MRC National Mouse Genetics Network

Invited Applicant Summaries for the MRC National Mouse Genetics Network – Full cluster proposals 2021 Call.

Addressing the clinical need to understand and treat age-related multimorbidity	Age-related multimorbidity (two or more chronic diseases) is responsible for over 50% of GP consultations and expected to rise. Currently, each disease is treated individually leading to polypharmacy, increased adverse effects, and reduced efficacy. New cost-effective ways to prevent multimorbidity are required to ensure sustainable healthcare costs. Clinical evidence suggests that the presence of one disease accelerates the onset of others with ageing being a key risk factor. The EU consortium MouseAGE has identified that a lack of animal models of multimorbidity in the context of an ageing physiology and the tendency to study each disease in isolation are barriers to developing new interventions. At present, mouse models reproduce characteristics of single diseases and largely involve young mice. This does not allow for the study of the interaction between diseases and/or drugs and the impact of ageing on their development and trajectories. We propose the formation of an interdisciplinary group to make use of artificial intelligence and patient data to drive the development and full characterization of complex age-appropriate models of multimorbidity. These models will improve the understanding of the commonality of biological mechanisms between diseases and will act as more reliable tools to test new cost-effective interventions.	Lead: Professor Ilaria Bellantuono Professor in Musculoskeletal Ageing Co-Director of The Healthy Lifespan Institute (HELSI) Healthy Lifespan Institute & MRC Versus Arthritis Centre for Integrated Research into Musculoskeletal Ageing (CIMA) Department of Oncology and Metabolism The School of Medicine. The University of Sheffield Contact: Dr Paul K Potter Group Leader Diseases Mechanisms and Ageing Department of Biological and Medical Sciences Faculty of Health and Life Sciences Oxford Brookes University ppotter@brookes.ac.uk
Infectious disease cluster	Globalisation has greatly contributed to the increased risk of further viral pandemics and the rise of antibiotic-resistant microbes among the human population. Thus, there is a major imperative to understand the clinical relevance of infection in health and disease and establish how host-derived parameters of infection influence clinical outcome in cancer and immune-mediated diseases. Our cluster brings together established infection biologists, immunologists, and pathologists across the 4 nations of the UK to develop new models of disease. Our remit is to address the shortfalls in current infection biology research to generate novel discoveries relevant to the diagnosis, stratification, and treatment of infections affecting global health. Our key objectives over the 5-year programme are: (1) To decipher the key contributing factors that influence patient clinical outcomes by applying a large-scale 'omic' approach to clinically relevant infection models. Leveraging the power of mouse outbred lines, and high-resolution phenotyping technologies we will embark on a large screen of infection studies with known clinical virulent pathogen isolates. All relevant samples and data from the ensuing screen will generate a database that will available to other researchers. When possible, we will connect this mouse data to data from human infection cohorts, and the UK Biobank. (2) Complete a humanisation of the mouse innate signalling system to dissect the host recognition of infections, and how human pathogens may interfere with this pathway in tractable models of disease. An entire pipeline of models will be developed to collectively replace key innate signalling and inflammasome molecules with their human orthologues. This approach further benefiting studies of endogenous innate sensing ligand commonly associated with cancer and immune-mediated diseases, and vaccine development This collective approach will overcome some of the current limitations to investigate human-pathogen interactions. In addition, significant findings in Objective 1 (eg SNPs) will feed into the pipeline of Objective 2. Collectively, this programme will shed light into the infection biology of human bacteria, fungi, and virus pathogens at an unprecedented scale. This information shall be the foundation of new therapeutics based on targeting protective host responses.	Lead: Professor Jose Bengoechea (Chair in Molecular Microbiology, Queen's University Belfast, School of Medicine, Dentistry and Biomedical Sciences), Director of Wellcome-Wolfson Institute for Experimental Medicine Contact: Dr Adrien Kissenpfennig (Reader in Molecular and Cellular Biology, Queen's University Belfast, School of Medicine, Dentistry and Biomedical Sciences), Deputy Director of Wellcome-Wolfson Institute for Experimental Medicine a.kissenpfennig@qub.ac.uk.
