Janet Thornton Fellowship Projects 2024

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Janet Thornton Fellowship

The Janet Thornton Fellowship, designed to support scientists who have taken a career break, was named in honour of Professor Dame Janet Thornton, former Director of the EMBL-European Bioinformatics Institute (EMBL-EBI).

The postdoctoral fellowship is aimed at getting scientists back into scientific research if they have had a career break of a minimum of 12 months. The fellowship was launched in 2014, as part of the Sanger Institute's commitment to retaining and developing talent.

Professor Dame Thornton has experienced first-hand the challenges of taking a career break and working flexibly in demanding scientific roles and raising a family.

Eligibility Criteria

The Janet Thornton Fellowship is open to scientists who:

- A minimum of 12 months break from scientific research, for any reason*
- have at least one years' postdoctoral research experience
- will be able to start within 6 months of being offered the role
- Not currently working in a scientific research role

Our Janet Thornton Postdoctoral Fellowship is aimed at those that have taken career breaks for any reason (for example, caring for dependants, ill health or if your career has been negatively impacted by COVID-19).

Application Process

The Fellowship is awarded after a competitive selection process, with applicants applying to one of the projects below. You are encouraged to make contact with the named supervisor.

Stage 1 of the Application process:

Please apply to the Janet Thornton Fellowship vacancy via our job site

Please have a copy of your current CV ready to upload

Stage 2 of the Application process:

If you meet the eligibility criteria we will invite you to complete stage 2 of the application process. Application form with a number of questions (between 1000 – 1500 words across the questions):

- Why are you interested in applying to this project outline?
- How do you think your research experience and broader contributions to the research environment will enrich your Fellowship experience at the Sanger Institute
- What academic achievements are you most proud of?
- What personal achievements are you most proud of?

Projects for 2024

Project title: Uncovering the Mechanisms of Natural Antisense Transcript (NAT) Interactions through CRISPR-Cas13 Screening
Supervisor: David Adams
Contact: da1@sanger.ac.uk

Recent analyses of large patient cohorts have identified several long non-coding RNAs (lncRNAs) with significant differences in expression levels between tumour and normal samples across cancer types. Downstream functional analyses have revealed multiple lncRNAs that regulate gene expression and post-transcriptional modification, including splicing. Alternatively spliced isoforms of lncRNAs also play distinct roles in tissue homeostasis and tumorigenesis. Furthermore, a subgroup of lncRNAs, known as antisense RNAs (asRNA), or "natural antisense transcripts" (NATs), consist of pairs of single-stranded non-coding RNAs transcribed from opposite strands of DNA, effectively creating antisense versions of one another. Few lncRNAs have been studied to elucidate their roles in oncogenesis with systematic large-scale analyses necessary to translate the growing list of cancer-associated lncRNAs into potential therapeutic targets. Cas9-based CRISPR technology disrupts genes by generating frameshifts/indels but lncRNA are tolerant to targeting via this approach. Cas13d has emerged as an alternative to Cas9, effectively silencing gene expression at the transcript level. We and others have demonstrated that Cas13d is effective in silencing lncRNAs and is compatible with single-cell analyses. In this project, we aim to identify the function of lncRNAs, including NATs, at transcript resolution using pooled and single-cell Cas13d screens in tumour derived cell lines. We will investigate the post-transcriptional mechanisms by which antisense RNA pairs regulate gene expression, hypothesizing that these interactions can be classified into distinct categories, such as synergistic or antagonistic. Additionally, downstream RNA sequencing of single cells derived from the CRISPR screen will provide a detailed understanding of isoform expression dynamics, facilitating the identification of disease-relevant isoforms. Screens in multiple cell lines will reveal broad oncogenic pathways and cancer-specific pathomechanisms.

