**FutureNeuro Summer Internships 2024 in Brain Research**

**We are inviting applications from high-achieving undergraduates planning to pursue a research career in the field of neuroscience. The paid summer placements will equip the applicant with practical research experience and an insight into neurological research.**

***Deadline for application is 10th May 2024.***

**(Application Form and Project list below)**

**FutureNeuro** is a Science Foundation Ireland (SFI) Research Centre to develop new technologies and solutions for the treatment, diagnosis, and monitoring of neurological, psychiatric and neurodevelopmental diseases. Our unique multi-disciplinary preclinical and clinical research addresses the major challenges in improving how we diagnose neurological disorders including the implementation of genomics, the development of next-generation precision and disease-modifying treatments and the rapid progress of data science to glean powerful insights from clinical datasets.

**FutureNeuro is expanding and in 2024 and 2025 we will be recruiting the best PhD candidates and Post-doctoral researchers and equipping them with multidisciplinary skills for a career in academic, clinical and industry-related research. Our paid Summer Internship for 5 high-achieving science undergraduates is designed for students interested in pursuing a research career in FutureNeuro and neuroscience . The candidates will be supervised by an investigator from the FutureNeuro network. See below for the projects on offer and eligibility criteria.**

**About Us :** Hosted by RCSI, our research network combines integrated expertise from eight leading universities (TCD, UCD, DCU, MU, SETU and UG) and a national research-active clinical network. Building on our strong focus on epilepsy and motor neurone disease, we leverage cross-disease expertise to deliver advances into other neurological diseases (e.g. Parkinson’s, MS), psychiatry and neurodevelopmental disorders and the serious co-morbid aspects of these diseases. We work with world-leading companies to address mutually-identified scientific challenges and public engagement and patient involvement is core to our mission. <http://www.futureneurocentre.ie/>

The projects on offer are:

**1: Developing approaches to target CHD2 deficiency in CHD23-related neurodevelopmental disorder**

**2: The (AB)C of Finding Short Tandem Repeats in SRS data: A Rapid Review of STR Search Tools and Approaches for Study Design**

**3: Validation of novel ALS endophenotypes through combinatorial serum biomarker analysis incorporating both microRNAs and tiRNAs**

**4: Understanding the mechanisms behind effective pharmaceuticals**

**5: Making a path through noise: distinguishing the real signals in gene systems analysis**

**6: Characterising distinct psychiatric correlates of habit expression**

**7: HLA Adverse Drug Reaction risk loci frequencies from a sample of world-wide ancestry in the UK Biobank**

**8: Determining the frequency of rare disease associated variation in individuals of Irish ancestry**

**9: Precision medicine for epilepsy - cell type-specific targeting of the purinergic P2X7 receptor in the brain**

**10: The CINDI project**

**See Appendix I for project descriptions and supervisors.**

**Eligibility and Application Process for Summer Internship**

* Applicants will be selected based on academic performance and their application form.
* Candidates must have completed 3rd or 4th year of an undergraduate life-science degree (e.g. physiology, biomedical, biochemistry, genetics etc.).
* Each candidate will be required to submit a short application and CV.
* The candidate must demonstrate an interest in pursuing a research career (e.g. PhD).

**Practicalities of FutureNeuro Summer Internship**

* The Summer Internship with run for 6 to 8-weeks (June – August 2024). Final dates will be agreed with FutureNeuro supervisor.
* The location of the Summer Internship will be agreed with the supervisor but will most likely be at the FutureNeuro supervisor’s academic institution or a hybrid model.
* Garda vetting may be required.
* A stipend of €250 per week will be provided by FutureNeuro (RCSI).

**Deadlines**

**Completed application forms and a short CV should be emailed to** **louisethomas@rcsi.ie** **by 10 am on 10th May 2024.**

**All successful applicants will be notified by 24th May. Unfortunately, only successful candidates will be contacted.**

We look forward to receiving your application.

