OXFORD INTERDISCIPLINARY BIOSCIENCE
Doctoral Training Partnership

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Interdisciplinary Bioscience Studentship Advertisement – for 2022 entry

Supervisor(s) names: *please include titles (e.g. Dr., Prof.). We encourage you to also include pronouns if you are willing to do so.*	Dr Robert Beagrie[1], Dr Robert Kitchen[2] and Dr Manu Verma[2]
Department(s)/Organisations:	[1]Wellcome Trust Centre for Human Genetics, University of Oxford, UK [2]Novo Nordisk Research Centre Oxford, UK
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Project title:	**Unbiased identification of regulatory region-target gene pairs in human adipocytes.**

Background: The human genome contains a vast number of putative regulatory elements and physiological trait linked haplotypes; the majority of which lie within non-coding regions and contain several association signals and genetic variants. Prediction of cell type-specific *functional regulatory elements* and their *target genes* within trait linked haplotypes is a major challenge[1]. This complexity of regulatory region-gene pairs is driven by cell specific biochemical compatibility and/or 3D genome organisation. Focussed cell type-specific functional studies for *validating* target genes of selected regulatory regions have been limited and often lack scale[2]. What is needed are high-throughput experimental manipulations of regulatory regions, combined with genome architecture mapping (GAM)[3], in specific cell-types to map out important region/gene interactions and understand the contribution of 3D chromatin organisation.

Human white adipose tissue (WAT) is a highly dynamic metabolic/endocrine organ functioning as an energy buffer in response to nutritional, metabolic, and environmental cues[4]. Adipocytes (ADs), arising from adipose progenitors (APs), are the major constituent of WAT and their proportion and function are strongly associated with glycaemic, lipid, and anthropometric traits. Investigation of the genetic circuitry regulating this AD plasticity (*i.e.,* cell fate and function) is required to further our understanding of human adipocyte biology and its role in systemic metabolism. However, current high throughput approaches often lack specificity whilst approaches focussed on specific loci lack scale.

Project Description: This project will apply a functional genomics workflow[5] leveraging advances in human cellular models, CRISPR, automation, high content imaging, and transcriptomics to perturb cell specific *candidate regulatory regions* (CREs) and identify altered target genes at scale. Briefly, the prospective student will establish a high throughput genome engineering workflow involving the generation of human adipocyte models, CRISPR, and automation protocols for experimental manipulation of selected *candidate cis-regulatory elements* (cCREs) at scale. In addition, the student

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will generate a GAM dataset to investigate the contribution of 3D genome organisation in regulating human adipocyte-specific regulatory region-target gene pairs. Finally, these multiple genomic features will be utilised to train machine-learning models to *predict* additional adipocyte-specific regulatory region-target gene pairs.

Impact: Successful completion of this project will improve our understanding of the role of non-coding regulatory elements in human adipocyte gene regulation. Additionally, direct functional annotation of selected non-coding regions may also generalise and aid statistical approaches to assign gene-cCRE pairs in different cell systems. In conclusion, this project will provide multi-disciplinary research training opportunities and the novel workflows and findings from this project will be of immense interest to wider research and drug discovery communities.

References:

1. Cano-Gamez, E. & Trynka, G. From GWAS to Function: Using Functional Genomics to Identify the Mechanisms Underlying Complex Diseases. *Frontiers in Genetics* vol. 11 Preprint at https://doi.org/10.3389/fgene.2020.00424 (2020).
2. Verma, M. *et al.* TCF7L2 plays a complex role in human adipose progenitor biology, which might contribute to genetic susceptibility to type 2 diabetes. *Metabolism* 133, 155240 (2022).
3. Beagrie, R. A. *et al.* Complex multi-enhancer contacts captured by genome architecture mapping. *Nature* 543, 519–524 (2017).
4. Sakers, A., de Siqueira, M. K., Seale, P. & Villanueva, C. J. Adipose-tissue plasticity in health and disease. *Cell* vol. 185 419–446 Preprint at https://doi.org/10.1016/j.cell.2021.12.016 (2022).
5. Gasperini, M. *et al.* A Genome-wide Framework for Mapping Gene Regulation via Cellular Genetic Screens. *Cell* 176, 377-390.e19 (2019).

The functional genomics screens and machine learning model development based on the generated datasets will be performed at the Novo Nordisk Research Centre Oxford. Genome architecture mapping will be performed at the Wellcome Trust Centre for Human Genetics.

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Attributes of suitable applicants[1]: *Please note any skills or qualifications[2] you are seeking in a prospective applicant, e.g. academic background, driving licence[3], specific research skills or interests. Please consider the implications of any attribute, and the phrasing of any description of attributes with respect to recruiting the most diverse and widest possible pool of qualified applicants[4].*

Ideal candidates for this D.Phil studentship will have strong academic background (Masters or 1st or 2.1 BSc) in Systems Biology, Genetics or Molecular and Cell biology.

Organisational skills, personal drive and ability to work well with others in a multidisciplinary research setting would be desirable. Familiarity with data wrangling and analysis (R or Python), basic understanding of machine learning, human adipocyte cell culture, and CRISPR protocols are desirable. However, further training will be provided to improve one or more of these skills.

Funding notes: This project is funded for four years by the Biotechnology and Biological Sciences Research Council UKRI-BBSRC and Diamond Light Source. UKRI-BBSRC eligibility criteria apply (https://www.ukri.org/files/funding/ukri-training-grant-terms-and-conditions-guidance-pdf/). Successful students will receive a stipend of £16,062 per year.

Required text to be included in all adverts: *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 participate in the training and networking opportunities available through the DTP, including a 12-week professional internship in a non-academic setting. For further, details please visit www.biodtp.ox.ac.uk. The DTP and its associated partner organisations aim to create a community that is innovative, inclusive and collaborative, in which everyone feels valued, respected, and supported, and we encourage applications from a diverse range of qualified applicants.*

[1] Please do discriminate clearly between essential and desirable attributes. Generally, the more prescriptive you are in your applicant specification, the smaller the pool of applicants.

[2] Do allow alternative ways of meeting a criterion where relevant, for example, to be eligible for UKRI studentship funding a candidate should have an honours degree with a predicted or achieved grade of 2.1 or above, a Master's degree or substantive relevant work experience.

[3] Please take care to avoid including criteria that could directly or indirectly discriminate against individuals with certain characteristics, for example, the requirement to hold a driving licence could indirectly discriminate against disabled people, unless driving a vehicle is essential for the project. However, where relevant the selection criteria should list any physical demands or safety-critical duties and responsibilities.

[4] Using welcoming and inclusive language may substantially increase the pool of qualified applicants. For example, using the text "experience with Python would be beneficial, but there is also potential to improve your programming skills" compared to "Python skills are essential" has been reported to result in an overall increase in qualified applicants, and an increase in female applicants.

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Statement of project description approval I confirm that all parties associated with this project have seen and approved the information provided above and are willing for it to be made publically available for the purpose of recruiting a student to undertake this project. I confirm that all parties who are employed by the University of Oxford who will participate in the interview to award this studentship have completed or will complete the "Recruitment and Selection" online training course (https://edu.admin.ox.ac.uk/training) prior to participating in an interview panel[5].	
Name:	Electronic Signature:

[5] Parties who will participate in the interview process who are employed other organisations should complete recruitment and selection training available via their organisation.