GMS Programme Update June 2020

1. Overview

We are delighted that the 4-year DPhil programme in Genomic Medicine and Statistics (GMS) was successfully renewed, and in particular would like to welcome the PIs joining the programme in 2020.

We have retained the structure of a 1+3 year programme and the first year comprises a taught term followed by 2 (or sometimes 3) rotation projects. Its broad-ranging nature emphasises the interplay of lab-based experimental work, the latest genomic techniques and computational data analysis. The mixed academic background of each cohort, while challenging in some respects, helps expose each student on the programme to a mix of practical and computational work and is one of the key reasons for the success of the programme.

As genomic technology and applications have continued to develop at pace over the past 5 years, the renewal focused on the core elements of the existing programme, complemented with an expanded set of interdisciplinary areas of genomic research. These are organised into 7 themes:

- Genomic and -omic technologies (including method development, single cell genomics, imaging, model systems, CRISPR screens, genome engineering; proteomics, metabolomics, high throughput screening)
- Functional genomics (gene regulation and epigenetics)
- Genome biology (genetic variation, recombination, human history, evolution, palaeogenomics, pathogen genomes)
- Genomics of disease (Mendelian, multifactorial traits, cancer)
- Genomic analysis (bioinformatics and statistical genetics)
- From genes to clinical proof of concept (integrated drug development pipeline spanning genetic-led target discovery, structural biology, medicinal chemistry)
- Application of genomics in the clinic (rare disease diagnostics, cancer therapeutics, personalised medicine and genome therapies)

2. Progress and planning for the GMS 2020 cohort new term

Recruitment

We had 128 applications this year, an increase from 76 the previous year. We successfully recruited 7 students: Nikolas Baya; Annie Forster; Frederik Heymann Lassen; Hrushikesh Loya; Jane Pernes; Vassilena Sharlandjieva and Piotr Sliwa. Many thanks to: Dan Crouch; Calli Dendrou; Cath Green; Valentina Iotchkova and John Todd for shortlisting and interviewing, and to Isabel Schmidt for supporting the whole recruitment process.

Preparations

We are currently planning the teaching content and timetable, as well as putting together the project booklet listing all supervisors and potential projects. When students arrive in October, they have various induction sessions and taught modules in the first term before choosing their rotation projects to complete their first year.

Project booklet and PI presentations to students

The project booklet summarises the research areas of all the PIs associated with the GMS programme, and outlines potential projects on offer to students for their rotations or final DPhil project. In the first few weeks of Michaelmas term, PIs will have the opportunity to

introduce their work directly to the cohort and students will often approach PIs they are interested in pursuing a project with. Given the larger pool of supervisors on the renewed programme (>40) we are proposing to run several themed sessions this October, with a small group of PIs presenting to the students; each session will last 1.5 hours and a range of dates will be offered. More information will follow about these sessions soon to confirm availability. Please note we can also make individual arrangements if needed/preferred. A couple of examples from last year's booklet can be found at the end of this document for your information.

Teaching
A series of taught modules are delivered in the first term. They aim to provide a firm grounding in relevant topics and orienting students in the current landscape of genomic research. Key areas include genomic technology and applications, tools and statistical methods to handle and analyse genome-wide data appropriately, and genomic medicine in the clinic. A particular example of how we cover all facets and add continuity to the teaching is through the Practical Genomics module which links to a later module in Genomic Data Analysis: students are able to work with a research group to prepare samples for RNA-Seq sequencing, which are then sequenced by the Genomics facility at WHG. The data analysis module includes a mini-project where the students analyse the data they generated and discuss the biological interpretation of the results with the research group.

We have reviewed the content and delivery based on feedback from students and faculty and will make some minor adjustments to existing content and formats. We are also keen to add topics to the teaching that cover some of the new areas in the expanded programme. There will also be special themed days this year (2 per term), in the format of an overview lecture followed by a series of research talks. We would welcome input from any PIs and their postdocs to the themed days or any other aspect of the teaching. Please contact Isabel Schmidt if you would be interested in contributing - we could either slot something into the first term timetable or run one-off events in later terms.

Skills training
Research and transferrable skills training is tailored to the individual student.

