## HRCI-HRB 2024 awards

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### INNEACH: Intergenerational Programmes to enhance social connectivity for people living with dementia

Principal Investigator: Catherine Houghton

Partner Charity: The Alzheimer Society of Ireland

Award amount: €199,550 (€112,667 HRB funding; €86,884 Partner charity)

Lay summary

Intergenerational programmes are formal activities for bringing generations together in a meaningful way. They enhance social connectedness for people living with dementia and help young people to communicate better with people living with dementia. While intergenerational programmes are currently available in Ireland, there is a lack of research into their development, process, or outcomes. The aim of this project is to identify the key components needed to develop a dementia inclusive intergenerational programme in Ireland that will enhance social connectivity and quality of life (QoL) for people living with dementia; generate empathy and understanding in young people; and identify the barriers and facilitators to intergenerational programme delivery. This will be achieved through three work packages:

1. A qualitative evidence synthesis exploring the views and perspectives of staff, caregivers, and family members of intergenerational programmes inclusive of people living with dementia. This will add to the evidence of a previous review exploring the views of young people and people living with dementia.
2. A qualitative process evaluation to identify and examine pre-existing intergenerational programmes in Ireland. We will identify current programmes available in Ireland, that are inclusive of people with dementia, and using developed and agreed criteria select one for in-depth examination.
3. Building on the finding of the first two work packages, a co creation team to develop, or adapt and existing, inclusive intergenerational programme will be established. This team will include people with dementia and young people and other partners\*.

Our project team will include PPI (Public & Patient Involvement) co-applicants who will advise and contribute to the appropriateness of our research processes across the three work packages. At project completion we will have a co-created, evidence informed, bespoke intergenerational programme ready for pilot testing in a future feasibility study and subsequent definitive trial to test impact on social connectedness and QoL.

\*we use the term partners rather than stakeholders

### Optimising Therapeutic Agents to Treat Multiple Sulfatase Deficiency by Combining DNA Encoded Chemical Libraries and Fragments

Principal Investigator: Dr Matthais Baud

Partner charity: Multiple Sulfatase Deficiency Action Foundation

Award amount: €164,546 (€130,965 HRB funding; €33,581 Partner charity)

Lay summary

This project focuses on optimising small molecules that stabilize the FGE protein, as pharmacological agents for therapeutic intervention of MSD. It has previously been shown that MSD is caused by SUMF1 missense mutations, resulting in unstable FGE with low catalytic functionality. Our therapeutic strategy is based on the rationale that small molecules potently binding at the surface of FGE mutants will act as pharmacological chaperones, stabilising the protein and rescuing its catalytic activity towards sulfatase substrates.

In earlier work (unpublished) we have identified/validated dozens of unoptimized ligands of FGE using 1) biophysical and crystallographic screening of ~ 3500 fragments; 2) DNA encoded libraries technology (DELT) for screening ~ 11 billion lead size compounds (Roche, Basel, Switzerland).

Here, we are delineating our strategy for optimising these hits into highly potent ligands that could be developed into sought drugs. A key focus is on medicinal chemistry, building on biophysical and structural data accumulated in recent years. This will involve:

1. the structure- based design of novel high-affinity molecules, by exploring “growing”, “merging” and “linking” approaches on structurally validated (i.e. crystal structures of protein-ligand complexes) hits from past fragment and DELT screens, supported by computational modelling;
2. the chemical synthesis and purification of the designed libraries of molecules;
3. assessment of their binding potency (Kd) and ability to stabilise FGE using in vitro biophysical/biochemical assays; and
4. evaluating the therapeutic effect of most promising in vitro candidates in MSD-derived cells.

This project brings together the synergistic expertise of the applicants spanning across complementary disciplines, including synthetic medicinal chemistry, biophysics, biochemistry, computational studies, molecular/structural/cell biology and clinical sciences. In a long- standing and well-established collaboration we showed that FGE is potentially druggable and successfully identified many promising hits. Reaping the benefits of our previous work, we will now optimize our hits into drug-like leads.

