivery and study of mRNA vaccines.

There are challenges to mucosal delivery of vaccines, as vaccines should be able to cross a mucosal barrier while resisting degradation and inducing immunity. Achieving this will require the careful formulation of protective delivery systems and the use of potent adjuvants. This PhD project will try and answer some of these questions. It will explore delivery systems based on the lipid nanoparticles (LNPs) currently used in COVID-19 mRNA vaccines or chitosan which was shown to be useful in sublingual delivery due to its mucoadhesive properties that extend the time antigen remains at the mucosal delivery site. Formulation studies will be conducted in collaboration with Dr. Sudaxshina Murdan (UCL School of Pharmacy). In addition to a protective coat, a potent adjuvant is also required to enable the induction of protective immunity and inhibit the development of tolerance. Non-toxic Cholera Toxin B subunit (CTB) or *E. coli* double-mutant heat-labile toxin (dmLt) have shown to work well in eliciting a mucosal immune response. This project will therefore fill some of the information gaps that exist in the mucosal delivery of mRNA vaccines, as this route has not been extensively explored. Using both the conventional protein vaccines and the novel mRNA approaches student will have the opportunity to compare both methods and mitigate any risks to the project which could occur by focusing on a single approach.

Objectives: To investigate the development of a universal mucosal protein subunit or mRNA vaccine against GBS to prevent colonisation and infection

1. Purify candidate proteins. Design mRNA vaccine candidate/s based on these proteins.
2. Synthesise, purify, and characterise the designed mRNA vaccine candidate/s
3. Formulate the protein candidates and mRNA into LNPs, Chitosan or other suitable carriers
4. Test the immunogenicity of the vaccine candidates (proteins & mRNA) intramuscularly/subcutaneously
5. Test the lead candidate formulations in sublingual and/or intranasal delivery *in vivo* (mouse model) using a mucosal adjuvant and evaluate systemic and mucosal immune responses
6. Evaluate the protective ability of the induced immune response, using *in vitro* bacteria killing and colonisation assays that are already established in our lab.

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 molecular biology, vaccinology, or formulation science.
- knowledge of most relevant molecular biology practices in genomics
- 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 polysaccharide and conjugate vaccines group, within the Division of vaccines, is a leader in the development of biological reference materials and evaluation of the safety and potency of vaccines. The group also pursues an ambitious research programme into vaccines against encapsulated bacteria.

Awarding institution
UCL is a world-renowned Institution for Research and Education and was ranked 8th in the world (QS World University Rankings 2022). UCL School of Pharmacy is one of the world's leading centres of excellence for pharmaceutical science, education and professional engagement, with a well-established track record in high quality research across a broad range of drug discovery, pharmacy and patient safety related areas, as well as in the development of spinout companies bringing new therapeutic strategies to the patient. The School of Pharmacy is situated with the Faculty of Life Sciences, which is committed to enhancing research and teaching in relation to major global challenges, including climate change, sustainability, technological change and the data revolution and inequality. Dr Murdan's research group at UCL is developing vaccines for human and veterinary use, as well as topical antifungal medicines.

The student will be supervised by Drs Arif Felek and Fatme Mawas (MHRA) and Sudaxshina Murdan (UCL). The student will be based primarily at MHRA South Mimms campus with a secondment to UCL during the first, second and third years for additional training and study.

Qualification requirements for University 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.

How 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.

Medicines & Healthcare products Regulatory Agency

UCL