THE UNIVERSITY of EDINBURGH
School of Chemistry

EastBio DTP – Design and synthesis of chemical probes to understand the role of glucokinase in pancreatic β-cell function

Background

Type 2 diabetes (T2D) is a global health problem characterised by chronic hyperglycaemia due to inadequate insulin secretion from pancreatic β-cells [1]. Current therapies treat the complications of T2D but none of these approaches provide any long-term benefit regarding β-cell health and insulin secretion. This project aims to develop chemical tools to better understand the biological pathways that underpin β-cell function in T2D.

Because glucose must be metabolised to stimulate insulin release, drugs that stimulate glucokinase (GK; the first enzyme in glucose metabolism) have been shown to enhance insulin secretion in diabetes. However, in the long-term, GK activators have been largely disappointing as drugs [2]. Recent studies show that hyperactivation of glucose metabolism--- rather than glucose itself--- drives the progressive decline in β-cell function in diabetes [3]. However, there are no useful chemical tools to probe the apparent role of GK in β-cell function.

The team involving Dr Chris Coxon and Dr Antonia Mey (School of Chemistry) and Dr Elizabeth Haythorne (Centre for Cardiovascular Science) have identified a promising chemical probe that inhibits GK enzyme, however, due to its non-selective nature, it is not very useful for unravelling the pathways in more complex β-cell models.

Aim

This project will design, synthesise and test new chemical probes that selectively inhibit GK in enzyme assays. We will then investigate whether slowing glucose metabolism under i) high glucose and ii) high glucose and high fat conditions, akin to T2D, protects pancreatic β-cell function in cellular models. This approach will inform the future development of a novel therapy for T2D with a focus on preserving β-cell health and insulin secretion.

Training and skill development

The highly interdisciplinary project will appeal to someone with an interest in applying chemical synthesis to interrogating biological problems. Therefore, we are particularly keen to recruit someone with some experience of organic synthesis.

The student will receive training in a number of skills, including: computational probe design/docking, synthesis and biochemical kinase assays; in vitro cell culture techniques (human pancreatic β-cell lines and islets from cadaveric donors); pancreatic hormone secretion assays; measurements of cellular metabolism (extracellular flux assays, real-time fluorescence microscopy, metabolomics), qPCR, western blotting.

For enquiries, please contact Dr Coxon, email: chris.coxon@ed.ac.uk.

References

1. UK Prospective Diabetes Study 16. (1995). 44, 1249-1258.

2. Ashcroft, FM. et al. (2023) Trends Endocrinol Metab. 34:119-130.

3. Haythorne, E. et al. (2022) Nat Commun. 13, 6754.

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Funding Notes

This opportunity is open to UK and international students and provides funding covering stipend and UK level tuition fees. The University of Edinburgh covers the difference between home and international fees meaning that the EastBio DTP offers fully-funded studentships to all appointees. There is a cap on the number of international students the DTP recruits. It is therefore important for us to know from the outset which fees status category applicants will fall under when applying to the University.

Please refer to UKRI website for full eligibility criteria:

Get a studentship to fund your doctorate – UKRI

https://www.ukri.org/apply-for-funding/studentships-and-doctoral-training/get-a-studentship-to-fund-your-doctorate/

How to Apply

Closing date is Friday 17 January 2025, 11.59 pm GMT.

This 4-year PhD project is part of a competition funded by EastBio BBSRC Doctoral Training Partnership (DTP). Detailed guidance on the application process, and the EastBio Application and Reference Forms can be found on the EastBio DTP website.

Please send your completed EastBio Application Form and a copy of your academic transcripts in pdf format to the Chemistry Graduate School, email: chemistry.gradschool@ed.ac.uk

Please also contact your referees and ask them to submit their references on the EastBio reference form template to Chemistry Graduate School, email: chemistry.gradschool@ed.ac.uk by the application deadline of 17 January 2025.

Equality and Diversity

The School of Chemistry holds a Silver Athena SWAN award in recognition of our commitment to advance gender equality in higher education. The University is a member of the Race Equality Charter and is a Stonewall Scotland Diversity Champion, actively promoting LGBT equality.

The University has a range of initiatives to support a family friendly working environment.

For further information, please see our University Initiatives website:

https://equality-diversity.ed.ac.uk/inclusion/family-and-carer