Cell Genomics

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Voices

Better translation via collaboration: The MRC National Mouse Genetics Network

The MRC National Mouse Genetics Network (NMGN) has been established in the UK to bring together researchers from academia and industry across the country from a wide range of disease areas and research backgrounds to rapidly facilitate clinical translation of mouse research findings and foster an environment of interdisciplinary learning.

Owen Sansom
NMGN director, CRUK Scotland Institute

Bringing together mouse genetics researchers

The NMGN was conceived as a new funding model for mouse genetics in the United Kindom that would be able to exploit the country's world-leading scientific and clinical expertise to investigate defined disease areas and improve and accelerate how research using animals is translated to clinical benefits. The NMGN aims to create a broad platform for open access to mouse genetics for translational medicine. By increasing points of contact between institutes and other networks and by actively engaging with industry, the NMGN aims to develop new therapeutics and initiate new collaborations. The Mary Lyon Centre (MLC) at MRC Harwell acts as a central hub for the network as well as being a repository for mouse resources with an established international reach. The work of the MLC includes generating novel mouse strains closely reflective of human diseases, developing complex phenotyping platforms that can be shared by the different clusters, and facilitating high-quality data collection and sharing.

The central aim of the NMGN is to develop platforms predictive of human pathologies using data from many sources. For example, the -omics and spatial biology revolution, alongside excellent access to human material, allows us to develop new and compare existing mouse models to human disease more thoroughly than ever. The network is continuously exploring the possibility to expand its reach and include new disease areas and challenges to the current portfolio with the aim to maximize the described synergies and include new areas of expertise even within the current funding cycle. In this context and in line with one of the UKRI Strategic Themes for 2022–2027 ("securing better health, ageing and wellbeing"), the Medical Research Council is funding an additional 8th cluster, which will focus on mapping age-related changes to mice and will start its work early in 2024.

The NMGN is also ideally placed to fulfill the role of key contributor in filling the STEM skills gap through its ability to bring together a wide variety of expertise in the MLC's Advance Training Centre, increasing the impact of the NMGN on the preclinical landscape in the UK and internationally.

Sara Wells
Director of the Mary Lyon Centre, MRC Harwell

A hub for the mouse genetics network

The MLC is the MRC's national center for mouse genetics, providing resources for academic and industrial partners whose research is at a stage where no alternative system other than an animal model can be used to progress toward therapeutics. We support *in vivo* aspects of the MRC's NMGN projects. The science support portfolio of the MLC extends from generating new genetically altered mouse lines to characterization and therapeutic testing, in addition to housing the UK National Archive for mouse strains. With expertise in mouse genetics and project management, and a critical mass of technically trained staff, the MLC team coordinates research collaborations between multiple laboratories and companies. Over many years, the MLC has built up a network of users who bring together disease- or technology-specific talents and ideas into truly innovative new projects. Sometimes acting as broker, or matchmaker, we bring together researchers who have shared interests in mouse models of disease to address challenging scientific problems. Working with our collaborators within the

NMGN, and others around the UK and internationally, we have expanded our technical capabilities in model generation, phenotyping, and disease modeling to establish experimental platforms that are now available to UK academia and industry researchers. We therefore aim to act as a central hub for the NMGN, for resources such as mouse strains and data, for technical capabilities from phenotyping to cryobiology, and for the organization of training through our Advance Training Centre.

David Kent
Haem Cluster; York Biomedical Research Institute, University of York

Filling the gaps for hematopoiesis

Despite remarkable progress in the transcriptional/genomic profiling of normal and diseased blood cells, there is an urgent need for tools to dissect cellular and molecular mechanisms underpinning normal hematopoiesis and its responses to stress and disease. We lack tools to accurately map the cellular identity of specific hematopoietic cell subsets *in vivo* and cannot selectively manipulate the expression of multiple genes in specific target cells in the correct spatiotemporal manner.

This motivated us to build the Haem Cluster within the NMGN to address these long-standing gaps by bringing together resources from world experts based across the UK to create new, ambitious combinatorial models that can account for the order of mutation acquisition, developmental timing of mutations, or the impact of different cells or extrinsic factors on disease initiation. The work extends well beyond the remit of a single research group, requiring input at multiple specialist levels. The models not only will inform efforts in normal and stressed hematopoiesis but willalso have broad relevance to the tumor microenvironment (e.g., tumor-associated macrophages and neutrophils), acute and chronic infectious diseases, various immune pathologies (rheumatoid arthritis, allergy, systemic lupus erythematosus, etc.), aging, and cellular/gene therapy.