### Exploring Innate Immune Pathways in Photoreceptors in Retinal Degenerative Disease

Principal investigator Sarah Doyle

Partner charity: Fighting Blindness

Award amount: €344,986 (€194,992 HRB funding; €149,994 Partner charity)

Lay summary

Retinal degeneration (RD) is a characteristic of inherited retinopathy and age-related macular degeneration and can lead to severe visual impairment and eventual blindness. There are a wide range of factors that can initiate retinal degeneration, but ultimately the endpoint is photoreceptor cell death. Identifying unifying pro-death or pro-survival mechanisms in these diseases has potential to offer global therapeutic approaches for facilitating protection of visual function across multiple diseases.

Stressed and dying cells can trigger immune reactions leading to pathological consequences that are often perpetuating in nature. In the retina we see this in the migration of microglia towards the photoreceptor outer nuclear layer and subretinal space, areas devoid of immune cells in healthy tissue. In a variety of animal models of RD it appears that inhibiting or slowing migration of immune cells to the photoreceptors coincides with preservation of photoreceptor cell numbers and prolonged visual function. To date, immune-related research in the retina has focused mainly on microglia and infiltrating mononuclear cells. The innate immune capacity of retinal neurons, distinct from that of immune cells, remains to be explored in RD representing a substantial knowledge gap.

In this proposal we will characterize innate immune Pattern Recognition Receptor (PRR)-signalling in human induced pluripotent stem cell hiPSC–derived photoreceptor precursor cells (PPCs), and iPSC–derived retinal organoids (ROs). Our preliminary data leads us to hypothesize that PRRs are engaged in photoreceptors in response to cellular stress, resulting in activation of gene signatures that attract and activate microglia/myeloid cells. It is possible that photoreceptor immune signalling could be an early modifiable factor in the initiating stages of retinal disease attracting microglia/myeloid cells toward the outer retina driving a cycle of pathogenic inflammatory signalling. Data generated has potential to provide new gene-agnostic therapeutic targets to slow the progression of blindness across multiple retinal degenerative diseases.

### Exploration of gene agnostic therapeutic approaches for ocular disorders modulating mitochondrial dysfunction

Principal Investigator: Professor G Jane Farrar

Partner charity: Fighting Blindness

Award amount: €345,000 (€195,000 HRB funding; €150,000 Partner charity(s) )

Lay summary

Inherited retinal degenerations (IRDs), such as retinitis pigmentosa and multifactorial ocular diseases, such as AMD represent the most frequent cause of visual impairment in the developed world. For example, in Ireland, approximately 300,000 people are affected by these conditions. While the genetic cause is known for many of the ~300 forms of IRDs and in principle could be treated by individual gene therapies, this approach may not be feasible for many IRDs. Multifactorial diseases are influenced by multiple genetic and environmental risk factors, and therefore may not be readily amenable to targeted gene therapies.

Advances in understanding the pathomechanisms of ocular diseases has revealed common cellular pathways of disease that are shared between many forms of IRDs and multifactorial ocular diseases. Such pathways include oxidative stress, mitochondrial dysfunction and metabolic dysregulation, inflammation, among others. Targeting these pathways in a gene- agnostic (gene-independent) fashion enables broad applicability for multiple ocular conditions including multifactorial diseases, very rare IRDs and those with unresolved genetic causes.

The aim of this study is to explore novel gene-agnostic therapies focused on enhancing mitochondrial function in retinal cells for the treatment of both IRDs and common ocular diseases. We previously demonstrated significant benefit in a variety of AMD and glaucoma murine and cellular models with an AAV-Ndi1 gene therapy. We now propose to use AAV- Ndi1 in two murine models of IRDs. Additionally, modulation of mitochondrial biogenesis with an optimised AAVPGC-1alpha in cell (including iPSC-derived RPE from AMD patients) and retinal organoid (from IRD patients) models, as well as, in three mouse models of AMD and IRDs is another strategy proposed in this application. While our main focus is to identify candidate gene therapies with high efficacy and broad applicability, we also plan to interrogate the therapeutic mechanisms of some of the proposed candidate therapies.