Bridget Doyle

FutureNeuro Centre Manager

Email: bridgetdoyle@rcsi.ie

**FutureNeuro Summer Internship 2024**

**Application Form (please delete previous pages and Appendix)**

**Your Selected Project - See Appendix 1 for project details**

**Project Name:**

**Your Personal Details**

**Name:**

**Address:**

**Telephone:**

**Email:**

**Your Academic Details:**

**Institution:**

**Faculty:**

**Degree:**

**Current year of study:**

**Student number:**

**Examination Results:**

|  |
| --- |
|  **Year 1** |
| **Subjects** |  |
| **Results Overall** |  |
| **Year 2** |
| **Subjects** |  |
| **Results Overall** |  |
| **Year 3 (if applicable)** |
| **Subjects** |  |
| **Results Overall** |  |
| **Year 4 (if applicable)** |
| **Subjects** |  |
| **Results Overall** |  |

**Academic Supervisor (who can be contacted as referee)**

**Name:**

**Email address:**

**FutureNeuro Summer Internship 2024**

**Application Form (continued)**

**Reason for Project Selection (max 100 words)**

**What do you hope to achieve from the Summer Internship? (max 100 words)**

**What are your career goals? (max 100 words)**

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**Please submit application along with a short CV to:**

Louise Thomas

FutureNeuro Admin Officer

Email: louisethomas@rcsi.ie

**Appendix I**

**Summer Internship Project List**

**Project #1: Developing approaches to target CHD2 deficiency in CHD23-related neurodevelopmental disorder**

**Supervisor name and location:** Dr Gary Brennan, Conway Institute, University College Dublin.

**Project Outline:** CHD2-related developmental disorder is a genetic disorder which emerges during childhood. It is a seizure disorder caused by genetic variants in the gene which codes for CHd2 and may be characterized by drug-resistant epilepsy, developmental delay, intellectual disability and autism. This project will use human brain cells and apply various molecular approaches to increase expression of CHD2 in cells. By understanding the mechanisms which regulate CHD2 it is hoped novel therapies can be developed to promote CHD2 expression from the non-mutated allele thus restoring normal CHD2 activity.

**Objectives:** The aim of the project is to uncover the relationship between microRNAs and CHD2 and test whether manipulating microRNA-CHD2 interactions can increase CHD2 levels in human brain cells.

**Methodology:** The student will learn cell culture techniques and design microRNA-targeting antisense oligonucleotides. They will then attempt to knockdown individual microRNAs using ASOs and measure expression of CHD2 using standard biochemical techniques.

**Expected outcomes / Potential to form basis of PhD application:** We expect to identify novel

microRNA-CHD2 interactions. This data can form the basis of a PhD/IRC application by then exploring the identified interaction in patient-derived cerebral organoids which we currently grow in the lab.

**Project #2: The (AB)C of Finding Short Tandem Repeats in SRS data: A Rapid Review of STR Search Tools and Approaches for Study Design.**

**Supervisor/Location:** Dr Lorna Lopez with Jake Kennedy (FN PhD Student), Maynooth University.

**Project Outline**: Short tandem repeats (STR) are an understudied source of genetic variation and are poised to contribute additive, de-novo, and epigenetic effects in complex disease. Limitations of short read sequencing (SRS) systematically obscure their identification, an issue prevalent even in SRS reference builds. A range of tools now exist to identify and characterize STRs in SRS data, however there is little guidance available on best practice. This dry lab project will address the literature gap and inform researchers on considerations for study design in complex disease.

**Objectives**: To inform on several questions relevant to study design.

1. Principles of tool methodology.
2. Sensitivity and Specificity in exploratory and nonexploratory applications.
3. Limitations of analyses in different databases and reference builds.

**Methodology**: To provide a framework for this review we will co-opt a structured approach like NCCMT’s Rapid Review Guidebook. The student will be trained in systematic literature search techniques and develop work towards publication.

**Expected Outcomes** / **Potential to form basis of PhD application**: The successful applicant will be immersed in a busy research environment and acquire fundamental research skills in academic writing and research presentation such as methodological literature searches and poster design, outreach activities and PPI session. They will learn foundational background in research data management and open-source publication such as FAIR principles. These skills are applicable in genomics research and so will facilitate the student for their future research endeavors.