Project rotations
The students have the option of taking 2-3 rotations. These start in January and each run for approximately 10 weeks. It is often the case that students start the course with a specific area already in mind for their DPhil. We encourage them to make the most of the rotation year and use it as an opportunity to experiment and explore areas outside their previous experience / comfort zones. Students are advised to make contact with the supervisors they would like to take rotation with as early as possible.

3. Student supervision and support

Formal DPhil project supervision
All students need to have a minimum of two supervisors selected from the programme's PIs. There is the possibility to have third supervisor taken from outside programme, to fit with scientific needs.

Supervisor limits
No individual may supervise more than 6 students in total at any one time. Co-supervision counts as a half, regardless of the total number of supervisors.

Thesis committee

Thesis Committees are an extension to the core supervision structure and have a purely advisory role on the student's academic work and progress and can flag any concerns. Each Committee includes a minimum two experienced academics with relevant skill sets who are not directly involved with the project or line of supervision. Committee members will also carry out the role of Assessors at Transfer and Confirmation of Status milestones.

Thesis Committees routinely meet once a year; sometimes more, depending on the student's needs. These meetings provide an opportunity for the student to take a step back and get feedback not only on their direct work but also on the bigger picture and impact of their studies as Thesis Committee members are likely to be further removed from the direct topic and bring additional expertise. Please see attached NDM Thesis Committees document for further information.

Mentorship
All students have a named mentor and this provides important source of advice and support for our students. Mentors meet the students on their first day (5th October this year) at a welcome lunch. We also arrange one-to-one meetings for each student with their mentor in the afternoon.

Mentors will act as their student's supervisor during Michaelmas term and will be responsible for submitting a supervisory reports on the Graduate Supervision Reporting System (GSR) for this period. Further information about the GSR process can be found on their webpage https://academic.admin.ox.ac.uk/graduate-supervision-reporting-gsr

Mentors continue to have the ability to submit a report each term during the supervisory submission window (or as soon as their student submits), and we would encourage them to do so. In Hilary term the first rotation supervisors are added to the GSR. In Trinity term the second rotation supervisors are added, and during the long vacation, the third.

Research culture
This is absolutely essential to our students and the future success of the programme. It was a major factor in our successful renewal and we are looking to continue to enhance this in the following ways:

Promoting a positive research culture We will promote a positive research culture through a strong sense of community and cohort effect. We aim to have an inclusive and supportive environment that puts the student first, recognises their contributions, is proactive in identifying students in difficulty for health, personal or academic reasons, and aspires to creative thinking, innovation and excellence. We actively seek and act on student feedback. We recognise the critical importance of preventing bullying and harassment. We will ensure this through a named responsible co-director (Cath Green). We will highlight the issue at induction for supervisors and students, setting expectations and being clear in our commitment. All supervisors will undertake compulsory supervisor training in preventing bullying and harassment. We will further prevent bullying and harassment by promoting an encouraging and enabling culture; and by working with Departmental responsible officers.

The GMS programme has a clear vision going forward to promote excellence in genomic science though training the next generation of leaders and innovators in this field. In this renewal we have sought to build on our success over the last 10 years, re-invigorating our course structure and recruiting to it supervisors able to offer cutting edge science and excellence in supervision. We have carefully considered how best to deliver the necessary tailored training for individual students, including specialist and general research skills, as well as transferrable skills, by maximising what we can offer within the course through our teachers and students, and by the unique graduate studies environment available in Oxford

that gives synergy and substantial added value. We will ensure access to the programme for the best students whatever their background and provide a greater emphasis on managing transitions at the start and end of the course to support students' careers, further enabled by the exciting range of internships we have established with partner organisations. We want to build on our strong research culture through training, monitoring and openness in our approach, by promoting a vibrant supportive cohort, setting clear expectations and the very highest standards in student welfare that through prevention, early recognition of problems and effective support can help ensure students maximise and deliver on their potential.

One key area that will see increased activity is EDI (Equality, Diversity and Inclusion), after a new EDI committee was recently set up at WHG; the remit includes mental health and well-being, which is already a high priority at WHG. The GMS management group will seek to integrate the Centre-wide efforts with specific actions for the GMS programme in terms of supporting existing cohorts and when recruiting in future.

