THE UNIVERSITY of EDINBURGH
School of Chemistry

mRNA display based development of peptidic chemical tools to modulate SUMOylation.

An interdisciplinary PhD studentship is available in the group of Dr Ewen Calder at the University of Edinburgh; School of Chemistry and Institute for Regeneration and Repair, https://www.ed.ac.uk/profile/dr-ewen-d-d-calder.

The studentship is fully funded for 42 months by the University of Edinburgh and covers tuition fees and an annual stipend at the UKRI rate, for 2025–26 this is £19,795 per annum, for a candidate satisfying UKRI home student residency criteria. https://www.ukri.org/what-we-do/developing-people-and-skills/esrc/funding-for-postgraduate-training-and-development/eligibility-for-studentship-funding/

Project Summary

SUMOylation is an important, highly dynamic post-translational modification which involves the conjugation of a small ubiquitin-like modifier (SUMO) to a lysine residue of a protein [1]. SUMOylation is important in the regulation of a multitude of cellular processes, including cell cycle progression, genome stability, transcription, and DNA repair. Misregulation of SUMOylation is implicated in a wide range of pathologies including Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and many cancers [2,3]. Additionally, due to its roles in innate immunity, the enzymes mediating SUMOylation are targeted by many pathogens. However, there remains a lack of high-quality chemical tools to better understand the role of these enzymes in disease.

mRNA display allows the screening of vast (>10^{13}) libraries of macrocyclic peptides against protein targets, and frequently generates hit compounds with very tight binding and high selectivity [4]. These libraries are orders of magnitude larger than classical high-throughput screening or other display technologies. Incorporation of unnatural amino acids and amino acid-like molecules into these libraries of displayed macrocycles can be achieved using the Random, non-standard, Peptide Integrated Discovery (RaPID) system of mRNA display. This allows bridging of the chemical space between small molecules and macrocyclic peptides and is important for improving the potency and permeability of the displayed molecules.

The aim of this project is to utilise the RaPID system to develop novel, best-in-class tools for modulation of the SUMOylation pathway. This interdisciplinary project will combine elements of organic and medicinal chemistry, and cell biology. It is therefore ideally suited to a student with a background in chemistry or natural sciences who is seeking to broaden their expertise.

Specific Objectives:

- Carry out RaPID screening to identify novel chemical tools to modulate the SUMOylation pathway.
- Assess and optimise these tools' selectivity, pharmacokinetics and modes of action.

  This will include learning solid phase peptide synthesis, biophysics techniques, as well as a wide range of *in vitro* biological assays and may include molecular biology.
- Apply the optimised molecules to probe the various roles of SUMOylation in multiple biologic systems, in collaboration with other labs both internal and external to the University of Edinburgh.

Educational and research opportunities afforded by this project include:

- Develop a wide range of practical skills at the interface of chemistry and biology.
- Opportunity to attend national and international conferences to disseminate your results.
- A strong emphasis and support to publish research in leading scientific journals, which will kickstart your career in academia or industry.

Applicants should hold (or expect to be awarded) a first class or upper-second class Masters degree (MSci, MChem, MSc, MRes) or equivalent in chemistry or a natural sciences related field and have some chemistry or biology research experience. Candidates should be able to demonstrate problem-solving, time-management, and independence in thinking.

Informal enquires are encouraged via email to Dr Ewen Calder, email: ewen.calder@ed.ac.uk

In the first instance, the initial application consisting of cover letter and CV should be directed by email to: Dr Ewen Calder, Institute for Regeneration and Repair, 4–5 Little France Drive, Edinburgh BioQuarter, Edinburgh, EH16 4UU, UK. Email: ewen.calder@ed.ac.uk

The position will remain open until filled. A closing date may be added later. The expected start is Autumn 2025 however earlier dates will be considered upon request for candidates already holding their degree.

References

[1] Celen, A.B. and Sahin, U., Sumoylation on its 25th anniversary: mechanisms, pathology, and emerging concepts. FEBS J, 2020, 287, 3110–3140. https://doi.org/10.1111/febs.15319

[2] Princz, A., Tavernarakis, N., SUMOylation in Neurodegenerative Diseases, Gerontology, 2020, 66 (2), 122–130. https://doi.org/10.1159/000502142

[3] Kroonen, J.S., Vertegaal, A.C.O, Targeting SUMO Signaling to Wrestle Cancer, Trends in Cancer, 2021, 7 (6), 496–510. https://doi.org/10.1016/j.trecan.2020.11.009.

[4] Huang, Y., Wiedmann, M. M., and Suga, H., RNA Display Methods for the Discovery of Bioactive Macrocycles, Chem. Rev., 2019, 119, 10360–10391. https://doi.org/10.1021/acs.chemrev.8b00430

Important

Before Submitting your cover letter and CV, please complete the online form:

School of Chemistry Equality, Diversity and Inclusion Form, entry 2025-26.

The form will automatically generate a unique 'Response ID number' that you must include in your cover letter.

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