From Lipid Stress to β-cell Resilience: Identifying Lipid-Sensitive Regulators of β-cell Function in Islet Transplantation

Department: Centre for Diabetes and Endocrinology Research, Westmead Institute for Medical Research.

Background: Diabetes is a major cause of illness and early death in Australia [1], affecting over 1.2 million people and more than 20% of hospitalised patients [2, 3]. There are two main types of diabetes: type 1 (T1D), caused by autoimmune destruction of insulin-producing β-cells [4] and type 2 (T2D), where β-cells fail to compensate for peripheral insulin resistance [5-7]. Although these conditions differ in origin, both ultimately result from inadequate insulin secretion by pancreatic β-cells, highlighting the central importance of β-cells in maintaining metabolic health.

Insulin secretory granules (ISGs) are the specialised vesicles in pancreatic β-cells that store and release insulin in response to glucose. Originally viewed as passive storage compartments, insulin granules are now recognised as dynamic organelles that undergo tightly regulated maturation [8-11], trafficking, docking, and exocytosis – processes that collectively determine the efficiency and timing of insulin release [11]. Disruption of these pathways has direct clinical relevance: many genes encoding granule or secretory machinery proteins (e.g. VAMP2, Syntaxin1A, Munc18, SLC30A8 and Scamp3) are linked to diabetes [10, 12]. Thus, understanding the molecular composition and regulation of ISGs is fundamental to defining how β-cells maintain glucose homeostasis, and to understanding how this fails under metabolic stress.

Chronic lipid exposure, a hallmark of obesity and type 2 diabetes, profoundly alters β-cell metabolism [13], but ***how*** lipids reprogram ISG composition and secretory function remains unclear. By integrating insulin granule proteomics under lipotoxic conditions, with ***human islet*** functional outcomes after metabolic challenges, this project aims to reveal lipid-sensitive regulators of ISG biology that contribute to β-cell dysfunction and diabetes pathogenesis.

Aim 1: Characterise and validate candidate proteins as lipid-sensitive regulators of insulin granule composition and function

Rationale and Preliminary Data: To better understand molecular determinants of β-cell function and survival, we performed **proteomic profiling** of isolated ISGs under lipotoxic (palmitate) stress conditions (Figure 1). This analysis revealed distinct sets of proteins whose abundance was altered under lipid stress, suggesting adaptive or maladaptive remodelling of the granule compartment. To link these proteomic changes to physiological outcomes, we integrated these data with **RNA-seq profiles from human islets transplanted into diabetic mice**, where graft function was monitored after **high-fat diet (HFD)** challenge. This cross-platform analysis identified two high-confidence candidates – **ACVRL1** and **ROBO1**.

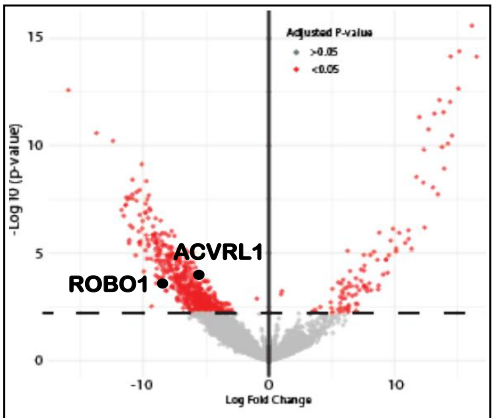

Fig 1. Differential protein abundance in ISGs from control vs palmitate conditions. Dashed line represents adjusted P-value significance threshold.

Both proteins were decreased in abundance within ISGs under lipotoxic conditions. Importantly, transcript levels in human islet grafts positively correlate with preserved graft function following high-fat diet challenge, indicating that **reduced expression, or loss of these proteins is associated with poorer β-cell performance**. ACVRL1 (ALK1) is a TGFβ-family receptor, which signals via SMAD1/5/8 and is involved in early stage development of the pancreas [14]. It is postulated to play a protective or stabilizing role in maintaining β-cell identity and secretory granule function [15, 16]. ROBO1 and its interaction with SLIT ligands has been shown to mediate autocrine and paracrine signalling critical for β-cell survival and function [17]. SLIT-ROBO signalling promotes actin remodelling and protects against ER stress-induced apoptosis and enhances glucose stimulated insulin secretion [18]. These suggest that reduced ACVRL1 and ROBO1 expression is a maladaptive response to lipotoxic stress, and preserving their expression may protect granule integrity and insulin secretion under lipotoxic conditions.