We will continue to increase the flow of initiatives between the GMS programme and the wider pool of DPhil students at WHG, especially those in their first-year. For example, several sections of the GMS teaching are suitable for a wider cohort of students and we expanded the teaching groups last year to between 10 (for statistics modules) and 20 (programming and bioinformatics) attendees. Some elements remain specific to the GMS programme, both for practical reasons (e.g. numbers limited for lab sessions) and to retain uniqueness of the programme. Similarly, existing DPhil-student led activities such as journal clubs and seminars within WHG and around the Old Road Campus are added to the GMS timetable to encourage their participation and help build local support networks.

Pre-entry support
We have increased support for students between their acceptance on the programme (usually February/March) and starting in Oxford the following October. This includes sending a skills questionnaire to assess the areas of existing knowledge and design the teaching accordingly; a virtual cohort meeting during the summer to introduce them to each other and key members of the programme; making information about the teaching topics and suggested reading material available in advance.

First-year support
We built a series of GMS programme lunches into last year's timetable, and these were a very useful way to maintain regular informal contact between the cohort and others involved in the programme (through teaching, rotations etc.), including some GMS students now in their second or third year. The students have a dedicated point of contact, Isabel Schmidt (GMS programme administrator) for any specific queries or issues they encounter.

Internships
We have engaged and established knowledge and skills exchange partnerships with stakeholders who can offer internship opportunities to our students. Stakeholders include clinical partners Genomics England, Genomics Education Programme in Health Education England (HEE) and Oxford NHS Genomic Medicine Centre (NHS lab and clinical); drug discovery (Structural Genomics Consortium and Target Discovery Institute); biotech (Genomics plc) and pharma (BMS-Celgene, Vertex, Astra Zeneca and Novo Nordisk). We have agreement for exchange visits with overseas academic labs for specific skills or knowledge required for project delivery including University of Southern California (Conti) and Broad Institute (Raychaudhuri). Specific stakeholders have expressed interest in funding additional places on the programme including HEE, Celgene, Vertex and Novo Nordisk. Having reduced the overall number of programmes, Wellcome are now able to offer more financial support to each student. They have introduced transitional funding and tailored

support for students at the end of their 4 years. This support will depend on each student's specific needs at the time.

Transition funding
Wellcome have introduced a new "transition fund" which may be used flexibly to support student career transitions. The length and type of support may vary as it is to be tailored to the individual student's needs.

Website and communication
The website is crucial for attracting high-calibre students and raising the profile of the GMS programme further. It has been updated to reflect the 7 genomic themes, potential supervisors and highlights the research outputs of previous and current GMS students.

https://www.well.ox.ac.uk/work-and-study/gms-dphil-programme

Management, organisation and support.

Course director: Prof Julian Knight

Co-directors: Prof John Todd and Prof Cath Green

Course administrator: Isabel Schmidt

MSDTC administrator: Louise Samson

Teaching co-leads: Helen Lockstone and Dr Gavin Band

The above group meet regularly to plan and review all aspects of the GMS programme. They meet twice a year with a wider management committee. Project supervisors and teaching staff are invited to these meetings to hear the updates and give their input to help shape the programme. The June/July meeting is open to all supervisors linked to the programme.

For anyone interested in joining the management committee, please email Isabel Schmidt ischmidt@well.ox.ac.uk.

We welcome ideas and input for developing the programme. Please do get in touch about this.

We have set up a Microsoft Teams group to facilitate communication and collaboration between supervisors on the programme. Please email Isabel Schmidt ischmidt@well.ox.ac.uk if you would like to opt out of this.

4. Supervisor responsibilities

We ask you to accept the following duties in order to become a supervisor for the programme:

- Mandatory training for DPhil supervision at Oxford (Sciences). This is a short online course and must be completed once every three years. https://www.ctl.ox.ac.uk/online-courses
- Training in Equality Diversity and Inclusion related courses listed here https://edu.admin.ox.ac.uk/training. They cover: an overview of EDI; implicit bias; race

awareness; LGBT+ role models, mentoring and allies; mentoring schemes for BME staff; harassment and bullying training; and recruitment and selection.
- Termly supervision reporting through GSR and eVision https://academic.admin.ox.ac.uk/graduate-supervision-reporting-gsr
- Contribute to teaching (team members' contributions)
- Supervise students for rotations
- Provide a project for the booklet and for you or a senior member of your team to give a short presentation on this at the beginning of Michaelmas term
- Be willing to act as mentor
- Report outputs involving students including destination following DPhil and publications
- Update us with any changes in your circumstances that may affect your ability to supervise. Please refer to the NDM supervisor webpage for information on this https://www.ndm.ox.ac.uk/for-supervisors