We are particularly excited by the network aspect of the NMGN—it has forged new partnerships within the hematopoiesis community and allowed us to engage with the other clusters and industry partners to maximize the impact of the tools we are developing.

Andrew Wood
Degron Cluster; MRC Human Genetics Unit, Institute of Genetics and Cancer, University of Edinburgh

Degron tagging technology and drug development

Degrons are sequences in proteins associated with regulation of degradation. Degron tagging allows potential drug targets to be validated using drugs rather than mutations, which has more similarity to the clinical application. Together with preclinical models that have been carefully positioned against human disease, this technology promises to enable researchers to more accurately model therapeutic interventions in physiologically relevant settings, decreasing the rate of attrition in subsequent clinical trials. The NMGN brings together experts in chemical genetics, disease modeling, and drug development to develop tools and protocols for degrading target proteins in tissues.

Several degron tags and ligands are already widely used in cultured mammalian cells. But how well do they perform in the more complex *in vivo* environment, where pharmacokinetics can strongly influence ligand activity? Can existing ligands be improved to generate tool compounds better suited to modeling drug activity in mice? To what extent does the activity of specific E3 ubiquitin ligase complexes, which underpin both degron tagging and protein degrader drugs such as proteolysis targeting chimaeras (PROTACs), vary across cells, tissues, and disease states? The Degron Tagging Cluster aims to address these questions and rapidly translate the knowledge through collaborations with industry and partners across the NMGN and beyond.

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Robert D.S. Pitceathly
Mitochondria Cluster; Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology

Advancing mitochondrial medicine

Mitochondria are sophisticated energy sensors that modulate their morphology and activity to meet the metabolic demands of the cell. They contain their own small, circular genome (mtDNA), although many mitochondrial genes are encoded by nuclear DNA. Primary mitochondrial diseases (PMDs) are the most common genetic metabolic disorders of children and adults. They cause significant disability and reduced lifespan, and most have no effective treatments.

Over the past decade, there have been major breakthroughs in mitochondrial medicine, including mitochondrial donation to prevent transmission of life-limiting mtDNA variants, and mtDNA gene editing. Several fundamental questions concerning mitochondrial biology and pathology remain unanswered, partly due to the complexity of mitochondrial genetics and diversity of causal genes. For instance, how do pathogenic mtDNA variants segregate? What are the molecular mechanisms behind the biochemical and clinical heterogeneity of PMDs? Which pathways contribute to pathophysiology outside of energy production? Mouse models play a pivotal role in bridging these gaps in knowledge and have the potential to help identify biomarkers and outcome measures for clinical studies. They also enable preclinical testing of novel therapeutics, ensuring that the most promising compounds progress to trials. Importantly, mitochondrial pathways are now recognized as key drivers of non-PMDs, including neurodegeneration, cancer, and aging. To give an example, recent evidence suggests that mitochondrial dysfunction contributes to cancer proliferation and pathogenic mtDNA variants promote tumorigenesis. Thus, deep phenotyping and disease-relevant models could predict effective therapies for PMDs and advance understanding of common diseases associated with mitochondrial pathology.

Anthony Isles
MURIDAE Cluster; Cardiff University Centre for Neuropsychiatric Genetics and Genomics