Aim 1a. *Validate lipid-dependent regulation of ACVRL1 and ROBO1 in human β-cells*. **Hypothesis**: We hypothesise that both ACVRL1 and ROBO1 are downregulated in insulin granules under lipotoxic conditions, and their expression levels correlate with β-cell function. **Methods**: Human islets (n=3-5 donors) will be treated with palmitate (0.5 mM) or vehicle for 24-48h. Protein and transcript levels will be assessed in total lysates

using Western blotting and RT-qPCR to determine if downregulation is transcriptional or post-transcriptional. Separately, human islet grafts harvested from diabetic mice after HFD or CHOW have been fixed and sectioned. These sections will be co-stained with antibodies against ALK1 or ROBO1, islet markers (insulin/glucagon/somatostatin) and vascular markers (VEGF/laminin) to assess protein abundance, granule association, and subcellular localisation relative to the islet microarchitecture. This will provide *in vivo* confirmation of lipid-sensitive changes and spatial context of the candidate proteins within human islets.

Aim 1b. *Characterisation of ACVRL1 and ROBO1 in ex vivo human & mouse islets*. **Hypothesis**: We hypothesise that reduced expression of these proteins impairs β-cell function, and that knockdown will reveal their contribution to insulin secretion and granule regulation. Human (n=3-5 donors) and mouse (n=6) islets will be transduced with **shRNA targeting ACVRL1 or ROBO1** (or scrambled control), delivered by rAAV (**Figure 1**). After 48-72h, β-cell function will be assessed using (**1**) static and perifusion insulin secretion assays using different secretagogues, (**2**) granule dynamics imaging (live-cell microscopy), (**3**) proteomics [10] to assess pathways modulated by ACVRL1/ROBO1, (**4**) electron microscopy to evaluate insulin granule morphology and ultrastructure, (**5**) Immunofluorescence staining as per Aim 1a and (**6**) remaining islets will be collected and saved for RNA-sequencing.

Aim 2: In vivo overexpression of ACVRL1 and ROBO1 to enhance β-cell function under conditions of metabolic stress

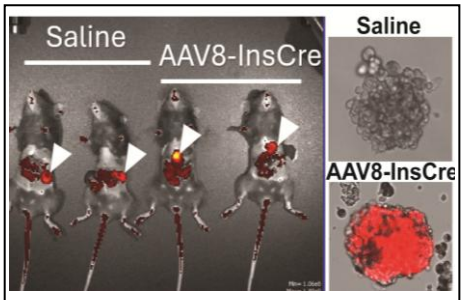

FIG 2. AAV-InsCre directs islet-specific expression (TdTomato+)

Rationale: Building on aim 1, which defines the functional role of ACVRL1 and ROBO1 *ex vivo*, we will test whether increasing expression of these proteins *in vivo* can protect β-cells from high-fat diet (HFD)-induced dysfunction. **Hypothesis**: We hypothesise that overexpression of ACVRL1 or ROBO1 in β-cells will improve insulin secretion, preserve granule integrity and enhance glucose homeostasis under metabolic stress. We have developed a recombinant AAV system that specifically targets β-cells. Fig 2 shows the rAAV expressing Cre-recombinase in Ai9 reporter mice. Cre-recombinase expression in these mice deletes a floxed **STOP** codon, driving TdTomato expression. Our vector is a modular "plug-and-play" design, allowing the insertion of mRNAs to overexpress human or mouse ACVRL1 or ROBO1.

