EASTBIO A combined physics and data-driven methodology for the rational design of molecular glues

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Funding: This 4-year PhD project is part of a competition funded by EASTBIO BBSRC Doctoral Training Partnership. This opportunity is open to UK and International students and provides funding to cover stipend and UK level tuition.

UKRI-funded studentships are open to students worldwide and will cover tuition fees at the UK rate, plus a stipend to support living costs and an annual research grant of £5,000 for the first three years of the PhD research (this is reduced to £1,500 in the fourth year of study). On 2nd May 2023, UKRI announced an increase in stipend levels in response to the ongoing cost of living crisis. The increased stipend of £18,622 full time equivalent applies to the current academic year 2023/24; UKRI is expected to announce stipend increases in spring 2024 for October 2024 starts.

The proportion of international students appointed through the EASTBIO DTP is capped at 30% by UKRI BBSRC. All students must meet the eligibility criteria as outlined in the UKRI guidance at UKRI Training Grant Terms and Conditions, esp. TGC 5.2 & Annex B. Please contact recruitment@eastscotbiodtp.ac.uk if you are unsure of your fee status.

Closing date for applications: 27th November 2023. We encourage early applications and enquiries.

Project Details:
Molecular glues are small molecules that induce the formation of a strong interaction between proteins that do not normally interact with each other in a functional manner.(1) Molecular glues offer a novel paradigm for developing therapeutics but rational approaches to discover them are lacking and they pose challenges for conventional computer-aided drug design methodologies.

The goal of this PhD project is to develop a combined data/physics-driven computational approach to support the rational design of molecular glues. The research will combine expertise in machine learning and atomistic simulations established in the Michel (www.julienmichel.net) group with expertise in structural and chemical biology in targeted protein degradation and molecular glues from the Ciulli group (www.lifesci.dundee.ac.uk/groups/alessio-ciulli).

Throughout the project the student will gain expertise in alchemical free energy methods for computing protein-ligand binding affinities, and in deep learning methodologies for structural modelling of protein assemblies.(2-3) The integration of these methodologies will deliver a computational platform applicable to a range of molecular glues design problems The computational methodologies will be applied to systems of interest to the Centre for Targeted Protein Degradation (www.dundee.ac.uk/cetpd), such as for instance the recently-revealed molecular glues stabilizing intrinsic interactions of bromodomain-containing protein 4 (BRD4) with DCAF16 E3 ligase.(4)

Applicants should hold a degree in a relevant subject (typically Chemistry, Biochemistry, Physics). Previous experience in Python programming is strongly desirable. The student will receive training in biomolecular simulation methods, deep learning methods for structural biology, and research software development. The student will collaborate with experimentalists to apply computational approaches to support molecular glues discovery projects. These activities will have equipped the successful candidate with a strong skillset for pursuing a career in academia or industry by the end of their PhD.

References

1 ''Proximity-Based Modalities for Biology and Medicine'' Liu, X. ; Ciulli , A. ACS Central Science, 9 (7), 2023 https://doi.org/10.1021/acscentsci.3c00395

2 " Energetics of a protein disorder-order transition in small molecule recognition." Mendoza-Martinez, C. ; Papadourakis, M. ; Llabrés, S. ; Gupta, A. A. ; Barlow, P. N. ; Michel, J. Chem. Sci. , 13, 5220-5229, 2022 https://doi.org/10.1039/D2SC00028H

3 'De novo design of protein structure and function with RFdiffusion'' Watson, JL et al. Nature 620, 1089-1100, 2023 https://doi.org/10.1038/s41586-023-06415-8

4 ''An intramolecular bivalent degrader glues an intrinsic BRD4-DCAF16 interaction' ' Hsia, O ; Hinterndorfer, M. ; Cowan, A. D. ; Iso, K. ; Ishida, T. ; Sundaramoorthy, R. ; Nakasone, M. A. ; Rukavina, A. ; Husnjak, K. ; Wegner, M. ; Correa-Sáez, A.; Craigon, C. ; Maniaci, C. ; Testa, A. ; Kaulich, M. ; Dikic, I. ; Winter, G. E. ; Ciulli, A. bioRxiv 2023 https://doi.org/10.1101/2023.02.14.528511

Application Process:

To apply for an EASTBIO PhD studentship, please follow the EASTBIO applications Guidance. EASTBIO can provide you with support for your application and details are available on the how to apply webpage.
Informal enquiries should be addressed to Prof Julien Michel, please send a cover letter outlining your previous research experience and reasons for applying, alongside an up-to-date CV to julien.michel@ed.ac.uk

After you have approached the project supervisor and discussed your application with them, download and complete the online EASTBIO Equality, Diversity and Inclusion survey; the survey will automatically generate a Unique Number that you should copy and paste on the relevant section of your EASTBIO Application Form.

Download and fill in the EASTBIO Application Form. You can only apply for one EASTBIO PhD project.

Send the EASTBIO Reference Form to your two academic/professional referees, and ask them to submit the references directly to Prof Julien Michel julien.michel@ed.ac.uk.

EASTBIO will conduct online interviews in early February 2024. Following the completion of the interviews, we will proceed to make PhD offers to successful candidates and we will notify candidates who were either unsuccessful, or added on to the EASTBIO reserve list. EASTBIO offers and notifications will be issued after the EASTBIO Management Group completes the selection process in March 2024.
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. See our University Initiatives website for further information. University Initiatives website.