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Project Ref: 2017 09 JH/SK - Southampton
Closing Date: 27.10.17
Anticipated Start Date: January 2018
Duration: 3.5 years full-time

Title: Natural resistance to viral diseases in cattle

Eligibility:

- This studentship is open to science graduates (with, or who anticipate obtaining, at least a **2.1 or equivalent, in a relevant biological subject in their undergraduate degree, or a Masters degree - subject to university regulations**). Other first degrees, e.g. veterinary science, will be considered. You should be looking for a challenging, interdisciplinary research training environment and have an active interest in the control of infectious diseases.
- This is a fully-funded studentship open to UK students and eligible EU students who qualify for home-rated tuition fees, in line with BBSRC criteria:
  http://www.bbsrc.ac.uk/web/FILES/Guidelines/studentship_eligibility.pdf
  International students are welcome to apply, however tuition fees will not be funded, therefore student's own funding will be required for tuition fees.
- Students without English as a first language must also provide evidence that they meet the English language requirement, e.g. with an IELTS score of 7.0 and no less than 6.5 in any of the subsections.

Supervision:

Principal Supervisors: John Hammond, The Pirbright Institute; Salim Khakoo, University of Southampton
Co-Supervisor: Toby Tuthill, The Pirbright Institute

Project Details:

This project aims to identify which MHC class I ligands bind ruminant NK cell receptors to initiate and control immune responses, and how the extensive variation between the genes encoding these molecules impacts binding and function. To accomplish this, this project adapts approaches that have recently been successfully adopted to both discover and investigate interacting receptor/ligand pairs in human populations. The specific objectives of this project will be used to address the following aims:

Aim 1: Identify the MHC class I ligands for selected NK cell receptors in ruminants.
Using the extensive genetic knowledge that we have built over the last few years, the student will use *in silico* analysis to identify receptor genes that are likely to have important functional roles by identifying hallmarks of positive selection and conservation between and within ruminant species. Receptors will then be cloned into vectors will allow the expression of the ligand binding domains with tags that allow the receptors to be dimerised or tetramerised. These can then be used as a higher-avidity reagent that can bind established cells lines expressing a panel of cattle MHC class I molecules and primary cells from MHC homozygous cattle of different genotypes. To confirm interactions or extend these analyses to different MHC class I, cattle MHC tetramers available through collaboration can be used to stain primary or transfected cells in reciprocal analyses.

Aim 2: Determine how copy number variation and genetic polymorphism influences receptor/ligand avidity.
A majority of the receptors and ligands studied will be polymorphic. Using high-throughput sequencing data already available and targeted amplicon sequencing as necessary, the student will identify frequent and significant polymorphisms at the predicted interface between receptor and ligand. This impact of this natural diversity can be further explored using mutagenesis studies and cellular reporting assays transfection to determine the impact on binding and signalling, or alternatively higher resolution studies measuring precise influences of substitutions using surface plasmon resonance techniques with expressed proteins. This approach could be developed into resolving the structure of these proteins and their interactions at atomic resolution. Quantitative measures of binding can be extrapolated onto naturally occurring haplotypes of receptors and ligands to assess the cumulative impact on gene transcription and ligand binding.

Aim 3: Measure the influence of genetic diversity on *in vitro* NK cell function.
Knowledge and predictions generated from the first two aims can be taken into *in vitro* experimental infection models using both primary cells from genetically defined animals and cell lines. We have established assays that measure NK cell function during bRSV and BHV-1 viral infection of cattle monocytes. These assays can be used to match receptor and ligand pairs during infection and test the predictions of function the molecular analyses reveals, or determine if MHC class I expression and antigen binding profiles alter the immune response. Novel findings can then be explored using the reagents generated and methods developed in the previous aims.

References for Background Reading:

1. Sanderson, et al (2014). "Definition of the cattle killer cell Ig-like receptor gene family: comparison with aurochs and human counterparts." Journal of Immunology. 193(12): 6016-6030.
2. Alasdair Allan, et al (2015). "Cattle NK Cell Heterogeneity and the Influence of MHC Class I." Journal of Immunology 195(5): 2199-2206.
3. Das J & Khakoo SI "NK cells: tuned by peptide?" Immunol Rev. 2015 Sep;267(1):214-27. doi: 10.1111/imr.12315.

Registration, Training and Funding:

This is a fully funded collaborative project between The Pirbright Institute and The University of Southampton. The student will be based both at The Pirbright Institute and the University of Southampton, and registered with the University of Southampton. Eligible students will receive a minimum annual stipend of £14,553 and university registration fees will be paid. A full range of research and transferrable skills training will be made available to the student as appropriate.

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Your application will only be considered if we have received the following documents:
- Application Form
- CV
- Two references sent directly by your referees

Please email to studentship@pirbright.ac.uk

Further information regarding the partner institutions can be found at:

http://www.pirbright.ac.uk http://www.southampton.ac.uk/