Methods: Male and female mice will be tested. C57Bl/6 mice will receive intraperitoneal injection of either control rAAV+tdTomato, or rAAV expressing tdTomato+ACVRL1 or ROBO1. Mice will then be cage-randomised to chow or high-fat diet for 8 weeks with twice-weekly weight measurements and weekly random-fed blood glucose. We will study N=12 mice per gender for each of the 3 rAAVs, per diet =2*3*2*12=144 mice, in several cohorts of 20-24 mice. At study end, a combined glucose tolerance test and glucose-stimulated insulin secretion test will be performed 24h pre-sacrifice when tissues will be collected. Islets will be isolated from 8 mice for molecular and functional studies as outlined in **Aim 1b** and 4/group will have pancreata removed for histology as outlined in **Aim 1a**. This will determine whether overexpression of ACVRL1 or ROBO1 enhances β-cell function or survival to prevent diabetes in a physiological relevant model of obesity and insulin resistance – providing direct preclinical data.

Expected Outcomes: This project will investigate the role of ACVRL1 and ROBO1 in β-cell function and metabolic resilience. Aim 1 will characterise their expression, subcellular localisation and lipid responsiveness in human and mouse islets (Aim 1a) and further define their functional role using shRNA-mediated knockdown *ex vivo* (Aim 1b). Aim 2 will test whether β-cell-specific overexpression of ACVRL1 or ROBO1 in mice protects against high-fat diet-induced dysfunction, evaluating glucose homeostasis, β-cell function, granule integrity and islet morphology. Together, these studies will establish ACVRL1 and ROBO1 as critical regulators of β-cell function and potential therapeutic targets to improve insulin secretion under metabolic stress, with the potential to enhance human islet transplant outcomes and its use in future human clinical trials.

Budget: $40,000 AUD is requested to support this project. Custom rAAVs and shRNA for ROBO1, ACVRL1, and control for mouse and human are $2500 each, $16000 total. Mouse costs (husbandry, diets) are $3000. Consumables, culture media, reagents, plasticware, antibodies, insulin ELISA kits are $8000. Imaging/microscopy facility use is $2000. RNA sequencing is $5000. Human islet reagents and shipping are $2000 (From St Vincent's Institute, Melbourne). Remaining $4000 will be used for salary support.

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Application References

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2. Bach, L.A., et al., *The high burden of inpatient diabetes mellitus: the Melbourne Public Hospitals Diabetes Inpatient Audit.* Medical Journal of Australia, 2014. **201**(6): p. 334-338.
3. Lee, K., et al., *XBP1 maintains beta cell identity, represses beta-to-alpha cell transdifferentiation and protects against diabetic beta cell failure during metabolic stress in mice.* Diabetologia, 2022. **65**(6): p. 984-996.
4. Gillespie, K.M., *Type 1 diabetes: pathogenesis and prevention.* Cmaj, 2006. **175**(2): p. 165-170.
5. Weyer, C., et al., *Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development.* Diabetes Care, 2001. **24**(1): p. 89-94.
6. Cheng, K., S. Andrikopoulos, and J.E. Gunton, *First Phase Insulin Secretion and Type 2 Diabetes.* Current Molecular Medicine, 2013. **13**(126-139).
7. Del Prato, S. and A. Tiengo, *The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus.* Diabetes Metab Res Rev, 2001. **17**(3): p. 164-74.
8. Albrethsen, J., J.P. Goetze, and A.H. Johnsen, *Mining the granule proteome: a potential source of endocrine biomarkers.* Biomark Med, 2015. **9**(3): p. 259-65.
9. Hickey, A.J., et al., *Proteins associated with immunopurified granules from a model pancreatic islet beta-cell system: proteomic snapshot of an endocrine secretory granule.* J Proteome Res, 2009. **8**(1): p. 178-86.
10. Norris, N., et al., *Optimised proteomic analysis of insulin granules from MIN6 cells identifies Scamp3, a novel regulator of insulin secretion and content.* Diabetes, 2024: p. db240355.
11. Norris, N., B. Yau, and M.A. Kebede, *Isolation and Proteomics of the Insulin Secretory Granule.* Metabolites, 2021. **11**(5).
12. Omar-Hmeadi, M. and O. Idevall-Hagren, *Insulin granule biogenesis and exocytosis.* Cellular and Molecular Life Sciences, 2021. **78**(5): p. 1957-1970.
13. Del Prato, S., *Role of glucotoxicity and lipotoxicity in the pathophysiology of Type 2 diabetes mellitus and emerging treatment strategies.* Diabetic medicine, 2009. **26**(12): p. 1185-1192.
14. Smart, N.G., et al., *Conditional expression of Smad7 in pancreatic β cells disrupts TGF-β signaling and induces reversible diabetes mellitus.* PLoS biology, 2006. **4**(2): p. e39.
15. Toren-Haritan, G. and S. Efrat, *TGFβ pathway inhibition redifferentiates human pancreatic islet β cells expanded in vitro.* PloS one, 2015. **10**(9): p. e0139168.
16. Lebrin, F., et al., *Endoglin promotes endothelial cell proliferation and TGF-β/ALK1 signal transduction.* The EMBO journal, 2004. **23**(20): p. 4018-4028.
17. Yang, Y., et al., *Paracrine signalling loops in adult human and mouse pancreatic islets: netrins modulate beta cell apoptosis signalling via dependence receptors.* Diabetologia, 2011. **54**(4): p. 828-842.
18. Yang, Y.H.C., et al., *Intraislet SLIT–ROBO signaling is required for beta-cell survival and potentiates insulin secretion.* Proceedings of the National Academy of Sciences, 2013. **110**(41): p. 16480-16485.