Project title: Establishment of endometriosis lesion and menstrual fluid organoid screening platform
Supervisors: Roser Vento-Tormo, Iva Kelava
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Endometriosis is a common condition characterised by the growth of endometrial tissue outside the uterus (called "lesions"). It affects at least 10% of women of reproductive age and is accompanied by many symptoms, including pain and issues with conception. Despite the high prevalence of the disease, non-invasive diagnostic tests and efficient, well-tolerated treatments are almost completely lacking. Current

treatments are limited to surgical and/or hormone/analgesic treatment, both being associated with high morbidity and significant side-effects. Therefore, there is an urgent unmet clinical need for reliable non-invasive diagnostic tools and novel therapeutic approaches. Also, there is a lack of knowledge of the cellular origins and composition of endometrial lesions. The project is aimed to address those knowledge gaps by using single-cell multiomics data produced by our team to generate a model of endometriosis lesions derived from patients. To do so, we want to adapt current protocols to derive organoids from endometriosis lesions (see recent publication by our team in Nature Genetics) and establish co-culture conditions for a robust multilineage organoid platform. The development and validation of this system will be invaluable for identifying new therapeutic targets and performing drug-screenings. We also want to make use of menstrual fluid as a rich, non-invasive cellular source for organoid derivation and profiling.

In our work we combine state-of-the art genomics technologies - single cell transcriptomics, multiomics and spatial transcriptomics to determine molecular pathways involved in development and disease, with a strong focus on gynæcological disorders. We welcome applicants with interest in organoids and complex co-culture methods, but also those with computational methods development background. The current team is composed of experts in computational methods, organoid techniques, histology and tissue processing. We are also fostering strong connections with endometriosis clinics as part of our worldwide multicentre biorepository.

Project title: Large-scale mutagenesis of human and other proteins for clinical variant interpretation, machine learning and biological design
Supervisors: Ben Lehner
Contact: bl11@sanger.ac.uk

We are generating reference atlases of how changes in DNA sequence – alone and in combination – alter the activities, interactions and regulation of proteins and RNAs. The resulting data will allow clinicians to better diagnose disease and understand disease mechanisms and serve as well calibrated data to train predictive and generative models for biological design and to understand molecular evolution. Potential projects could focus on any of these aspects, from large-scale data generation, through protein family-focused studies to machine learning and engineering.

https://www.sanger.ac.uk/group/lehner-group/

https://www.sanger.ac.uk/person/lehner-ben/

Project title: Comparative cell type biology for important species as part of the Biodiversity Cell Atlas
Supervisors: Mara Lawniczak and Arnau Sebe-Pedros
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Through the Darwin Tree of Life Project led out of the UK, more than 1500 UK species already have reference genomes and many more are underway. The availability of so many reference genomes presents an opportunity to dig deeper into the biology of sequenced organisms. Another budding project – the Biodiversity Cell Atlas – has the ambition to expand our understanding of cellular diversity through creating cell atlases across the animal phylogeny. This postdoctoral fellowship project will focus on building and comparatively integrating cell atlases for

10 organisms from the same taxon group. The work will entail R&D in the lab to ensure robust sample handling and dissociation methodology that leads to high quality cell atlases and then this will transition into a comparative project, studying conservation and innovation in cell type expression programs across species. While the taxon group of focus can be flexible for the right candidate (e.g. if you are keen to do this project on a totally different group of animals, please get in touch to discuss feasibility), it needs to have some global health and/or evolutionary importance. We suggest that the project could focus on flies because flies are incredibly diverse with over 100,000 described species and they are easy to access and rear. Flies can be important pollinators (e.g. Syrphidæ) or disease transmitters (e.g. Culicidæ) and of course Drosophila melanogaster is an important model organism and already has a cell atlas that can be used as a reference to help annotate cell types in other species. The fellow working on this project would also have a great opportunity to contribute in various ways to the wider Biodiversity Cell Atlas initiative.

Tree of Life
Supervisor: Mark Blaxter
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The diversity of life is reflected in the diversity of the genomes that - through rules that we are still only starting to understand - generate both form and function.

The Blaxter lab has wide interests across eukaryotic groups, largely focussed on exploring the dynamics of genome evolution, and the links between genome structure and biological diversity. Working closely with colleagues in the Darwin Tree of Life, Aquatic Symbiosis Genomics, European Reference Genome Atlas and others, we have access to an unprecedented richness of high quality genomic data.