5. Project booklet examples

Ben Davies

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Research Focus:
Genetically modified models represent one of the most powerful methods of functional gene analysis. The ability to introduce specific mutations into the genome enables models of human disease to be generated, facilitating insights into the pathophysiology of disease and providing a model with which therapeutic strategies and diagnostic tools can be optimized. SNPs associated with genetic disease can be interrogated using this technology in an attempt to unravel the functional significance of genetic variation, both within the coding and the non-coding genome.
The research activity of the group is focused on the development of novel methodologies for the generation of genetically modified models. In recent years, we have been exploring the use the CRISPR/Cas9 site specific nucleases, to manipulate genomic sequences in human induced pluripotent stem cells (iPS) and directly within the mouse embryo. As well as manipulating the DNA sequence directly, we are also investigating the delivery of CRISPR/Cas9-based transcription factors which can be used to perturb gene expression networks, modelling the consequence of non-coding mutations.

Project areas: physiology, cellular & molecular biology, transgenic, knock-out, knock-down, genetically modified, embryonic stem cell and animal model
Specific project proposals:
- 'Genome Editing – manipulation of stem cells by CRISPR nucleases', page 26.
- 'Re-engineering the DNA binding characteristics of a speciation gene' (in conjunction with Professor Simon Myers), page 27.

Title: Genome Editing – manipulation of stem cells by CRISPR/Cas9 nucleases

Supervisor: Dr Ben Davies

Description:
Site-specific modification of the genome represents a powerful tool to investigate the functional consequences of DNA sequence mutation and variation. Techniques, which enable specific nucleotides to be precisely modified, facilitate the generation of disease models harbouring pathogenic human mutations (Davies et al., 2017). These models can be used to explore the biological underlying the disease process and may also serve as a resource for therapeutic approaches. Genome Wide Association Studies (GWAS) and resequencing experiments are revealing sequence variants that associate with disease susceptibility. Tools enabling the experimental introduction of putative disease SNPs into the genome represent a vital validation tool to commence the functional dissection of this vast data set.

Traditional methods of gene manipulation have relied on homologous recombination between the chromosome and purpose build DNA constructs, frequently in stem cells. These cells can then be used to generate disease models or can be monitored for functional consequences, e.g. gene expression changes in vitro.

New technology has become available which allows the manipulation or editing of the genome to be achieved at high efficiency, using nucleases known as TALENs (Davies et al., 2013) or CRISPR/Cas9 (Cebrian-Serrano, 2017). Site-specific nucleases can now easily be constructed against specific genomic target sites and can be used either within stem cells or oocytes to introduce specific double strand breaks within the genome. These double strand breaks are repaired by the cellular machinery, which can lead to the introduction of mutations or (if a template is presented to the cell) the introduction of specific nucleotide changes.

Alternatively, nuclease deficient CRISPR/Cas9 can be used to recruit transcriptional control machinery to regions of non-coding DNA, lying proximal to target genes. Using these techniques, gene expression can be up- or down-regulated. Potentially, these experimentally induced subtle changes in gene expression may provide a fast and efficient means to assess a gene's contribution to a specific disease, since they more accurately model the consequence of non-coding mutation change in humans.

This project aims at examining the application of site-specific technology to achieve precise genome editing and targeted gene expression changes in model systems, and will make use of CRISPR based technologies. Enzymes will be designed against specific sequences and used to introduce disease relevant SNPs into the genome or to recruit transcriptional control machinery to promoter regions. The tools developed in this project will enable an understanding of how mutation can influence specific disease susceptibility. There would be opportunities to work with a stem cell model, or with animal models, depending on the disease focus.