Nicholas Wai Lung Norris

Postdoctoral Research Associate

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Professional Summary

Dedicated and detail-oriented scientist with a PhD in pancreatic beta-cell biology and a strong background in molecular biology, cell biology, and metabolic research. Experienced in a broad range of wet lab techniques, advanced microscopy, and quantitative data analysis within collaborative, multidisciplinary environments. Passionate about translational research aimed at understanding and treating metabolic diseases, with a proven ability to drive independent projects and contributing to team-based projects.

Work History

2024 Nov – Current | *Centre for Diabetes, Obesity and Endocrinology Research, Westmead Institute for Medical Research* | **Postdoctoral Research Associate**

2025 – Current | *Chronic Diseases, School of Medical Sciences, Faculty of Medicine and Health, University of Sydney* | **Adjunct Associate Lecturer**

2024 | *University of Sydney, Charles Perkins Centre* | **Nikki Lee Lab** | Research Assistant

2021-2025| *University of Sydney* | **Casual Academic** | Laboratory demonstrator for second- and third-year Physiology units PHSI2007, PHSI3009), Nutrition & Metabolism (NUTM3001), Systems Physiology (PHSI3010), Teaching assistant and Academic marker for all above units & online learning units (OLET1504: Health Challenges, Diabetes).

Dec 2020- Feb 2021| *University of Sydney, Charles Perkins Centre* | **Islet Biology and Metabolism Group Research Assistant** | Collaborations with multidisciplinary institute members to develop research methodologies for insulin granule isolations

Education

2021- March 2025 | **Doctor of Philosophy** | *School of Medical Science, University of Sydney* | Thesis: Interrogating the Insulin Granule, Investigating the Composition and Function of Insulin Secretory Granules | Supervisors: A. Prof. Melkam Kebede, A. Prof. Mark Larance and Dr. Alistair Senior

2017-2020 | **Bachelor of Science (Advanced) (Honours Class I)** | *University of Sydney* | Biochemistry and Biology. Thesis: Characterization of Insulin Secretory Granules as a Function of Age.

Research & Technical Skills & Teaching Experience

- Proficiency in animal handling and procedures including pancreatic islet isolations, transcardial perfusions, organ dissections & extraction, surgical experience and islet transplantation in mice

- Human sample handling of pancreatic tissue and islet preparations

- Great competency with diverse statistical software and bioinformatics tools for small to large datasets (RStudio, GraphPad Prism, Excel, Huygens, QuPath & FIJI)

- Expertise in Western Blotting, DNA/RNA Extractions, PCR, Tissue culture, subcellular fractionation, slide preparation immunohistochemistry and immunofluorescence, FACS

- Wide range of assay experience: ELISAs, Fluorescence assays (HTRF), Protein/DNA assays

- Deep understanding of imaging techniques using wide-/bright-field, confocal, STED and live cell imaging. Experience in TEM sample preparation & imaging.