We would be excited to host a Janet Thornton Fellow working in, and would be happy to discuss projects in, any one of a number of our areas of interest:
The Genomics of Symbiosis. Much of the natural world lives in mutualistic symbiosis with other organisms, and many of these associations are phylogenetically ancient. This ancient association gives time for the genomes of the cooperating species to adapt to each other. Parasites are also symbionts of a kind, but instead of offering benefits to their hosts they impact its fitness in favour of their own. As Richard Dawkins has pointed out, organisms in close association may transition between mutualism and parasitism based on how shared their “desiderata” are. For example, a parasite needs the host to survive long enough for the production of additional parasites, but is uninterested, or opposes, nutritional effort put into host reproduction. How dœs mutualist symbiosis shape genome evolution? How do parasites shape their hosts’ genomes? [In passing, in Tree of Life we are generating reference genomes from wild-caught individuals, and frequently find they are “infected” with other organisms, mostly bacteria. The study of these “cobionts” is a project in itself.]

The Phylogenomics of Animals. While much of the core structure of the phylogenetic tree of life has been well resolved in the last two decades of intensive molecular work, there is much still to be learnt from the close detail of the emerging tree. We know that ancient polyploidy has been resolved in many groups, with, for example, our own human genome showing the “fossils” of two rounds of whole genome duplication. We know that hybridisation can result in rapid speciation amongst modern organisms, and there is no reason to think that this was not also true in the past. The histories of genes within a genome may thus differ from each other, and the quality and taxonomic breadth of the

genomes being generated in Tree of Life and elsewhere offers an emergent opportunity to explore the fine-grained detail of genome evolution. Several approaches, including large scale gene orthology mapping, ancestral linkage group inference and analysis, and whole genome alignment across major taxa can all be used to explore patterns and processes in genome content and structure evolution.

From genome to function via single cells. Each cell "reads" its genome to produce a functioning response to the environment, and in multicellular organisms the cells cooperate to produce an individual. The advent of high-throughput single cell (or single nucleus) approaches to measuring gene expression activity, and other genome properties such as accessible chromatin, offers new opportunities in understanding how each species genome is mobilised to generate the particular phenotypes we can associate with species. Tree of Life is part of the nascent Biodiversity Cell Atlas, an international collaboration applying single cell approaches to understand cell type diversity and dynamics across Eukaryota. We would welcome the opportunity to host a fellow working in this area, using the genomes generated in Tree of Life as a platform to explore the developmental and evolutionary dynamics of cell types in diverse organisms.

Project title: Developing machine learning models to predict human genetic interactions in different cellular contexts
Supervisor: Mathew Garnett
Contact: mg12@sanger.ac.uk

Seminal genetic interaction studies in model organisms (such as yeast and drosophila) have provided knowledge on mechanistic connections between genes. However, it has not yet been possible to comprehensively map genetic interactions (GI) in a human cell due to technical limitations, representing a major gap in our knowledge, particularly since many genes, biological processes and regulatory mechanisms are not evolutionarily conserved, including those involved in disease. Furthermore, the lack of large-scale systematic screening of human GIs limits systems-level approaches, such as machine learning (ML), for accurate GI prediction. Using an innovative ultra-scale CRISPR/Cas9 perturbation platform, we are assembling the first GI map of all possible gene-gene interactions in a human cell. Whilst this is a unique and rich dataset of unprecedented scale, it is not able to elucidate how GIs vary across environmental and cellular contexts, necessitating new powerful approaches to predict GIs in different contexts. This computational project proposes to leverage the unparalleled richness of the human GI map, along with other smaller scale GI datasets available in our group, to develop ML models to accurately predict GIs in untested cellular contexts, providing deeper insights into gene regulatory mechanisms. Importantly, due to the collaborative nature of computational and wet-lab science in our group, focused ML model predictions can be validated experimentally through further CRISPR/Cas9 screening. The overall aim would be to make our GI prediction model generalisable across a range of different environmental and disease contexts through iterative cycles of GI mapping and ML model improvement.

Project title: Characterising genetic diversity across the Tree of Life
Supervisor: Kamil Jaron and Joana Meier
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The levels of genetic diversity vary immensely between species across the tree of life. From negligible levels in frequently selfing organisms to very high levels in species with large and stable populations. At least, that is what we are told in the population genetics classes. However, the observed differences of genetic diversity do not correspond well with differences in population size, which is referred to as the Lewontin paradox [1]. Empirical evidence reveals differences in genetic diversity of two orders of magnitude among animal orders [2]. Also within an order, there is no strong correlation between genetic diversity and proxies of population size as seen in moths and butterflies (order Lepidoptera) [3]. Other factors must thus contribute strongly to genetic diversity differences across the tree of life.