Using complex state of the art mouse models of cancer to improve the understanding and treatment of human cancer	Of all disease areas, cancer has one of the worst rates for converting preclinical leads into successful new therapies. The genomic sequencing of difficult to treat cancers such as pancreatic cancer, hepatocellular carcinoma, and metastatic colorectal cancer has yielded fewer successfully actionable mutations than expected. Furthermore, the biggest breakthrough in cancer therapeutics this decade, the use of immune checkpoint inhibitors, is limited by the inability to predict which cancer patients will respond. Therefore, the key challenge is to develop a preclinical platform that will allow us to better understand the biology underpinning the major cancer types, generate novel targets, test therapeutics and ultimately predict therapeutic outcomes. Importantly, the members of the cancer cluster have generated a powerful range of novel complex models of cancers over the past decade and these are now ready to employ in this cancer cluster and within the larger NMG Network. Key for this cluster is cross comparison of these diverse models, improving disease positioning with the human disease, and their use in preclinical testing. Further, refining the models and developing novel strategies (in harmonization with NMGN expertise) to model target inhibition to more accurately align with future drug discovery efforts will be performed.	Co-Lead: Professor Louis Chesler Professor of Paediatric Cancer Biology, Head, ICR Centre for Paedeatric Oncology Experimental Medicine, The Institute of Cancer Research, London, SW7 3RP Co-Lead and contact: Professor Karen Blyth Professor of In Vivo Cancer Biology University of Glasgow, CRUK Beatson Institute, Garscube Estate, Bearsden, Glasgow G61 1BD Karen.Blyth@glasgow.ac.uk

Engineering of complex alleles	Mutations associated with human disease can be engineered into the equivalent genes in mice, and the resulting genetically modified mice provide important insights into disease mechanism. Furthermore, these mouse models of human disease have considerable utility for preclinical testing of therapeutic strategies in vivo and can help the development of new diagnostic tools. To date, most disease mutations explored using mouse models are restricted to mutations which affect the DNA that encodes proteins. Investigations into genetic variation in humans over the last decade, however, have revealed that mutations and variation in non-protein-coding DNA sequences and the overall structure of human genes play an important role in defining disease and disease-risk. Significant differences exist between mouse and human in these non-coding sequences and overall gene structure. Consequently, new technologies are required to allow more sophisticated modelling of human gene pathology in the mouse. Our cluster will address this unmet need, providing technologies and methodologies for engineering complete human genes and chromosomal segments into the mouse, either into analogous positions on mouse chromosomes or on freely segregating artificial chromosomes. The technology and the resulting models will assist in our understanding of disease and the development of new therapies.	Lead: Professor Benjamin Davies Group Leader, Head of Genome Engineering Facility, Wellcome Centre for Human Genetics, University of Oxford, OX3 7BN ben.davies@well.ox.ac.uk
Sound and Vision	Progressive loss of vision and hearing are major contributors to age-related deterioration of quality of life, impacting on social interactions, mental health and cognition. They are a major burden on the UK economy and are largely untreatable. Beyond general age-related decline, specific genetic changes can lead to accelerated degenerative diseases of the eye and ear. Genomic sequencing has facilitated the rapid identification of many genes associated with degenerative disease, but the molecular and physiological mechanisms by which these diseases progress are not clear. Tissue-specific gene expression and splicing patterns mean these pathologies cannot be studied in cell lines. The mouse represents an excellent model for investigating mechanisms leading to degenerative disorders of the eye and ear and for exploring therapeutic interventions. The accessibility of these two sensory organs also lends itself to non-invasive longitudinal phenotyping. This mouse network cluster proposes to focus on mouse models of progressive human retinal and corneal pathologies and age-related hearing loss, with the aim of improved understanding of disease processes and identifying molecular pathways along which degeneration progresses. These may result in identification of potential therapeutic targets. Phenotypic assays developed by the cluster will aid detection of impaired sensory function in other disease models.	Lead: Dr Toby Hurd Group Leader, MRC Human Genetics Unit, IGMM, University of Edinburgh, EH4 2XU Toby.Hurd@igmm.ed.ac.uk