**Project #3: Validation of novel ALS endophenotypes through combinatorial serum biomarker analysis incorporating both microRNAs and tiRNAs**

**Supervisor Name and location**: Prof Jochen Prehn (RCSI), Prof Orla Hardiman (TCD/BH)

**Project Outline:** Identifying diagnostic ALS biomarkers and patient stratification tools is a prime focus of FN. We performed small RNA sequencing on n= 423 samples from ALS patients, ALS ‘mimics’, and Controls. We identified microRNAs and tiRNAs that were differentially expressed between controls, ALS mimics and ALS. Through unsupervised clustering of these DE non-coding RNAs we identified 4 distinct ALS endophenotypes, with one subtype nearly exclusively consisting of slow ALS progressors. In this project, the summer student will employ PCR-based multiplexing and data analysis of a set of combinatorial biomarkers to validate these novel ALS endophenotypes, using the newly established FN ALS cohort.

**Objectives:**

1. Development of TaqMan assays for newly identified, differentially expressed small non-coding RNA.

2. Analysis of small non coding RNAs in serum samples from n=200 ALS patients collected in Beaumont Hospital at diagnosis. Ethics 19/68 in place.

3. Data analysis: Validation of ALS endophenotypes and integration with genetic (C9ORF72 repeat expansions) and clinical data.

**Methodology:**

1. A Random Forest analysis identified a reduced combinatorial biomarker signature of n=11 small non coding RNA which will be prioritised and for which TaqMan assays will be developed.

2. TaqMan-based analysis of DE small non-coding RNA in serum samples collected at diagnosis at BH from n=200 ALS patients.

3. Data analysis including cluster analysis and Receiver Operating Curve analysis to validate and distinguish ALS endophenotypes.

**Expected Outcomes / Potential to form basis of PhD / IRC application**:

1. Validation of a novel, serum-based endophenotype signature in sporadic ALS patients which represent the vast majority of ALS patients.

2. Delivery of stratification tools for clinical trials, in particular the early identification of slowly progressing ALS patients.

3. Novel IP and commercialisation opportunities.

4. Training at the interface of molecular biology, clinical neurology, and data analysis.

5. Through the novelty of this approach and the developed analytical and clinical infrastructure, very strong potential to form a basis for a PhD / ‘IRC’ application.

**Project #4: Understanding the mechanisms behind effective pharmaceuticals**

**Supervisor Name and location:** Daniela Tropea, Trinity Translational Medicine Institute (TCD)

**Project Outline:** Insulin-like growth factor 1 (IGF1) and its active peptide: Glypromate (GPE) have been reported to be potential therapeutics for a variety of brain disorders: monogenic neuropsychiatric disorders, autism, Parkinson disease and others. One of such compounds: Trofenitide has been approved by FDA as the first treatment for a rare condition: Rett Syndrome. Despite the high therapeutic value, the mechanisms of action of this class of compounds remain unclear.

**Objectives:** The goal of this project is to clarify the main effects induced by the treatment of IGF1 and GPE at a cellular level. through two main objectives:

1. Compare the effects of IGF1 and GPE administration on the expression level of molecular markers for cell activity (PCREB, PAKT) and metabolism (TOMM 20, Glut4).
2. Clarify the interaction between GPE and NMDA receptors in the activation of intracellular pathways.

**Methodology:** We will perform experiments in cell cultures and will use immunocytochemistry and PCR.

**Expected Outcomes / Potential to form basis of PhD / IRC application:** Since we have already preliminary data showing that IGF1 and GPE act through different mechanisms, we believe that the outcomes of this project will produce significant insights that will support applications for PhD Scholarships such as those from Irish Research Council (IRC).