Psychiatric genomics during development

Psychiatric genomic studies have moved apace, with ever increasing lists of common and rare gene variants linked to disorders such as schizophrenia. However, preclinical animal studies aimed at understanding the consequences of these variants on brain function have had limited translational utility. A key problem has been a focus on modeling the outcome of a variant, namely looking for brain and behavioral deficits in adults. We know that the symptoms of genetically driven neuropsychiatric disease emerge from complex and non-linear interactions at molecular, cellular, and brain circuit levels over the course of development, in particular during early life (birth to early 20s). MURIDAE (Modalities for Understanding, Recording and Integrating Data Across Early life) is taking a novel, multidisciplinary, and systematic approach, bringing together leading UK scientists in partnership with the MLC. The aim of MURIDAE is to build on recent developments in home-cage video technology and machine-learning-based behavioral analysis and apply this to behavioral development across early life of genetic mouse models for schizophrenia. By coupling with measures of brain structure and neurophysiology, analyses of early-life changes will give insights into the developmental trajectory of brain and behavioral deficits that can augment standard studies of behavior and cognition in adult mouse models. Assessing the impact of early life and how it may shape adult behavior will give a more rounded insight into functional consequences of genomic variants associated with schizophrenia and represents an important shift in the study of neuropsychiatric disorders using genetic mouse models.

Karen Liu and Stephen Twigg
Congenital Anomalies Cluster; Kings College London (K.L.) and Radcliffe Department of Medicine (S.T.)

Modeling clinically relevant gene variants in congenital disorders

A key objective of the NMGN Congenital Anomalies Cluster is to link clinical gene discovery to disease causality by modeling variants of uncertain significance (VUS) in mice. Recapitulation of patient phenotypes in mouse models enables genetic diagnosis and potential as a therapeutic platform.

Globally, approximately 6% of babies are born with severe anatomical malformations, leading to hundreds of thousands of deaths within the first 4 weeks of life. These anomalies contribute to lifelong health complications and place a huge burden on families, healthcare, and society. Genetic causes are estimated to account for at least 25% of congenital anomalies. Sequencing approaches are increasingly feasible, making genetic changes readily discoverable. In the UK, this is exemplified by the 100,000 Genomes Project and the NHS Genomic Medicine Service, which use whole-genome sequencing (WGS) to improve health as part of routine care. While identification of causative genes is increasing rapidly, a bottleneck occurs when demonstrating the causative link between genetic changes and anatomical anomalies. Most patients with WGS do not have a molecular diagnosis, primarily due to inadequate assessment of pathogenicity and the large number of undiscovered disease genes. We aim to provide genetic diagnoses for families with rare genetic diseases by establishing causality for VUS and are creating a route for modeling these variants in mice. Investigating and correlating mouse phenotypes with patient features substantiates the genetic diagnosis. In-depth investigation of the mouse phenotype can then lead to greater understanding of how genetic changes cause disease and provide preclinical models for the development of therapies. This approach has the potential to change lives by enabling quicker diagnosis to inform treatment and providing better information for families through accurate genetic counseling.

Karen Blyth and Louis Chesler
Cancer Cluster; CRUK Scotland Institute and University of Glasgow School of Cancer Sciences (K.B.), UK and ICR Centre for Paediatric Oncology Experimental Medicine, The Institute of Cancer Research and The Royal Marsden NHS Trust (L.C.)

Translating cancer genetics to the clinic

Of human diseases, cancer has one of the worst rates for converting insight from preclinical research into clinically useful treatments. It is frustrating that the efforts and resources that have gone into genomic sequencing of common cancers has yielded fewer clinically druggable mutations than might have been expected. Associated with this is the complex tumor microenvironment and dynamic cellular crosstalk that plays an instrumental role in driving tumor initiation, metastasis, and therapeutic resistance. There is therefore an urgent need for patient-relevant, immunologically competent mouse models to further our understanding of cancer processes and expedite improved therapies to the clinic.

The NMGN has given us a golden opportunity to garner a unified team of clinicians, biologists, and data scientists studying adult and pediatric cancers and sharing expertise and state-of-art technologies while leveraging resources, capabilities, and excellence at the MLC to realise our ambition of advanced preclinical models. This allows us to molecularly and phenotypically catalog our models of common cancers such that these can be positioned to the human subtypes and to develop more sophisticated models that can be benchmarked to our patients. A unique benefit of the network is the wonderful collaborative stage for multi-disciplinary cross-cluster engagement. Exemplifying this are combined efforts across the clusters designing a novel model in which gene mutations can be altered in a temporal and spatial way to more accurately emulate tumor evolution. We are also enthused by the prospect of growing the network to improve connectivity between academia and industry; to invest in training the future generation of preclinical modelers; and to advocate for the 3R's, promoting replacement, reduction, and refinement in humane animal research.

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DECLARATION OF INTERESTS

The authors declare no competing interests.