- Scientific writing and producing figures for manuscripts and abstracts for projects

- Experienced in mentoring Honours and PhD students and junior researchers, lab managing including ordering lab supplies and maintenance of lab spaces and equipment

- Supervision of undergraduate students and Interns – Supervised numerous undergraduate (Dalyell Scholarship Students, University of Sydney), and high school work experience students, providing training in laboratory techniques, data analysis and research project management

- Undergraduate teaching (University of Sydney): Delivered tutorials and practicals across physiology and medical science units, including advanced courses, with individual supervision of undergraduate students in laboratory techniques and science communication for research.

Honours and Awards

2025 | *International Diabetes Federation (Western Pacific)* | **Best Basic Science Paper EMCR Prize Q1 (Jan-Mar), 2025**

2025, August | *Westmead Hospital* | **Best Poster Presentation Awardee, Westmead Hospital Week**

2025, August | *Australasian Diabetes Congress 2025* | **ADS Travel Grant**

2024, August | *Australasian Diabetes Congress 2024* | **Australian Diabetes Society (ADS) Pincus-Taft Young Investigator Award** | Best Oral Presentation

2024, November | *Charles Perkins Centre* | **EMCR Professional Development Award**

2024, August | *Australasian Diabetes Congress 2024* | **ADS Travel Grant**

2021-2024 | *University of Sydney* | **University Postgraduate Award** | PhD Scholarship

2021 | *Australasian Diabetes Congress 2021* | ADS Basic Science Poster Awards: Proteomics of the Insulin Secretory Granule

2021, January | *Charles Perkins Centre* | **Islet Biology and Metabolism Scholarship (CPC)** | Multidisciplinary Research Scholarship

2020, January | *Charles Perkins Centre* | **Summer Research Scholarship** | Multidisciplinary Research Scholarship

Publications

1. **Norris, N.,** Kebede, M.A., Laybutt, D.R. and Gunton, J.E., 2025. β-Cells: So Sensitive. *Diabetes*, *74*(6), pp.863-866.
2. **Norris, N.,** Yau, B., Famularo, C., Webster, H., Loudovaris, T., Thomas, H.E., Larance, M., Senior, A.M. and Kebede, M.A., 2024. Optimized Proteomic Analysis of Insulin Granules From MIN6 Cells Identifies Scamp3, a Novel Regulator of Insulin Secretion and Content. *Diabetes*, *73*(12), pp.2045-2054. (cont.)
3. ***And*** bioRxiv 2024/04 23.590838: **Norris, N.**, Yau, B., Famularo, C., Thomas, H.E., Larance, M., Senior, A.M. and Kebede, M.A., 2024. Optimised proteomic analysis of insulin granules from MIN6 β-cells identifies Scamp3, a novel regulator of insulin secretion and content. *bioRxiv*, pp.2024-04.
4. Hao, H., Yuan, Y., Ito, A., Eberand, B.M., Tjondro, H., Cielesh, M., **Norris, N.,** Moreno, C.L., Maxwell, J.W., Neely, G.G. and Payne, R.J., 2025. FUT10 and FUT11 are protein O-fucosyltransferases that modify protein EMI domains. *Nature Chemical Biology*, pp.1-13
5. O'Reilly, L., Reibe-Pal, S., Sue, N., Holliday, H., Small, L., Schmitz-Peiffer, C., Dhenni, R., Tsai, V.W.W., **Norris, N.**, Yau, B. and Zhang, X., 2023. β-cell function is regulated by metabolic and epigenetic programming of islet-associated macrophages, involving Axl, Mertk, and TGFβ receptor signaling. Iscience, 26(4)
6. Adams, M.W., Grant, L.S., Kovacs, T.G., Liang, S.Q., **Norris, N.,** Wesley, H.E., Alessi, M.M. and Banks, P.B., 2023. Commensal black rats Rattus rattus select wild vegetation over urbanised habitats. Oikos, 2023(3), p.e09671.
7. **Norris, N.,** Yau, B. and Kebede, M.A., 2021. Isolation and proteomics of the insulin secretory secretory. Metabolites, 11(5), p.288.
8. Wu Linda, Wentworth John M, Liddle Christopher, ... **Nicholas Norris**, ..., Gunton Jenny E. 2025. Pancreatic volume and immunological biomarkers predict checkpoint inhibitor-associated autoimmune diabetes in humans. **Journal of Clinical Investigation**. Accepted September 3rd, 2025. In press.