**Project #5: Making a path through noise: distinguishing the real signals in gene systems analysis.**

**Supervisor Name and location:** Daniela Tropea, Trinity Translational Medicine Institute (TCD)

**Project Outline:** The advance in the techniques of gene sequencing facilitated the realization of many genetic and transcriptional studies where lists of candidate genes are generated, and they are thought to be important as signature of disease or treatment. To clarify the biological pathways and mechanisms that are associated to these many genes, software is present- and freely available- to associate each list of genes to molecular mechanisms or pathways and offer the possibility to better interpret the results of the experiment. However, some bias present in the datasets amplify the noise of such analysis allowing for the presence of several false positive results in the outcome of the study.

**Objectives:** The goal of this project is to test a new approach designed to improve the signal/noise data in this process.

**Methodology:** We will retrieve data from existing literature, and we will reprocess them using the software for the identification of false positives. For this project is essential the knowledge of R programming.

**Expected Outcomes / Potential to form basis of PhD / IRC application:** Our preliminary data show that the approach is helpful in molecular studies and can be used to correct the outcome of new and existing studies. This project will produce significant insights applicable in many molecular studies. The outcomes will support applications for PhD Scholarships such as those from Irish Research Council (IRC).

**Project #6: Characterising distinct psychiatric correlates of habit expression**

**Supervisor Name and location:** Prof. Claire Gillan, Trinity College Dublin

**Project Outline:** Performing rigid, repetitive behaviours (RB) are characteristic of several psychiatric diagnoses from more motoric acts such as skin-picking and hair-pulling to complex compulsions such as excessive hand washing and binges. Despite huge clinical importance, the latent mechanism of action underlying these behaviours remains somewhat elusive. We aim to quantify individual and clinical differences related to the two systems of action control: one that supports stimulus-response (SR) learning, and one that supports goal-directed (GD) control, to test whether they are associated with similar, yet dissociable, presentations of repetitive behaviour i.e., motoric acts and complex compulsions.

**Objectives:** We aim to test if two variations of repetitive behaviours i.e., “lower order” repetitive motor acts vs “higher order” complex compulsions, are associated with dissociable cognitive mechanisms: stimulus-response (SR) and goal-directed (GDC), respectively.

**Methodology:** Individuals will complete a gamified habit-learning task and a gamified reinforcement learning task, delivered through the lab’s smartphone app Neureka, to quantify differences in SR and GD respectively. They will also self-report on a battery of clinical questionnaires related to disorders including repetitive behaviours.

**Expected Outcomes / Potential to form basis of PhD / IRC application:** Using novel gamified and remote applications of cognitive and self-report assessments allows us to gather richer data from considerably larger numbers than traditional methods. The candidate will gain expertise in data management, data cleaning, and data analysis of large datasets. The project could also form a basis for a PhD exploring tailored treatments/interventions based on an patient’s precise action-control deficits.

**Project #7: HLA Adverse Drug Reaction risk loci frequencies from a sample of world-wide ancestry in the UK Biobank.**

**Supervisor Name and location:** Prof. Gianpiero Cavalleri, RCSI; Dr Edmund Gilbert, RCSI

**Project Outline:** This study aims to improve our understanding of how genetics can be used to reduce adverse reactions to pharmaceuticals, and to spread such benefit across different ethnic groups.

Adverse drug reactions (ADRs) are a major health concern, in terms of their impact on the individual, their cost to the healthcare systems and that they can potentially lead to hospitalisation and even death. The Human Leukocyte Antigen (HLA) genes represent an important factor in many ADRs, as they help regulate the adaptive immune system and are highly genetically variable. Multiple genetic variants across the HLA have been identified as clinically valuable predictors of immune-mediated adverse drug reactions. However, most studies of such pharmacogenetic variants have been conducted in populations of European-like ancestry. It is well appreciated that genetic variation can vary widely in frequency, across different ancestries. The UK Biobank (UKB) is a large, diverse study of over 500,000 people resident in the UK. A characterisation of pharmacogenetic HLA alleles in the UK Biobank (UBK), stratified by communities of specific genetically-inferred ancestry may identify specific global communities at an unappreciated high risk ADRs that could be prevented through pharmacogenomic tests.