Modalities for Understanding, Recording and Integrating Data Across Early life (MURIDAE)	Your childhood shapes your future adult life. From conception through adolescence and to early adulhood, key developmental milestones are influenced by a wide range of factors; some are inherited, while others stem from physical and/or social environmental factors. For neuropsychiatric disorders, it is well established that early life is critical as three-quarters of mental health problems emerge before the age of 24. Yet major clinical and scientific challenges remain: to determine exactly when brain development is perturbed early in life, why it can manifest into such debilitating behavioural outcomes, and how modelling the underlying pathological mechanisms can be harnessed therapeutically. In the MURIDAE Cluster, we will address these important challenges by using mouse models to study fully characterise these critical time-windows. First, we will establish new, integrated approaches for studying the early postnatal period in the mouse with experts in rodent developmental and behavioural neuroscience. Using the latest clinical discoveries, novel models of neuropsychiatric disorders will be generated and studied on this platform, focusing on selected genes and environmental manipulations directed by our collaborative team. Our goal is to better understand the shared mechanisms that underlie neuropsychiatric disorders and define novel, critical intervention points during early life that will improve clinical outcomes.	Lead: Professor Anthony Isles Professor, MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University IslesAR1@cardiff.ac.uk
Novel tools for modelling normal and perturbed haematopoiesis	Haematopoiesis is a finely tuned process, producing trillions of new blood cells daily. Dysregulation leads to a wide array of haematological diseases including bone marrow failure and leukaemia. Despite generating detailed molecular profiles of individual blood forming cells at unprecedented resolution and comprehensively mapping genetic drivers in numerous haematological diseases, we lack effective tools to map and manipulate key cellular subsets involved in normal and stressed haematopoiesis which would provide fundamental insight into disease aetiology and potential intervention strategies. Our cluster of world-leading experts in developmental and malignant haematopoiesis, the haematopoietic niche, and oligogenic mouse modelling will develop new tools to revolutionise how we study and manipulate haematopoietic/immune-cell function for clinical benefit. Building on our extensive transcriptomic datasets from normal, post-infection and pre-leukaemic cells, we will work with the Mary Lyon Centre to develop next-generation mouse models, harnessing restricted intersectional recombinase gene expression to precisely map and manipulate haematopoietic cells. These approaches will support fundamental breakthroughs in haematopoiesis and facilitate production of new models with genetic manipulations (e.g., deletions, translocations, reporters) restricted to highly defined cell populations with temporal regulation. This collaborative network will also involve cross-institutional model-sharing and standardisation, and catalyse disease model development in other fields.	Lead: Dr. David Kent Reader, Department of Biology, York Biomedical Research Institute, University of York david.kent@york.ac.uk

Congenital Anatomical Anomalies: patient-centred modeling of gene function	Approximately 1 in 20 babies, equating to 8 million each year, are born with serious anatomical anomalies. These disorders are the leading cause of infant mortality in developed countries, and worldwide, 300,000 children die within their first 28 days of life. Children living with these anomalies often have ongoing complications and require long-term medical care. Many anomalies are syndromic, affecting multiple systems in parallel, such as skull, eyes, ears, heart and neural tube. Most structural malformations have a genetic component. With recent advances, identification of potentially causative genes is increasing rapidly. However, there is a need to both prove the link between a genetic change and an anatomical anomaly, and to understand how these changes disrupt normal development. This is not ethically possible to study in humans; so, animal models remain essential. Embryogenesis is a complex 3D process with spatially and temporally defined cell, tissue and environment interactions. Mouse models of mutations are key to understanding how genetics influences these interactions. With our expertise in clinical genetics, mouse development, human development and stem cell models, our aim is to efficiently carry out functional analysis of novel disease genes, to understand the causes and to provide new models for therapy development.	Lead: Professor Karen Liu Professor of Genetics and Development, Centre for Craniofacial & Regenerative Biology (CCRB), King's College London Email: karen.liu@kcl.ac.uk
MitoCluster: mouse models, expertise, and training for research into primary mitochondrial diseases and disorders associated with mitochondrial dysfunction	Primary mitochondrial diseases (PMDs) are caused by mutations in nuclear DNA or mitochondrial DNA (mtDNA) impairing energy production and other aspects of cellular metabolism. They are among the most common inherited neurological diseases (1/5,000 live births) and are associated with severe disability and shortened lifespan in children and adults. PMDs are challenging to study because genetic changes have variable effects across different tissues, with greatest impact often on tissues inaccessible for diagnostic or experimental studies (e.g., muscle, CNS, liver, heart). Mitochondrial dysfunction is also involved in cancer, neurodegeneration, inflammation, and ageing. Lack of treatments and biomarkers reflects a poor understanding of the underlying biology of PMDs. Existing PMD mouse models do not always fully recapitulate their human disease equivalent, hampering preclinical evaluation of treatments. While technical hurdles to modifying mtDNA have limited development of new models, emerging technologies may help overcome these. MitoCluster is a consortium of clinicians and research scientists in academia and industry, with worldleading expertise in PMDs, mitochondrial biology, mtDNA editing, and drug discovery. Our overarching aim is to develop novel, clinically meaningful, PMD mouse models and optimise translational value of existing mouse models. Network partner engagement will maximize our work's relevance via coordinated mitochondrial research.	Lead: Dr Robert Pitceathly Clinician Scientist and Honorary Consultant Neurologist based at the UCL Queen Square Institute of Neurology r.pitceathly@ucl.ac.uk