### ARMOR: tAilored peRsonalised Medicine fOr gastric canceR

Principal investigator: Prof Jacintha O'Sullivan

Partner charity: Breakthrough Cancer Research

Award amount: €344,850 (€194,853 HRB funding; €149,997 Partner charity)

Lay summary

Gastric cancer (GC) has a poor overall survival at 5 years. More recently, the incidence levels in patients under 50 years is also rapidly rising. A significant proportion of patients have little to no response to neoadjuvant treatment with curative intent. There is an urgent need to improve treatment options and overcome treatment resistance. In this translational project, we will use a personalised approach to understand resistance to tailor more effective treatments using novel machine learning algorithms and patient-derived organoid models for drug testing. This is an international collaboration bringing expertise together from Trinity St. James’s Cancer Institute, Technical University Dresden, Germany, and with Vivan Therapeutics, UK. We hypothesise that Artificial Intelligence (AI) machine learning tools will identify chemotherapy-refractory patients at diagnosis. In collaboration with the Technical University Dresden, combining radiology, histology, and other clinical data, this multimodal AL model will integrate multiple data types to generate a novel algorithm for treatment resistance. The development of patterns of treatment resistance will also be identified through performing genomic data assessments. In collaboration with Vivan therapeutics, this data will be examined against their library of avatars and treatment recommendations will be given to test in our generated gastric cancer patient organoids. Molecular subtypes of gastric cancer will also be assessed using immunohistochemistry for mismatch repair proteins / Claudin 18.2 / FGFR2b / PD-L1 CPS score & HER2 to inform treatment testing. Using this data, new combination treatments will be tested using patient-derived organoid models. These novel models will guide personalised treatment options tailored to each gastric cancer patient. The impact of this work will allow the introduction of more effective systemic anti-cancer treatments which will have a positive impact on management and improve outcomes for gastric cancer patients with dismal survival rates.

### Development of a Personalised Near Patient (PNP) Allogeneic NK-Cell Immunotherapy (PNP-NKimunnoT) for Platinum Resistant High-Grade Serous Ovarian Cancer

Principal investigator: Dr Sharon O’Toole

Partner charity: Breakthrough Cancer Research

Award amount: €344,817 (€194,818 HRB funding; €149,999 Partner charity)

Lay summary

High-grade serous ovarian cancer (HGSC) comprising cancers of the ovary, fallopian tube, and peritoneum, is the most common and aggressive form of epithelial ovarian cancer with a dismal 5-year survival rate of 28%.

Unfortunately, even with surgery, cytotoxic, and maintenance therapies, most patients relapse, and some develop platinum-resistant disease resulting in a median survival of 12-15 months.

Natural killer (NK) cells are crucial anti-cancer immune cells and their lower prevalence in ovarian tumours is associated with poorer prognosis. NK cell therapies are emerging as an adept alternative to T cell therapies and their lack of requirement for antigen specificity places them as excellent candidates for an off-the-shelf approach to cellular therapy. It is well established that HGSC exhibits a ‘cold’ or ‘immune-excluded’ phenotype and this can be influenced by their chemokine profiles. Engineering an NK cell therapy to home towards the chemokine profiles of HGSC tumours presents an opportunity to improve their infiltration of such tumours and offers a novel treatment option for HGSC patients with platinum-resistant disease.

Using primary patient material together with cutting-edge molecular cell engineering and xenograft models we aim to develop novel tumour-informed, near-patient immunotherapeutic approaches through the following:

1. Retrospectively characterise the NK cell receptor ligand (activation and inhibitory) and chemokine profiles of HGSC to inform NK cell therapy design.
2. Prospectively characterise NK cell phenotypes and function in blood, and tumour and correlate to the soluble profiles detected in the retrospective screen.
3. Generate highly cytotoxic NK cell therapy and engineer to home towards HGSC tumours, based on chemokine profile of platinum-resistant tumours.
4. Evaluate engineered tumour homing engineered-NK therapy using an established platinum resistant orthotopic xenograft mouse model of HGSC.