The research project will thus focus on the technological aspects of achieving site specific genome modification ("genome editing"), appropriate delivery and screening methods. We will be able to take advantage of the disease relevant SNPs that have been identified within the centre as contributing to increased susceptibility to a variety of diseases, such as cancer, cardiovascular disease and diabetes and thus to explore this new technology for the generation of novel disease models. Close collaboration between our technology focussed core group and one of the disease groups within the centre is anticipated.

Training Opportunities:
- Disease models
- Molecular and cell biology skills for functional analysis
- Designing and validating site specific nucleases

- iPS and embryonic stem cell culture
- Embryo microinjection

Publications:
- B Davies, LA Brown, O Cais, et al., 2017. A point mutation in the ion conduction pore of AMPA receptor GRIA3 causes dramatically perturbed sleep patterns as well as intellectual disability. Human Molecular Genetics, ddx270
- Cebrian-Serrano A, Zha S, Hanssen L, Biggs D, Preece C, Davies B. 2017. Maternal Supply of Cas9 to Zygotes Facilitates the Efficient Generation of Site-Specific Mutant Mouse Models. PLoS One, 12 (1), pp. e0169887.
- Davies B, Davies G, Preece C, Puliyadi R, Szumska D, Bhattacharya S. 2013. Site specific mutation of the Zic2 locus by microinjection of TALEN mRNA in mouse CD1, C3H and C57BL/6J oocytes. PLoS One, 8 (3), pp. e60216.

Title: Re-engineering the DNA binding characteristics of a speciation gene

Supervisors: Dr Ben Davies, Professor Simon Myers

Description:

In most species, including humans, all genetic variation is generated by two interlinked processes: mutation, which generates new variable positions, and recombination, which randomly shuffles mutations into new combinations, which then drive genetic differences in our disease risk, are acted upon by natural selection, and provide information on our genetic ancestry. Recombination is probably why sexual reproduction exists. It is also essential for human fertility, while errors in recombination can lead to aneuploidy (e.g. trisomy 21) and diseases cause by deletions, or duplications, of large genomic segments. Remarkably, recombination differences between subspecies, alongside mutational differences, have been shown to drive infertility in hybrids, connecting these basic biological processes with the formation of new species, i.e. speciation. Why hybrid infertility occurs is still unknown, but it appears to involve failure of proper pairing - synapsis - of homologous pairs of chromosomes in meiosis.

An interdisciplinary team of researchers at the centre are working together to study recombination and these links to speciation/chromosome pairing, using diverse approaches including genome engineering, statistical genetics, microscopy and fertility measurement. Team members (in a paper [Myers et al., 2010] recently included within the top 21 achievements of WHG researchers, across the 21 years of the centre's existence) previously identified a rapidly evolving gene, PRDM9, at the heart of the recombination process in most mammals, including humans. PRDM9 positions almost all our recombination events, into specific "hotspots", by binding DNA at specific motif sites, and trimethylating nearby histones at H3K4. Now, we have generated mice carrying specific genetic manipulations at PRDM9. For example, this has revealed that humanization of the DNA binding domain of PRDM9 rescues fertility in previously sterile hybrids (Davies et al., 2016). This project will involve generating and/or analysing genome-wide ChIP-Seq datasets measuring where recombination occurs in mice carrying this and other manipulations at PRDM9. This will allow us to better understand the links between recombination, variation in PRDM9 - whose DNA-binding domain also varies among humans - and infertility and disease.

Alongside direct data generation and analysis, the project will also provide exposure to many additional research approaches, ranging from molecular cell biology and protein biochemistry, through animal models to statistical analysis of genome-wide datasets - within a unique collaboration forming an interface between experimental biology and statistical genetics.

Training Opportunities:

- Genetic modification of the genome
- ChIPseq analysis
- Analysis of genome-wide datasets
- An opportunity for hands-on experience in both wet-lab experimental biology and statistical genetics

Publications:

- Myers S, Bowden R, Tumian A, Bontrop RE, Freeman C, MacFie TS, McVean G, Donnelly P. 2010. Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. Science. 327(5967):876-9.
- Davies B, Hatton E, Altemose N, Hussin JG, Pratto F, Zhang G, Hinch AG, Moralli D et al. 2016. Reengineering the zinc fingers of PRDM9 reverses hybrid sterility in mice. Nature, 530 (7589), pp. 171-176.
- Hinch AG, Zhang G, Becker PW, Moralli D, Hinch R, Davies B, Bowden R, Donnelly P. 2019. Factors influencing meiotic recombination revealed by whole-genome sequencing of single sperm. Science, 363 (6433), pp. 1300