Grants

2025 | *Charles Perkins Centre* | **Charles Perkins Centre Metabolic Initiative Grant ($20K)** | Chief Investigator A / Project Lead

Organizations and Committees

2020-present Member, Australian Diabetes Society

2024-present Member, Endocrine Society of Australia

2024-present | *Westmead Research Hub* | **Westmead Research Hub Early and Mid-Career Researcher Committee Member** | Leading and assisting in developing events and initiatives to

advance professional development, educational experience and social aspects of the EMCR community including funding opportunities.

2024 | *Charles Perkins Centre* | **Charles Perkins Centre Early- and Mid-Career Researcher Committee Member**| Involvement in developing events and initiatives to advance professional development, educational experience and social aspects of the EMCR community including funding opportunities

2023-2024 | *Charles Perkins Centre* | **Research Advisory Group (Level 5)** | Involved in maintaining and managing laboratory spaces at the Charles Perkins Centre

2021 | *Australasian Diabetes Congress 2021* | **Session Monitor** | Responsible for monitoring Poster and Oral sessions during COVID online congress attendance

Conferences

2025 | *Australian Islet Study Group Meeting 2025* | Poster Presentation

2025 | *Australasian Diabetes Congress 2025* | Poster Presentation

2024 | *Australasian Diabetes Congress 2024* | Pincus Taft Young Investigator's Award; Oral Presentation

2023 | *DiscoverBMB 2023 (ASBMB) Seattle, Washington* | Oral Presentation

2023 | *Australian Islet Study Group Meeting 2023* | Poster Presentation Award Session

2022 | *Australasian Diabetes Congress 2022*

2021 | *Australasian Diabetes Congress 2021* | ADS Basic Science Poster Awards: Proteomics of the Insulin Secretory Granule

Referees

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Professor Joanne Wright
Deputy Vice-Chancellor (Education)

26 March 2025

Nick Norris
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Dear Nick,

I am pleased to offer my congratulations on satisfying the requirements for the award of the degree of **Doctor of Philosophy** at the University of Sydney. The details of your candidature are as follows:

Thesis Title:	**Interrogating the Insulin Granule, Investigating the Composition and Function of Insulin Secretory Granules**
Lead Supervisor:	**Melkam Kebede**
Supervisor:	**Dr Alistair Senior; Mark Larance**
School/Department:	**Medical Sciences**
Student ID:	**470254631**
Date of commencement:	**1 March 2021**
Date of submission:	**13 December 2024**

The next step is for you to have your degree officially conferred by the University through the graduation process. The University's current graduation ceremony schedule and eligibility for inclusion into a ceremony can be viewed at sydney.edu.au/graduations.

If you choose not to attend your graduation ceremony, or if you would like to graduate earlier, please refer to the contact details for our Graduations Office on our website.

To ensure that your graduation documents are sent to your current mailing address, you should update your address by logging in to Sydney Student.

Additionally, you can access a formal completion verification from Sydney Student under My Studies>Assessments>Awards.

Please note, the Graduations Office will complete additional checks that all payments to the University have been completed ahead of graduation, including your Student Services and Amenities Fee, so please check you have nothing outstanding that could prevent you graduating.

Once your degree is conferred, you may use the title associated with that degree.

