OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

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Industrial CASE Studentship Advertisement – for 2020 entry

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Department(s)/Organisations:
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Project Title: Elucidating the Molecular Machinery of Intracellular Insulin Handling

Brief description of project*:

Insulin is secreted from pancreatic β-cells in response to alterations in blood glucose levels. Insulin binding to its receptor triggers a cascade of phosphorylation events to regulate metabolism and growth by influencing enzyme activity and gene transcription. Additionally insulin may induce receptor internalization, particularly in hepatocytes which clear the majority of insulin, and the insulin receptor complex can continue to signal in the early endosome. The insulin receptor has also shown to bind DNA in the nucleus to directly influence gene expression. Thus insulin stimulated signalling may take place at the plasma membrane, within endosomes or in the nucleus. The factors regulating the uptake and intracellular fate of insulin are incompletely understood.

The first aim of this studentship is to identify regulators of insulin binding, uptake and nuclear import using genome wide CRISPR screens with fluorescently-labelled insulin. Preliminary data show that the fluorescently labelled insulin rapidly accumulates in the nucleus of hepatoma cells. To accomplish this aim the prospective student will learn to generate stable cells lines, FACS cells, perform DNA sequencing and analyse CRISPR screening data. Following identification of genes that alter insulin handling, these effects will be validated using siRNA in primary human hepatocytes with live cell imaging, immunofluorescence and classical biochemistry cell fractionation techniques. Lastly, the impact of altered insulin handling will be assessed by measurement of protein phosphorylation, metabolic flux and gene expression in insulin stimulated primary human hepatocytes with validated genes knocked down.

Successful completion of this project will identify novel factors involved in insulin binding, uptake and import into the nucleus in hepatocytes and determine how altered insulin handling influences downstream responses. This research will largely be performed at the Novo Nordisk Research Centre Oxford which houses the equipment and expertise necessary to perform genome-wide CRISPR

*References:

- Hancock ML, Meyer RC, Mistry M, et al. Insulin Receptor Associates with Promoters Genome-wide and Regulates Gene Expression. *Cell*. 2019;177(3):722-736.e22. doi:10.1016/j.cell.2019.02.030.
- Najjar SM, Perdomo G. Hepatic Insulin Clearance: Mechanism and Physiology. *Physiology (Bethesda)*. 2019;34(3):198-215. doi:10.1152/physiol.00048.2018.

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screens. Additional validation studies will be performed at the Department of Genetics, Anatomy and Physiology.

Attributes of suitable applicants:

Ideal candidates for this PhD studentship will have strong academic background (1st or 2.1 BSc) in a relevant scientific subject. Organisational skills, personal drive and ability to work well with others are desired in a suitable candidate.

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/publications/rcuk-training-grant-guide-pdf/ Annexe 1). 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 £15,285 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.