This project will utilise high-quality reference genomes created within the Tree of Life Programme, Wellcome Sanger Institute, with a special focus on British species sequenced within the Darwin Tree of Life project. The aim is to provide a high quality characterisation of genetic diversity in these genomes, capturing both nucleotide diversity as well as structural variant diversity (inversions, deletions/insertions, transposable elements) and larger-scale rearrangements like polymorphic chromosomal fusions. We will find predictors of genetic diversity by correlating the genetic diversity with different factors such as phylogenetic lineage, size of the propagule, demography, ploidy, repetitiveness, genome size, etc. This project will reveal patterns of genetic variation at an unprecedented genomic resolution and taxonomic scale.

References

1. Ellegren & Galtier (2016) Nature Review Genetics https://www.nature.com/articles/nrg.2016.58
2. Romiguier et al. (2014) Nature https://www.nature.com/articles/nature13685
3. MacKintosh et al. (2019) Nature Communications https://www.nature.com/articles/s41467-019-11308-4

Project title: Host-parasite interactions during soil-transmitted helminth infections

Supervisor: Stephen Doyle
Contact: sd21@sanger.ac.uk

Soil-transmitted helminths are a group of gastrointestinal parasites that collectively infect over 1.5 billion people worldwide. Infections can cause significant disease - of which children and women of reproductive age and pregnant women are most vulnerable - and contribute to the cycle of poverty in many low- and middle-income countries. As a gastrointestinal pathogen, soil-transmitted helminths directly impact and are impacted by interactions with the microbial community of the host. These interactions likely play a role in the establishment, persistence, and infection load of soil-transmitted helminths. Importantly, these interactions may play a role in the response of soil-transmitted helminths to drug treatment. Although there are an increasing number of studies focused on characterising human microbiomes, there is a significant underrepresentation of microbiomes from Africa relative to Western countries. Therefore, no existing datasets are suitable to address questions relevant to STH and host-microbiome interactions in soil-transmitted helminth-endemic countries.

The Doyle lab is conducting a large-scale genetics study of soil-transmitted helminths in Africa, focusing on Trichuris trichiura and treatment response to albendazole and fixed-dose coformulation of albendazole and ivermectin. This study will use whole-genome sequencing performed at the Wellcome Sanger Institute to identify genetic variants associated with treatment response. Sampling both parasites and microbiomes from patients will enable new insights into host-parasite interactions and treatment responses, with the overall aim of improving the health and well-being of people living in soil-transmitted helminth-endemic countries.

Equality, Diversity and Inclusion

Our global reputation for excellence is strengthened by our commitment to developing and maintaining a positive, fair and healthy working environment – our Equality, Diversity and Inclusion (EDI) Programme is about valuing our people and supporting them to be their best.Our leaders play a key role in nurturing a positive and inclusive culture where everyone can thrive and diversity is celebrated.

We have developed an ambitious programme of activity that drives organisational culture change, empowers our leadership and ensures that equity and inclusion principles are embedded across all of our processes – from recruitment, promotion, reward, to accessing career development opportunities

In order to further reinforce our commitment to being a fully inclusive workplace, we became Stonewall Diversity Champions in 2020 to support LGBT+ inclusion. We are also signatories of the Race at Work Charter and Disability Confident scheme and are working towards these principles.

Our broader Wellcome Genome Campus-wide EDI initiatives include our LGBT+, Race Equity, Neurodiversity and Parent and Carers' Staff Engagement Networks. These bring people together, raise awareness, provide specific and relevant support and development opportunities and are safe spaces for people to be themselves.

We are committed to providing equal opportunities for everyone, regardless of their background. We acknowledge that people from certain backgrounds are under-represented

in our sector and we are committed to doing what we can to correct this. We positively encourage applications from candidates regardless of sex, race, disability, age, sexual orientation, gender reassignment, religion or belief, marital status, or pregnancy and maternity status.

For more information about EDI at GRL see our Equality in Science Programme.

> Our strength lies in the diversity of our people, skills and ideas."