With best wishes,

Professor Joanne Wright
Deputy Vice-Chancellor (Education)

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THE UNIVERSITY OF SYDNEY

26 March 2025

To whom it may concern,

This is to confirm that **Nicholas Wai Lung Norris**, student number: **470254631**, date of birth: **17 October 1997**, has completed the requirements for the below degree at the University of Sydney as of 26 March 2025:

Degree: Doctor of Philosophy

Nicholas Wai Lung Norris commenced this course on 1 March 2021 and their enrolment details are as follows:

Enrolment start date:	1 March 2021
Thesis Submission date:	13 December 2024
Completed requirements:	26 March 2025

It is expected that upon conferral, graduation documents for the Doctor of Philosophy degree (RPPHDMDH-02) (CRICOS:0100244) will be made available to the student.

The degree is taught in English.

Contact us
If you have any questions, call us on 1800 SYD UNI (1800 793 864) or +61 2 8627 1444 (if outside Australia), or ask a question online at sydney.edu.au/contact

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Associate Professor Melkam A. Kebede
The Charles Perkins Centre
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20 September 2025

To the ESA Ken Wynne Memorial Postdoctoral Research Award Selection Committee,

It is with great enthusiasm that I write in support of Dr Nicholas Norris's application for the 2025 ESA Ken Wynne Memorial Postdoctoral Research Award. I have had the privilege of supervising Nick throughout his Honours and PhD studies at the University of Sydney, and I continue to be impressed by his scientific insight, dedication, and capacity for collaboration and leadership.

Nick is an exceptionally talented early career researcher. He has already made significant contributions to the field of diabetes research, building a strong independent profile within an impressively short time frame. His PhD, awarded in March 2025, produced high-quality publications and new conceptual advances in β-cell biology. He is highly motivated, rigorous in his approach, and demonstrates remarkable vision for his career stage. Notably, his work is already positioning him to define new directions in understanding β-cell dysfunction and to identify potential therapeutic avenues for type 2 diabetes.

His scientific promise is underscored by external recognition. In 2024, Nick was awarded the prestigious Pincus Taft Young Investigator Award at the Australasian Diabetes Congress, the leading discovery science prize of the Australian Diabetes Society, recognising the best abstract presentation by a junior investigator. This honour highlights both the calibre of his science and his excellent communication skills.

Nick also contributes meaningfully to research culture. At both the Charles Perkins Centre and Westmead Institute for Medical Research, he has been an active and generous member of the EMCR community. He invests time in supporting colleagues, sharing expertise, and helping to foster an inclusive, collaborative environment. These qualities make him a role model for other early career researchers.

In my view, Nick exemplifies the values of the ESA Ken Wynne Memorial Postdoctoral Research Award: excellence in research, leadership within the early career community, and a clear trajectory toward becoming a leading independent investigator. I offer him my strongest endorsement and have no doubt he will continue to make outstanding contributions to diabetes research.

Please feel free to contact me should you require any further information.

Best wishes,

Melkam Kebede

Melkam Kebede | Associate Professor
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Head, Kebede Islet Biology and Metabolism Laboratory
Unit of Study Coordinator – PHSI3009 *Cell Physiology of Disease*
Charles Perkins Centre
School of Medical Sciences

Centre for Diabetes, Obesity and Endocrinology

Date: 30th October 2025

To the ESA Ken Wynne Memorial Postdoctoral Research Award Selection Committee,

It is my great pleasure to support Dr Nicholas Norris' application for the Ken Wynne Postdoctoral Award. Nick completed his PhD in March 2025 and has already made an outstanding start to his postdoctoral career in my laboratory. He has shown exceptional initiative, independence, and productivity.

Nick's research focuses on understanding β-cell function and insulin granule biology – an area in which he is establishing himself as an early-career scientist. He is exceptionally talented in the lab, producing high-quality publications (e.g. contributing to an in press JCI paper) and demonstrates a strong track record this early in his career stage. Beyond scientific achievements, Nick is also a generous and effective mentor to students in the lab, contributing greatly to our team environment and training culture.

I confirm that we have the facilities and expertise available within our group and at the Westmead Institute for Medical Research and with my collaborators provide an excellent setting for Nick's ongoing work, including advanced imaging, viral vector production, and human islet studies. He will be well supported by experienced collaborators and the strong research infrastructure of our Centre.