Ultimately, this study aims to improve treatment options for women with platinum resistant HGSC.

### Hepato-ProMet: Proteomic assay of metabolic progression from steatosis to hepatobiliary cancer development

Principal Investigator: David J. Hughes

Partner charity: Breakthrough Cancer Research

Award amount: €258,328 (€144,843 HRB funding; €113,486 Partner charity)

Lay summary

Obesity, metabolic dysfunction, and hepatic steatosis are dominant drivers of increasing hepatobiliary cancer (HBC) incidence. Preclinical studies have demonstrated that the High-density lipoprotein (HDL) proteome mirrors the liver proteome in health and disease transition. Here, we propose that early metabolic liver disease and cancer can be distinguished by a novel, targeted proteomic assay ‘MetHealth’ developed at UCD (University College Dublin) that enables blood measurements of >80 HDL-derived proteins known to be associated with liver and metabolic dysfunction. We will assess associations between these HDL protein signatures with liver diseases and HBC using existing data and biospecimens from well-phenotyped French and Irish clinical studies including patients with metabolic dysfunction-associated steatotic liver disease [MASLD], metabolic dysfunction-associated steatohepatitis [MASH], liver cancers (230 cases/230 controls) and an HBC case-control study nested within the European Prospective Investigation into Cancer (EPIC) cohort (515 HBC cases, 515 controls with pre-diagnostic data and biospecimen collections). These will also be correlated with proteomic assays from a matched subset of 70 MASH/MASLD (n=70) disease and HBC (n=50) tumour tissue samples. The HDL proteome will be isolated from plasma or tissue by a novel solid-phase extraction method and assayed by mass spectrometry (MS) using targeted and discovery MS respectively in UCD.

Multivariable adjusted logistic regression models will be used to assess associations (odds ratios (OR), 95% confidence intervals (CI), and tests for linear trends) between metabolic liver disease and HBC (plus anatomical subsites) risk and individual plus combined peptide concentrations, including mediation by obesity and dietary/lifestyle data. Hepato-ProMet will be a large, unique study combining powerful prospective and patient cohort resources with an innovative Irish-developed diagnostic technology. The findings will provide robust information on how novel proteomic biomarkers of metabolic dysfunction may identify and potentially differentiate metabolic liver disease and HBC risk, thereby enhancing public cancer prevention policy, cancer diagnosis, and patient risk stratification.

### Evaluate the protective effect of Astaxanthin for the treatment for nephropathic cystinosis in a cystinotic rat model

Principal Investigator: Minnie Sarwal

Partner charity: Cystinosis Ireland

Award amount: €344,204 (€194,550 HRB funding; €149,654 Partner charity)

Lay summary

Nephropathic/infantile cystinosis, characterized by the development of renal Fanconi syndrome and glomerular dysfunction, results in end-stage renal disease (ESRD) by 10 years of age, extendable to the second decade of life with cystine depletion therapy, Cysteamine. Nevertheless, persistent Fanconi and progressive renal failure remains a reality for these individuals, despite robust adherence with cystine depletion therapies. In this proposal, we seek to greatly improve the treatment of cystinosis by advancing a more potent combination therapy based on cysteamine and Astaxanthin (ATX). Previously we showed that ATP6V0A1 plays a crucial role in cystinosis-associated renal pathology and among other antioxidants, ATX specifically upregulated ATP6V0A1, improved autophagosome turnover (or reduce autophagy) and mitochondrial integrity. This proposal is the required next step, where we will study the effect of ATX on renal Fanconi in Ctns-/- rat model to clarify ATX’s utility in clinical settings. In this preclinical study, we will test if the treatment of our Ctns-/- rats with a combination therapy of Cysteamine and ATX will be more renal-protective than cysteamine treatment alone. This work will lay the groundwork for moving combination treatment, Cysteamine and ATX, into clinical trials.