Parkinson's Disease and Related Neurodegenerative Processes	Parkinson's disease (PD) and related neurodegenerative disorders are incurable and represent a leading cause of disability and death worldwide. Greater understanding of molecular mechanisms remains the best hope of developing drugs that slow down or arrest the disease. Genetic breakthroughs have identified ~20 genes that cause inherited forms of PD, however, their function remains poorly understood. Progress has been hampered by the generation of variable mouse models and experimental tests in individual laboratories that prevent systematic comparison. We propose to develop a mouse model resource for PD and related disorders by partnering with the Mary Lyon Centre to generate gene edited models of every known PD-causing gene on the same mouse genetic background, alongside models that explore associated pathways relevant for ageing and cellular stress. These mouse lines will be carefully characterized (behavior & brain activity) at Harwell and at the applicants' laboratories to confirm robustness and reproducibility. Research will be closely aligned with clinical progress to ascertain translatability and face validity; models and data generated will be made available to others working on complementary experimental systems (e.g. molecular studies, drug discovery, stem cell research, human genetics) to accelerate research progress and identify new therapeutic strategies for these brain disorders.	Lead: Professor Bettina Platt Chair in Translational Neuroscience Program Co-Lead, Translational Neuroscience, University of Aberdeen School of Medicine, Medical Sciences & Nutrition, Institute of Medical Sciences Foresterhill, Aberdeen, AB25 2ZD Scotland, UK. E-Mail: b.platt@abdn.ac.uk
Mouse genetic models of barrier immunity dysfunction: Role of the microbiome in modifying disease phenotype	Interaction between host genetic and environmental factors, such as the microbiome, shapes the balance between health and disease. The ability to control and manipulate microbiomes is therefore crucial for advancing mouse genetics research. A key challenge limiting mouse microbiome research in the UK is a lack of basic understanding of the molecular mechanisms underpinning host-microbiome interaction in many genetic models of disease. Compared to other countries, we also lack critical resources and expertise required to generate and maintain gnotobiotic (defined microbiome) and germ-free (no microbiome) mouse colonies. Maladaptation between host and microbiome at barrier surfaces leading to local and systemic inflammation underlies a number of genetic diseases, for example, cystic fibrosis and inflammatory bowel disease. We propose a 'Microbiome and Barrier Function' cluster that addresses these challenges by: 1) developing a pipeline for creating and studying models of human genetic diseases involving barrier surfaces, with a focus on understanding the impact of the microbiome in these diseases. 2) establishing a national infrastructure for cutting-edge mouse microbiome research that will be accessible to all UK researchers. Better understanding of the microbiome contribution to the clinical phenotypes (or endotypes) of genetic diseases has the potential to identify novel therapeutic targets, leading to novel treatments.	Lead:Professor Fiona Powrie Professor of Musculoskeletal Sciences, Director of the Kennedy Institute of Rheumatology and Oxford Centre for Microbiome Studies, University of Oxford. Contact:Dr Jethro Johnson Deputy Director, Oxford Centre for Microbiome Studies, Kennedy Institute of Rheumatology, University of Oxford. jethro.johnson@kennedy.ox.ac.uk

Metabolic Systems and Comorbidities Cluster (MC2)	Obesity, diabetes and associated comorbidities including heart, liver and kidney diseases, cancer, and neurodegenerative diseases, cause human suffering and an enormous burden for health services and economies. These comorbidities simultaneously affect many organs and systems, so living animals are studied using sophisticated technologies to identify causes and treatments. We surveyed UK scientists and learned that while the science community can perform these complex “phenotyping” studies on mice, is it hampered by fragmentation, limiting access to cutting-edge technology and expertise. The recent MRC Unit and Centre Portfolio Review also recommended an increased capacity in physiology and multimorbidity research. The MC2 Cluster aims to drive innovation within Metabolic and related Comorbidities. MC2 will integrate the unique knowledge in mouse phenotyping and human genetics found in academic and private sectors. MC2 will collaborate with MRC Harwell on three goals: 1) identify, develop, and disseminate innovative, cutting-edge mouse metabolic phenotyping technologies. 