OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

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Diamond-Pirbright Studentship Advertisement – 2017-18

Applications for this studentship must be made via the University of Oxford - please visit University of Oxford for further details.

Project Title: Structural analysis of the cattle antibody repertoire

Supervisors: Prof. John Hammond (Pirbright), Prof Dave Stuart (Diamond & Oxford), Prof Ray Owens (Oxford)

Departments/Organisations: The Pirbright Institute, Diamond Light Source, the University of Oxford

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Brief description of project:

Introduction:
Antibodies are the fundamental humoral component of adaptive immunity and different species have evolved alternative strategies to generate antibody sequence diversity. In contrast to human and mice, germ-line immunoglobulin variable region gene diversity in cattle is highly limited. The antibody repertoire is derived from a single polymorphic VH gene family and is dominated by one of two VL gene families. V region diversification in cattle is generated following VDJ, VJ segment rearrangement and somatic hyper-mutation. A unique feature of the antibody response in cattle is the generation of a subset (10 %) of heavy chains that have a highly extended Complementary Determining Region (CDR) 3 sequences of over sixty residues. This compares to an average of 20 residues for most bovine heavy chains which in itself is longer than in other species such as human and mouse. It has been proposed that these unique structures can recognise epitopes that would remain invisible to human or mouse antibodies. Hence there is high interest in bovine-derived antibodies as potential immune-therapeutics. Understanding the structural basis of bovine antibody assembly and antigen-binding will provide insights not only into the biological mechanism that generates diversity, but also enable future studies in vaccine design and antibody discovery, for both veterinary and medical research.

Aims of the project:
1. To elucidate the structural constraints that determine the unique architecture of cattle antibodies
2. To analyse how this determines the antigen-binding specificity of cattle antibodies.

Experimental plan:
The Pirbright Institute has successfully developed methods to identify heavy and light chain pairs from sorted cattle B cells and is investing in droplet based sequencing technology to increase throughput. This will enable the identification of antibody chains from a range of historical samples from vaccine and challenge experiments and will provide a wealth of data to establish the influence of the light chain on the structure of the heavy chain CDR3, and begin to parameterise the structural constraints of heavy and light chain pairing. Methods have already been developed to rapidly convert sequence data into recombinant antibody and Fab fragments for structure determination will use MX beamlines for crystallographic analysis (appropriate and antibody fragments and smaller complexes) and electron microscopy, for example for Fab-virus complexes using the cryoEM infrastructure at Diamond.

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The project is a collaboration between The Pirbright Institute, Diamond Light Source and University of Oxford and the student will be working in all three locations. The student's main base for the project will be the Research Complex at Harwell next to the Diamond Light source on the Rutherford Appleton Laboratory and commutable to Oxford. Work on the bovine immune response and bioinformatic analyses will be undertaken in John Hammond's group at Pirbright. Protein production and structural studies will be carried out in Ray Owens' laboratory at the Research Complex in close collaboration with Dave Stuart (Diamond). This multi-disciplinary project will provide training in a range of molecular biology, biochemical and structural methods leading to a mechanistic insight into the antibody response in cattle to important veterinary pathogens.

Attributes of suitable applicants:
First degree (at least 2.1) in biochemistry or related subject**.**

Funding notes:
This project is funded for four years by the Biotechnology and Biological Sciences Research Council BBSRC. BBSRC eligibility criteria apply (https://www.ukri.org/files/legacy/news/training-grants-january-2018-pdf/). EU nationals who do not meet BBSRC residence criteria are encouraged to contact the programme administrator to check their eligibility for BBSRC funding before submitting a formal application. Successful students will receive a stipend of no less than the standard RCUK stipend rate, currently set at £14,777 per year, which will usually be supplemented by the industrial partner.

This project is supported through the Oxford Interdisciplinary Bioscience Doctoral Training Partnership (DTP) studentship programme. The student recruited to this project will join a cohort of students enrolled in the DTP's interdisciplinary training programme, and will be able to take full advantage of the training and networking opportunities available through the DTP. For further, details please visit www.biodtp.ox.ac.uk.

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