Obtaining grants as an ECR is a major milestone which increases chances of future independent funding. An ESA fellowship would make a huge difference for future career progression. I have no doubt that Nick will continue to make significant contributions to discovery science research, and I give him my strongest support for this award.

Feel free to contact me should you require any further information.

Kind regards,

Prof Jenny Gunton

Professor Wayne Hawthorne
Chair, WSLHD AEC
Dr Ross Matthews
Executive Officer
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Western Sydney Local Health District Animal Ethics Committee
Department of Animal Care

20 March 2024

Prof Jenny Gunton
Centre for Diabetes, Obesity & Endocrinology
Westmead Institute for Medical Research

5195.03.24 - Investigating the role of beta cells in diabetes and transplantation

At the 2 of 8 meeting held on Friday 1 March 2024 the Western Sydney Local Health District Animal Ethics Committee (AEC) considered your Application for Animal Research submission. A question was raised on the submission and has subsequently been answered satisfactorily.

Decision/s: The Committee **APPROVED** the application for animal research for **3** years:

RESEARCH LOCATION/s
Westmead Bioresources Facility, Westmead Institute for Medical Research, 176 Hawkesbury Road, Westmead NSW 2145

Animals Approved				
Species	**Strain**	**Age/ Weight**	**Sex**	**Number Approved**
Mouse	C57Bl/6, NOD, RAG	>6wks	M/F	2016

Project Administration and Reporting
The project number allocated to you is **5195.03.24** The first four digits signify the project number, followed by the month of review, and the year of project approval.
The project number should be used to identify any correspondence, cages and animals, and to facilitate record keeping regarding the welfare, health and disposal of any animals on site.

Professor Wayne Hawthorne
Chair, WSLHD AEC
Dr Ross Matthews
Executive Officer
Leigh Burns
Animal Ethics Officer
wslhd-aec@health.nsw.gov.au
02 8890 6176

Western Sydney Local Health District Animal Ethics Committee
Department of Animal Care

It is a condition of approval that you provide a completed Annual Report each year at least one month prior to the review date, summarising the years' work, any animal welfare issues and details of any scientific progress made.

Upon acceptance of the Annual Report the Animal Research Authorities (the ARA) will be renewed for a twelve month period. All personnel listed on the project ARA must have a copy of the project as approved, including any modifications.

It must be remembered that it is your responsibility as the Principal Investigator to guarantee compliance with the Guidelines for Animal Welfare as outlined in the National Health and Medical Research Council's (NHMRC) "Australian Code for the care and use of animals for scientific purposes 8th Ed. 2013 (updated 2021) and NSW Animal Research Act and associated Regulations. The Animal Ethics Committee is responsible for ensuring that this compliance occurs.

The Principal Investigator is responsible for ensuring appropriate training and/or supervision of research personnel is provided for researchers working on approved AEC protocols, taking into account the level of comjpetency of each person, and the tasks assigned.

Animal Welfare

After receipt and identification of your animals on site, their welfare and health is your responsibility. If any animal is in distress you are required to notify the person in charge of Research Holding, Biological Services Facility (WIMR) and/or the Vivarium, the Veterinarian on duty or Department of Animal Care staff.

Monitoring records must be kept in compliance with the conditions applied to their protocols by the AEC and in accordance with established institutional operating procedures and that these records are kept available in the same location as the animals, for audit by the institution and any authorised external reviewers. (NHMRC Code 2.4.30-2.4.33).

Investigators are reminded that animals must be identifiable whether individually or in groups. Once animals are allocated to a research protocol it is the responsibility of the investigator to ensure that this is done. (NHMRC Code 3.3.6).

Adverse Events

Animal/s that die unexpectedly, or are required to be euthanased for animal welfare reasons, should undergo a post mortem and the report should be included with the Adverse Event submission. Adverse Events reports must be submitted within 48 hours of the event, as required by the Code.

Professor Wayne Hawthorne
Chairman
WSLHD Animal Ethics Committee