**Objectives:**

1. Identify a set of HLA alleles that are risk loci for ADRs.
2. Identify genetic communities within the UKB at risk of ADR due to HLA risk carrier rates.
3. Explore whether HLA risk carriers have a phenotypic signature and investigate its use in predicting novel HLA risk loci.

**Methodology:** This project will utilise the UKB, a genomic dataset with deep phenotyping and HLA imputed alleles. Using approximately 70,000 individuals with non-UK “world-wide ancestry” the student will investigate carriers rates in world-wide communities and explore the use of signature detection using tools such as nonnegative matrix factorisation (NMF).

**Expected Outcomes / Potential to form basis of PhD / IRC application:** This project is well suited to a student interested in population/human genetics as applied to the clinic. It is computer based. It involves a preliminary investigation of the utility of large genomic datasets with deep phenotype data to explore and extend current knowledge on ADR HLA risk loci. As well as provide immediate results of risk loci carrier rates in specific communities within a diverse UK sample, this project has potential future avenues of investigation. Providing a model to predict novel risk loci from generating a HLA-ADR “risk profile” from NMF or machine learning (ML) approaches may lead to further investigations, as would be extending this work to other large “biobank-scale” datasets such as All of US.

**Project #8: Determining the frequency of rare disease associated variation in individuals of Irish ancestry.**

**Supervisor Name and location:** Prof. Gianpiero Cavalleri, RCSI; Dr. Laura Whelan, RCSI

**Project Outline:** Rare diseases, characterized by their complexity, chronicity, and multi-systemic nature, are defined as affecting approximately 5 in 10,000 individuals. However, they can be considered collectively common with approximately 6% of the Irish population having a rare disease during their lifetime[[1]](#footnote-1). Challenges in accurately diagnosing rare diseases in Ireland stem from factors such as limited utilization of data standards, absence of a unique patient identifier, and fragmented datasets, potentially leading to underestimations of the true prevalence of disease[[2]](#footnote-2). Determining the allele frequency of recessive disease-causing genetic variation among individuals of Irish descent is crucial for enhancing our comprehension of these diseases in the Irish population.

**Objectives:**

* To create a catalogue of recessive genetic diseases present in the Irish population at an appreciable frequency.
* To create a list of known disease-causing variants for these recessive genes.
* To determine the frequency of these variants in a community of Irish-descent individuals present in the UK-Biobank.

**Methodology:** This study proposes a “genotyping-first” methodology; A review of existing literature will be undertaken to compile a list of the most prevalent rare diseases and associated pathogenic variation in Ireland. Subsequently, pathogenic variation in genes implicated in these diseases will be catalogued. The allele frequency of each identified variant will then be determined among individuals of Irish ancestry utilizing data from the UK BioBank dataset.

**Expected Outcomes / Potential to form basis of PhD / IRC application:** This project offers a unique opportunity to engage with cutting-edge genomic research. The student who joins this project will gain valuable skills in data analysis, bioinformatics and DNA variant interpretation. This experience provides a solid foundation for future research endeavours in rare disease and acquired skills will be applicable to careers in research and clinical genetics. This project would be suited to a student interested in clinical/rare disease genomics and who has an affinity for or interest in working with DNA sequence data. This is a computational project, with limited or no wet-lab work.

**Project #9: Precision medicine for epilepsy - cell type-specific targeting of the purinergic P2X7 receptor in the brain**

**Supervisor Name and location:** Dr Tobias Engel, Department of Physiology, RCSI

**Project Outline:** Anti-seizure medications (ASMs) remain the frontline treatment for epilepsy although 30% of patients do not respond to treatment. Critically, ASMs have no impact upon the underlying causes, may exacerbate co-morbidities and can cause adverse side-effects**1**. There is a need for the identification of new druggable targets with a different mechanism of action and with drugs being effective in drug-refractory patients and with a disease-modifying potential.

Extracellular ATP increases rapidly under pathological conditions (*e.g*. seizure) where it functions as signalling molecule activating specific purinergic P2X receptors (P2XRs) including the P2X7R. While data have demonstrated anti-convulsive and, importantly, anti-epileptogenic potential of targeting P2X7Rs during acute seizures and epilepsy**2-5**, what P2X7R-dependent pathways contribute to seizures and what are the cell type-specific contributions of P2X7R to seizures and epilepsy remain to be determined.