Cath Green

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Research focus:
Problems during DNA replication result in genome alterations, in the form of mutations and translocations. In somatic cells these can cause cancer and possibly other age-related pathologies, while in the germ line they contribute to the production of diversity. The Green lab (chromosome dynamics) takes two main approaches to investigate replication-related genome instability. Firstly we are investigating how the three-dimensional organisation of the genetic material within the nucleus influences the prevalence and the outcome of translocation events. We are developing novel approaches to monitor DNA contacts during replication, in collaboration with the high throughput genomics core. Secondly we aim to understand how protein interactions at the replication fork are utilised to regulate the co-ordination of DNA replication with DNA repair and the re-establishment of epigenetic information. To do this we use a wide range of biochemical and molecular biology approaches in vitro and tissue culture systems. Recently we identified and characterised the first reported disease-causing variant in the human replication protein PCNA, which give us insights into the importance of correct protein interactions to prevent carcinogenesis and neurodegeneration (Baple et al., JCI 2014; Green et al., Cell Cycle, 2015, Wilson et al., DNA Repair, 2017). We also work particularly closely with the cellular imaging core to measure protein interaction dynamics in live cells in real time. This enables us to monitor the recruitment of proteins to the replication fork in normal and replication stress conditions, and explain how defective replication protein function can result in genome instability.

Project areas: cancer biology and protein science & structural biology, DNA replication, epigenetics and chromosome dynamics.
Specific project proposal: 'New cell cycle regulators in human cells', page 30.

Title: New cell cycle regulators in human cells
Supervisor: Professor Cath Green

Description:
In collaboration with Prof Ross Chapman's group we are investigating previously uncharacterised proteins identified in an RNA-Seq screen to identify cell cycle regulated genes. The new genes that we are studying are likely to have roles in DNA replication and in mitotic regulation, both of which are important areas for target discovery for the cancer clinic. We are applying biochemical, genetic (e.g. CRISPR-Cas9), and state-of-the-art imaging approaches to uncover new cell biology and to investigate whether these novel genes are potential druggable targets,

In the rotation project, and extension into a DPhil, the intended aims are:
a) Generate CRISPR-Cas9 knockout cell lines and use the lentiviral system and Auxin-inducible degrons to complement the knock out lines with wildtype and mutated versions of each gene.
b) Perform phenotypic investigations (RNA-seq, ChIP-seq, interactome analysis, cell biology assays, protein-protein interaction studies) to identify cellular functions.
c) Mine existing datasets for correlations of expression with cancer incidence/prognosis.
d) Develop assays for high throughput small molecule inhibitor studies.

The project will suit a student interested in a combination of wet-lab research and bioinformatic analysis of genome wide datasets.

Background reading:
53BP1 Integrates DNA Repair and p53-Dependent Cell Fate Decisions via Distinct Mechanisms.
Cuella-Martin R, Oliveira C, Lockstone HE, Snellenberg S, Grolmusova N, Chapman JR.
Mol Cell. 2016 Oct 6;64(1):51-64. doi: 10.1016/j.molcel.2016.08.002.
PMID: 27546791

Calliope Dendrou

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Research focus:
Immune-mediated diseases (IMDs) affect ~10% of the population worldwide and pose a substantial healthcare and socioeconomic burden as they can be highly debilitating and have no cure. Currently available immunomodulatory treatments can help to alleviate symptoms, but have variable efficacy and can lead to severe side effects. Progress in identifying and characterising the genetic determinants of IMDs is helping to improve our understanding of the pathophysiological pathways that underlie these conditions, and may thus allow for the refinement of therapeutic strategies. In

parallel, advances in single-cell genomics profiling methods are increasingly facilitating gene signature characterisation of cells at the site of pathology. The main research interests of my group are to better understand the genetic predisposition and molecular and cellular mechanisms common across multiple IMDs, and to explore the functional relevance and potential clinical utility of such disease cross-comparisons.

