

PhD studentship (reference number PhD_ATD_NIBSC)

A 3-year full-time PhD studentship is available in the Division of Advanced Therapies, National Institute for Biological Standards and Control (NIBSC), in collaboration with the University of Glasgow. The studentship is anticipated to commence on 1st October 2020.

Title

The development of a genomic variant ‘truth set’ to aid next-generation sequencing-based cancer diagnostics

Project description

The PhD candidate will have the unique chance to participate to an exciting area under development in genomics and cancer diagnostics: the release of a comprehensive set of validated variants for somatic analyses. Various reference standards have been developed to benchmark NGS pipelines, including well-characterized biological samples, synthetic controls and *in silico* data sets. However, this reference set contains germline samples only and does not contain the types of variants commonly found in cancer samples. The assessment of somatic variants introduces challenges that are quite different from those present in the germline and therefore an equivalent somatic reference standard with “ground truth” variants would enhance not only the development of multiplex cancer assays, platforms and pipelines but also study reproducibility, interpretation of results generated using different platforms and pipelines, validation using orthogonal techniques, assays calibrations and consistent reporting of somatic events. By contributing to both bioinformatics activities, as well as to laboratory validation and testing, the PhD. student will contribute building such an important reference material, which to date has not yet been created.

Towards this, NIBSC has developed WHO International Standards that are variant specific. Despite these efforts, the lack of a ‘truth set’ of wider cancer genomic variation associated with a reference material that is able to support NGS workflows (from wet lab to bioinformatics analysis and final clinical reporting) has yet to be filled.

In order to tackle this challenge, the PhD project will focus on the hypothesis that **through a variety of bioinformatic approaches and orthogonal wet lab validation of mutations in individual tumour cell lines, a ‘truth-set’ of thousands of pan-genome somatic mutations will be fully characterised to improve NGS-based cancer diagnostics.**

The study programme will be therefore organised according to three major research questions:

- 1) What are the additional characteristics of the genomics alterations present in the NIBSC WHO International Standards for cancer genomes?
- 2) What are the best strategies for developing universal ‘truth sets’ for somatic genomic variation?
- 3) What would be the best design for a comprehensive set of whole genome sequencing reference standards and associated reference sequences, and how this can be used to evaluate the measurement of uncertainty in NGS-based cancer diagnostics?

The student will answer these key questions by analysing a large source of genomic data already present at NIBSC, and by performing a discovery analysis on additionally variants, including INDELs and larger structural variants. The student will orthogonally validate the variants identified with the implemented bioinformatics using wet laboratory approaches (Sanger sequencing and if necessary, digital Polymerase Chain Reaction). Additionally, long read NGS analysis with the appropriate bioinformatics will be carried out to improve the characterisation of genomic locations.

Data obtained will be further analysed with the bioinformatics pipeline already in use at Glasgow University. Should the materials not represent enough genomic complexity, the analysis will be extended to other NIBSC materials, with the possibility of using CRISPR-Cas9

based mutagenesis to introduce additional variants. Finally, the 'truth set' of curated variants will be used to investigate the empirical cumulative measure of uncertainty by calculating the difference between the expected values and the measured values. Analysis of the 'truth set' somatic samples alongside patient samples will allow not only the measurement of uncertainty associated with the final diagnosis but also the development of exemplar NGS quality assurance schemes for to allow oncology sequencing assays to be used safely in clinical trials and clinical practice.

Key responsibilities

- To undertake the research projects in line with the project aims
- To communicate effectively, orally and through written media, undertake presentations at scientific meetings and maintain excellent records
- 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, cancer genomics, or applied genomics or bioinformatics
- knowledge of most relevant bioinformatics 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
- a 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 NIBSC

The National Institute for Biological Standards and Control (NIBSC) is a centre of the MHRA and a global leader in the characterisation, standardisation and control of biological medicines. NIBSC is the world's major developer and distributor of World Health Organisation (WHO) International Standards and reference materials and our expert scientists provide advice on a routine basis and in response to emergencies.

About the Group

The Genomic Reference Materials group, within the Division of Advanced Therapies, is leader in the development of reference materials, to ensure accurate diagnosis of genetic and genomic disorders.

Awarding institution

The student will be registered with the Institute of Cancer Sciences in the College of Medical Veterinary and Life Sciences. The successful candidate will be affiliated with the Glasgow Precision Oncology Laboratory (GPOL), a major component of the Cancer Research UK West of Scotland Cancer Centre and world-leading institute in the clinical cancer genomics field.

The student will be supervised by Drs Angela Pia Sanzone and Francesco Lescai (NIBSC), Susie Cooke and Prof. Andrew Biankin (University of Glasgow). The student will be based primarily at NIBSC with a secondment to the University of Glasgow during the second and third years for additional training and study.

Qualification requirements for University of Glasgow

As a candidate you will be a motivated individual with a keen interest in undertaking research in the field of cancer genomics with a focus on NGS and bioinformatics analysis. You will have, or expect to achieve a 1st or 2:1 (or international equivalents) in a relevant subject; or a 2:2 (or

international equivalent) and a masters' degree (or substantial experience), both in a relevant subject.

Funding

Tuition fees 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

Applicants whose first language is not English (and whose undergraduate degree was not taught in English) must fulfil the minimum requirements of an IELTS score of 6.5 with no less than 6.0 in any element.

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 Ph.D. to studentship@nibsc.org by 5 pm (UK time) on Friday, 27th March 2020.

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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