Oligodendrocytes play a crucial role in supporting and insulating nerve fibers through the formation of myelin sheaths. Emerging evidence suggest an involvement of oligodendrocytes in various neurological diseases, including epilepsy**6**. What role the P2X7R has on oligodendrocytes during epilepsy and whether its function on this cell type contributes to seizures and epilepsy has not been investigated to date.

**Objectives:**

1. Use tissue from pre-clinical animal models of epilepsy and patients to determine the cell type specific expression profile of proteins involved in myelination.

2. Analyse sequencing datasets from P2X7R knock-out mice to identify specific pathways altered during epilepsy and involved in myelination.

3. Apply MRI analysis in the setting of epilepsy and how to detect white matter (myelination) changes.

**Methodology:** The student will use basic laboratory techniques such as Western blotting, PCR and immunostaining. In addition, the student will learn how to perform MRI analysis and how to apply MRI analysis in the setting of epilepsy and how to detect white matter (myelination) changes.

**Expected Outcomes / Potential to form basis of PhD / IRC application:**

1. Learn basic essential laboratory skills

2. Learn how to analyse big datasets and apply this to disease models

3. Learn how to present data via assisting and presenting data at weekly lab and department meetings

4. Opportunity to apply for future funding (e.g. PhD positions). The student will be closely supervised at a day-to-day basis – support includes 2 PhD students and two postdoctoral researchers including weekly meetings with the PI.

**1**Thijs (2019), *Lancet*, PMID:30686584; **2**Engel (2012) *FASEB J* PMID:22198387 **3**Jimenez-Pacheco (2016) *J Neurosci* PMID:27251615 **4**Amhaoul (2016) *Neuropharmacology* PMID: 26775823 **5**Beamer (2022) *Br J Pharmacol* PMID:34962289; **6**Barateiro (2016) *Curr Pharm Des* PMID:26635271

**Project #10: The CINDI project**

**Supervisor Name and location:** Dr. Susan Byrne, CHI Crumlin and FutureNeuro RCSI

**Project Outline:** The CINDI register (**C**ollaboration for **I**nnovation in Ge**n**omic **D**isorders in **I**reland) is a cloud-based research register within Children’s health Ireland and supported by FutureNeuro, RCSI. The aim of this register is to enable rapid identification of children with a known neurogenetic condition, should a clinical trial or precision therapy become available. In addition, it allows re-analysis of exome data or variants of unknown significance (VUS) in undiagnosed patients. Children within the registry will be followed longitudinally. May be of interest to students with an interest in neurology/paediatrics/genetics/epidemiology.

**Objectives:** Primary objectives are i) review all cases with a diagnosis to see if eligible for active research/trial and ii) VUS re-analysis. The student researcher will also work with Dr Byrne and her team to recruit patients to the register, gather clinical data, attend research clinics and input data.

**Methodology:** Learn research methods with respect to study recruitment, patient phenotyping/genotype correlation, interpretation of genetic variants, chart review, database techniques and data entry. The study will be based on site in the neurology department in CHI at Crumlin and Tallaght. The student will have the opportunity to present their work.

**Expected Outcomes / Potential to form basis of PhD / IRC application:** This summer project will assess the utility of the first year of the CINDI registry. There are multiple opportunities for PhD/IRC/Academic Intern track applications as the CINDI registry forms the basis for i) longitudinal cohort follow up for patients with specific genotype (e.g SCN1A associated disorders) or phenotype (e.g Infantile Spasms), and ii) allows access to an undiagnosed cohort of patients with multi-omic data available for re-analysis.

1. https://www.nature.com/articles/s41431-022-01144-4 [↑](#footnote-ref-1)
2. https://rdi.ie/wp-content/uploads/2023/04/Rare-diseases-deserve-equity.pdf [↑](#footnote-ref-2)