### Sustained delivery of cysteamine prodrugs from nanobarrier contact lenses

Principal Investigator: Professor Anuj Chauhan

Partney charity: Cystinosis Ireland

Award amount: €344,204 (€194,550 HRB funding; €149,654 Partner charity)

Lay summary

Cysteamine eye drops are utilized for treating the ocular complications of cystinosis. While the eye-drop based therapy is effective, it suffers from potential problems related to drug stability and compliance. The cysteamine eye drop formulation (CystaranTM) is required to be kept frozen at temperatures < -15 oC and after thawing it has a maximum shelf life of a week, even under refrigerated conditions, due to oxidation into an inactive form. A more severe problem with the eye drops based cysteamine therapy is the potential for poor compliance due to the high frequency of eye drops needed to treat the disease effectively. We will address each of these limitations by developing a contact lens (Cystalens) that will be designed for sustained release of drug over 8 hours to mimic the current delivery but in a more patient friendly way.

Since the drug cysteamine is prone to oxidation, we will design Cystalens to deliver a cysteamine prodrug, which will be hydrolyzed in the eye to release cysteamine. Contact lenses have been proposed in the past as optimal devices for drug delivery but, a crippling factor has been the difficulty in delivering drugs for an extended period without altering the properties of lenses. We solve this problem by an innovative approach of dispersing nanobarriers in contact lenses to allow extended release of drugs from the lenses, without impacting any critical property. We have already developed a vitamin E loaded contact lens for delivering cysteamine and conducted preliminary safety study in rabbits.

These results are promising but drug oxidation remain an issue. This proposal is focused on designing contact lenses for sustained release of prodrugs and pharmacokinetic studies measuring drug concentrations in the eye to demonstrate the prodrug can be delivered and that the prodrug is hydrolyzed inside the eye to release cysteamine.

### Reducing SSc-ILD Progression - Targeting the effects of the pulmonary microenvironment

Principal Investigator: Bettina C Schock

Partner charity: Irish Thoracic Society

Award amount: €114,999 (€64,999 HRB funding; €50,000 Partner charity(s) )

Lay summary

Systemic sclerosis (SSc) is a devastating auto-immune disease, in which a high proportion of patients (40%) develop clinically significant lung fibrosis (SSc-ILD). Early onset and premature mortality of SSc-ILD place a vast social burden on patients and their families. Annual treatment costs (over £10k) and early retirement (over 40%), contribute to the huge economic burden to patients, healthcare systems and society. Despite some improvement in the treatment of autoimmune diseases, poor outcomes from lung complication remain a challenge and advances in SSc-ILD management are lacking. There are still limited therapeutic options leaving patients with high disease-related morbidity, healthcare utilization, and mortality, strongly implicating an unmet need for further research.

However, SSc-ILD research is significantly hindered by reduced accessibility to lung fibroblasts and disease relevant models. To overcome these limitations, we established a novel pre-clinical model of peripheral-blood-derived induced pluripotent stem cell (iPSC) differentiated fibroblasts.

We recently described the disease specific inflammation and the lung specific microenvironment for SSc-ILD, which is pro-inflammatory and pro-fibrotic on fibroblasts. We propose here that pharmacologically targeting the SSc-ILD disease specific microenvironment will reduce inflammation and progressive fibrosis in SSc-ILD. Using our patient-derived disease model, we will:

1. Characterise the fibrogenic and inflammatory effect of the microenvironment in SSc-ILD.
2. Identify antifibrotic and immunomodulatory therapies for SSc-ILD through drug repurposing to target the effects of the microenvironment.

Disease-specific gene signatures from SSc-ILD fibroblasts stimulated with the microenvironment will be applied to statistically significant connection map (sscMap), to identify candidate drugs that can be repurposed to manage SSc-ILD. Drug repurposing accelerates the drug development pipeline so that new treatments come to the clinic faster than through conventional drug discovery.

Finally, our collaboration between Northern Ireland, the Republic of Ireland and our patient partners in research will bring direct benefits to all patients on the island.