2) share skills/knowledge and innovative technology through training and enhanced collaboration 3) develop more human-relevant mouse models to improve our understanding of human disease, enabling therapeutic developments and refine our use of animals through the 3R principles. This strategy will add value and competitiveness to existing efforts addressing this global health care issue.	Lead: Professor Antonio Vidal-Puig MD PhD FRCP FMedSci EMBA; Professor of Molecular Nutrition and Metabolism at the University of Cambridge, Associate Director MRC Metabolic Disease Unit, MRC Investigator. Wellcome Trust-MRC Institute of Metabolic Science Scientific Director MRC MDU Disease Model Core; Level 4, Institute of Metabolic Science Box 289, Addenbrooke's Hospital Cambridge, CB2 0QQ Contact: Dr. Chris Lelliott Head - MRC MDU Disease Model Core, Wellcome-MRC Institute of Metabolic Science; Level 4, Institute of Metabolic Science Box 289, Addenbrooke's Hospital Cambridge, CB2 0QQ Cjl39@medschl.cam.ac.uk
Genes X Environment: Challenging Early Life Adversity	In the UK, some 56,000 live births (7%) per year are low birth weight (LBW) while nearly 3000 pregnancies end in a stillbirth. LBW significantly increases risk of perinatal mortality and life-long adverse health outcomes. Pregnancy-related care costs the NHS some £5.8 billion per year, yet only 2.4% of all direct, non-industry health-research funding is spent on pregnancy related research, (RAND report, 2020). This identifies pregnancy research as one of the most underfunded areas of research in the UK and yet this is where human health begins and where we can make the most effective changes to improve the health not only of the mother but also for future generations. Our goal is to identify epigenetic mechanisms and markers that can be used to stratify disease risk and develop interventions, potentially through simple changes in diet or lifestyle. Mouse models have played a central role in the study of epigenetic mechanisms and the UK boasts a world-leading track record in this field. We intend to harness this academic excellence to produce translational outcomes in order to tackle one of the most challenging and fundamentally important questions in human health: how to maximise the chances of a healthy and successful pregnancy.	Lead: Professor Andrew Ward Professor of Molecular Genetics Department of Biology & Biochemistry University of Bath bssaw@bath.ac.uk
Somatosensation and Pain	Pain is numerically the biggest clinical challenge of the age, with more than half the adult population having a chronic pain problem and 6% of the global population enduring debilitating daily pain. The impact on mental health and general well-being is profound, and no new pain-killers have recently been developed. Our research cluster brings together world leading human and mouse geneticists who are identifying key causative genes for human pain, migraine and headache. These insights can be modelled in genetically modified mice where mechanisms can be dissected to provide new, human relevant drug targets. Our cluster will provide new human validated targets for pain control to be exploited by the pharmaceutical industry, as well as new approaches such as gene–targeted therapies that will drive forward new treatments for chronic pain. In addition, many of the mouse lines we generate and techniques we develop will help address other neurobiological disorders. Pain is a major problem in an aging population and may be associated with infection, cancer and metabolic disorders like diabetes. Working with specialist teams focused on these disorders should add value by improving the quality of life of patients through the development of targeted pain treatments.	Lead: Professor John N Wood FRS Professor of Molecular Neurobiology; Wolfson Institute for Biomedical Research, University College London, Gower Street, London WC1E 6BT J.Wood@ucl.ac.uk
Precision control of protein dosage in vivo	Technologies to perturb gene function underpin mouse genetics. However, genetic manipulation typically occurs at the nucleic acid level, whereas proteins mediate most biological functions. This currently limits the utility of mice to model human disease mechanisms and therapeutic interventions for the following reasons: 1)DNA manipulations impact protein function slowly, depending on protein and mRNA half-life. This makes it challenging to separate direct from downstream events following gene deletions, complicating inferences of mechanisms and causality. 2)DNA changes are hard to reverse. Restoring gene function in vivo could determine whether and at what critical time-points genetic diseases are curable. 3)Targeted proteolysis is an important new modality in drug development. Better approaches are needed to more accurately model the in vivo effects of these new compounds in pre-clinical studies. This cluster will address these challenges by developing standardized methods to enable any protein to be targeted by small molecules that allow rapid and reversible depletion, or controlled manipulation of dose, in mouse tissues and primary cells. Our vision is that targeted proteolysis technologies will complement, extend, and in many cases replace Cre-Lox approaches, simultaneously reducing and refining animal use while producing data that are easier to interpret.	Lead: Dr Andrew Wood Research Group Leader at the MRC Human Genetics Unit and Reader at the University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU andrew.wood@igmm.ed.ac.uk