Projects can be tailored to personal interests but will involve both a wet lab and a data analysis/bioinformatics component.

Project areas: Autoimmunity; Molecular & cellular immunology; Genetics & genomics; Functional genomics; Gene regulation; Single-cell genomics
Specific project proposals:

- 'Tyrosine kinase 2 as a genetically determined drug target against multiple immune-mediated diseases', page 28.
- 'Spatially resolved molecular and cellular profiling of inflammatory lesions', page 29.

Title: Tyrosine kinase 2 as a genetically determined drug target against multiple immune-mediated diseases

Supervisor: Dr Calliope Dendrou

Description:
Cross-trait genetic associations are common for the immune-mediated diseases (IMDs), indicating a sharing of etiological mechanisms, despite variation in the precise organs affected for each disorder. However, more systematically profiling these associations - not just between IMDs but across the broader disease phenome - is beginning to provide valuable translational insights. Given the hundreds of loci that can be associated with any single IMD, the scale and nature of cross-trait association patterns can help to pinpoint genetic variants and biological pathways to be prioritized for further investigations in a therapeutic context. For example, associations across multiple diseases can reveal targets amenable to drug repositioning approaches, whilst different directions of association for different diseases may suggest trade-offs that can inform patient stratification and that may predict potential side effects as a result of therapeutically manipulating particular biological pathways.

Based on such cross-trait analyses and investigating genetic variants with the same patterns of association, the tyrosine kinase 2 (TYK2) locus serves as an immunological 'hub' around which several other associated loci can be organized, suggesting that TYK2 functions at the centre of several different signaling pathways each implicated in different IMDs. Moreover, TYK2 has emerged as a promising drug target. The project will involve interrogating the relationship between disease-associated genetic variation and the dynamics of TYK2-dependent immune cell signalling, as well as assessing the how the genetic effect relates to the impact of a novel allosteric TYK2 inhibitor. The project will be well suited to a student interested in the combination of wet-lab research and bioinformatics/data analysis.

Training Opportunities:
The proposed project will involve: primary human cell culture, flow cytometry, confocal microscopy, single-cell RNA sequencing, ATAC-Seq, chromatin-conformation capture, ChIP-Seq, viral transduction, CRISPR-Cas9 genome engineering, and computational biology. The student will additionally receive training in scientific writing and communication through oral presentations to the scientific community at international conferences, as well as to the general public through public engagement opportunities.

Background Reading:

- Cortes A et al. (2017) Bayesian analysis of genetic association across tree-structures routine healthcare data in the UK Biobank. Nature Genetics, 49, 1311-1318.
- Dendrou CA et al. (2016) Resolving TYK2 locus genotype-to-phenotype conflict reveals therapeutic optimum for autoimmunity. Science Translational Medicine, 8, 363ra149.

Title: Spatially resolved molecular and cellular profiling of inflammatory lesions

Supervisor: Dr Calliope Dendrou

Project Overview:

Molecular profiling techniques are valuable tools for understanding cellular function in health and disease, investigating pathophysiological mechanisms, setting clinical diagnoses, monitoring disease prognosis and identifying drug targets. Recent technological advances, such as single-cell-level genomics, are helping to overcome past limitations associated with availability of only small amounts of tissue and the capacity to study only a small set of molecules at any given time. However, maximising the utility of these newer technologies requires the integration of methods that can provide different types of information, including biochemical and gene expression data, to obtain an unbiased, holistic and high-resolution view of biomolecular signatures.

The project will involve the integration of biochemical signatures derived from Fourier-transform infrared microspectroscopy with gene expression signatures derived from the application of spatial transcriptomics and single-nuclear transcriptomics techniques, using central nervous system tissue from patients with rare neuroimmunological diseases versus controls. A particular interest is in cross-correlating the biochemical and gene expression signatures in the tissue areas around the infiltrating immune cells to assess how the damage spreads from the immune lesions to the adjacent tissue.

Training Opportunities:

The proposed project will involve: microspectroscopy, single-nuclear RNA sequencing, single-nuclear ATAC-Seq, spatially resolved transcriptomics, confocal microscopy, and computational biology. The student will additionally receive training in scientific writing and communication through oral presentations to the scientific community at international conferences, as well as to the general public through public engagement opportunities.