### Restful Nights Happy Days: Promoting Healthy Sleep and Wellbeing Practices Among New Parents in Ireland

Principal Investigator: Anna Donnla O'Hagan

Partner charity: The Rotunda Foundation

Award amount: €227,736 (€128,593 HRB funding; €99,143 Partner charity)

Lay summary

Sleep loss and postpartum fatigue are regarded as some of the most prevalent challenges during the transition into parenthood. Depression, anxiety, stress, poor mood, and less effective parenting behaviours are strongly linked with the severity of postpartum fatigue and sleep loss. Traditionally, the research has tended to focus on mothers, however, fathers also experience similar levels of sleep loss and fatigue during the early parenting period. Whilst disrupted sleep and tiredness are often anticipated, new parents are largely under-prepared for it. Given that fatigue can impact parents’ functioning, it is essential to develop interventions to aid first-time parents in managing and dealing with fatigue and exhaustion during the postpartum period.

This two-study research project aims to increase knowledge and education of positive sleep health and wellbeing practices which in turn will enhance sleep quality and feelings of wellbeing and reduce feelings of tiredness and fatigue during the postpartum period (i.e., up to 6 months postpartum) among first-time parents in Ireland. Guided by the Medical Research Council framework for developing a complex intervention, firstly a qualitative study design will be conducted to identify perceptions, experiences, and attitudes to sleep, fatigue, and wellbeing during the postpartum period among first-time parents and expectant parents. In addition, relevant stakeholders (e.g., HSE (Public Health Nurses), Rotunda Hospital Parent Education, Family Resource Centres) will be asked to give their views on best formats and methods to educate, assist, and inform first-time parents on sleep loss, fatigue, and tiredness during the postpartum period.

Following this, the project will design, implement, and evaluate the effectiveness of a bespoke evidence-based intervention to educate first-time parents on positive sleep health and wellbeing practices in the first 6 months postpartum. Parents’ voice will be central at all stages of this research process in order to maximise impact of the research.

### Glycosylation related changes in Multiple Myeloma and T cell Immunity (GlycoiMMuniTy)

Principal Investigator: Michael O’Dwyer

Partner charity: Irish Cancer Society

Award amount: €344,755 (€194,783 HRB funding; €149,972 Partner charity)

Lay summary

MM is Multiple Myeloma (MM) is a malignancy of plasma cells that remains incurable despite many recent advances in treatment options. Aberrant hypersialylation is a feature of many cancers, including MM. Via pleiotropic mechanisms, which include engagement of inhibitory receptors on immune cells by sialylated Siglec ligands, hypersialylated MM cells can induce immune suppression within the bone marrow (BM) microenvironment and elevated expression of genes implicated in Siglec ligand synthesis are associated with inferior outcome, even with intensive Daratumumab based induction and transplant approaches. Recent evidence also suggests an important role for sialylation of stromal cells in contributing to this immune suppression. Together, hypersialylation of MM cells and BM stroma could be an important factor in resistance to treatment with T cell redirected therapies, such as bispecific antibodies.

We aim to test this hypothesis by evaluating the in-vitro sensitivity of MM cells to killing by bispecific T cell engaging antibodies in the presence of treatments designed to selectively remove sialic acids from the surface of MM and/or BM stromal cells. This will include samples from patients who have progressed on treatment with these antibodies. We aim to further assess the translational relevance of our findings, including an analysis of transcriptomic data from the ongoing MajesTEC-4 study. In particular, we aim to assess the prognostic relevance of genes known to be involved in sialic acid biosynthesis and generation of Siglec ligands.

Finally, as a pilot study we aim to explore the value of spatial multiplex imaging in bone marrows from MM patients treated with bispecific antibodies, focusing on interactions and identity of cell types expressing Siglec ligands and their receptors, respectively. Understanding how sialylation in the MM TME is regulated and functions to enhance immunosuppression could uncover novel immune checkpoints to reactivate T cell anti-tumor immunity.