

Outcomes of the MRC National Mouse Genetics Network community workshop held virtually on Wednesday 25 November

1. Introduction

The Medical Research Council (MRC) is investing £20m in a new National Mouse Genetics Network, recognizing the critical importance of the mouse as an experimental model and capitalising on cutting-edge technologies and data-rich outputs from human / clinical genetics. The investment will be delivered through a UK-wide call to support a national distributed network of approx. 4-5 research clusters (funded over 5-years in the first instance, anticipated start March 2022), leveraging the strengths of MRC Harwell's Mary Lyon Centre (MLC) directed by Dr Sara Wells, and the approx. £150m pa that MRC contributes to national research using mouse models. The network vision is that it will enable and support the development of more refined, targeted and clinically-relevant complex mouse models to better align mouse studies with human health / clinical studies, and generate more sophisticated data-sets from such models to capitalise on recently emerging rich human / clinical data.

2. The Workshop

As part of a managed process to help the community coalesce around developing cluster funding bids, the newly appointed MRC National Mouse Genetics Network Director, Professor Owen Sansom convened a community workshop that was held virtually on Wednesday 25 November 10:00-15:00. The workshop was attended by approx. 120 delegates, bringing together scientists from the mouse and clinical genetics communities, together with industry representatives. The workshop aims included to:

- Bring the community up to speed on Professor Sansom's plans for the Network;
- Stimulate discussion on maturing ideas including:
 - developing the cluster challenge-led themes (disease areas, technologies, concepts);
 - building critical partnerships with the Mary Lyon Centre
 - deploying cluster resources, cluster integration and networking opportunities;
 - cross-cutting themes – e.g. genome engineering, data science, innovative phenotyping;
 - broader stakeholder partnerships including academia (e.g. currently not using mouse models), industry (pharmaceutical, SMEs), technology platforms etc;
- Gain insights from the community on balance of developing themes and key issues / opportunities to help refine plans, ahead of the research clusters call (opening early 2021).

The workshop consisted of plenary talks (from the Network and MLC Directors, and from clinical, industry and national institute stakeholders) followed by breakout sessions, the first examining 'how the network vision and opportunities will support a challenge theme' (with participants split into broad themes of expertise), the second examining 'what does a cluster need to function - key components, ways to engage, partnerships?' (with participants randomly assigned). The workshop programme is at **Annex 1**.

3. Outcomes

A broad range of discussions from breakout groups and at the reconvening plenary sessions explored needs, opportunities and challenges for developing cluster themes (disease research areas, technology development etc.). Also discussed were ways in which investment in the new network could add value and potentially unlock currently less tractable, or support new, research challenges set in the context of the existing mouse genetics research portfolio and the broader national landscape. Discussions also considered key interacting activities (data and infrastructure), training and best practice, support for early career researchers, and how the network could act as a springboard to access other funding streams.

Network opportunities

The ultimate goal of the network should be reduction in the national burden of disease and delivering better patient care. It will be important to make best use of the proposed investment to deliver real added value and benefits to existing mouse and clinical genetics research. The network should support clusters and broader national research, not just focused on diseases, but also systems or approaches, and seek to make mouse research (relatively expensive in the UK, and varying regionally, e.g. high costs in London) as efficient and affordable as possible to retain international competitiveness.

Disease challenges

A networked approach could better address a range of (more) complex, cross-disciplinary disease challenges. Areas include pathogen mixture exposures, co- / multi-morbidities, gene-environment interactions (e.g. through the life-course), and systems interplay such as infection / inflammation (e.g. currently relevant 'long-Covid'), or immune system interactions with cancer and metabolism dysfunction. The network can build on ongoing research activities in single disease model studies and, through economies of scale and efficiency, facilitate studies currently limited by individual institute capacity or expertise. The network could also address more intractable or under-researched rare diseases, that present technical and conceptual challenges. Examples of how the network could facilitate include:

- **inter-connecting diverse expertise** – e.g. bringing together specialists studying different individual organs to address multi-morbidities
- **more efficient use of national infrastructure** – e.g. allocating resource (e.g. staffing) for dedicated laboratories / facilities to undertake more complex / cross-disciplinary activities on behalf of the network – e.g. C3 facility for multiple pathogen studies, or central germ-free facility for diet-gene-environment interactions
- **better discovery-clinical research linkage** – e.g. for rare diseases - linkage between *in vitro* / 3D organoids / *in vivo* mouse models, and experimental medicine, with improved access to patient materials, tissue samples / cell resources to tackle challenges such as phenotyping heterogeneity

Other complex / cross-disciplinary areas discussed that could potentially be better supported through a networked approach include studies into healthy aging, immune system / neurological system function in health and disease, functional genomics in health and disease, mitochondrial disorders and fibrosis.

Mouse models

Building on the internationally-recognised strengths of the UK, a new national network creates the opportunity to better connect the community to develop the models and genetic tools to tackle ever more multi-disciplinary and complex challenges in mouse genetics research. Examples of how the network could add value include:

- **human-relevant disease models** – e.g. 'humanized' mice (e.g. to understand variations in human genetic background in obesity) – improving attractiveness to stakeholders such as the pharmaceutical industry and facilitating both forward and reverse translation between discovery and clinical research
- **sophisticated control of models** – for example in cancer to understand the drivers of later stages of disease, or tuneable constructs for switchable and highly controlled experiments in neuroscience studies
- **'next-gen' genome engineering** – gene editing tools (e.g. Crispr) are now commonplace, but the network could support:
 - technically more difficult engineering, e.g. repeat expansions, mitochondrial DNA, simultaneous introduction of large numbers of mutations to explore polygenic risk scores
 - more sophisticated construct design, e.g. leveraging cross-network resources using different recombinases available at different locations
- **parallel model development** – mouse organoid / iPSC equivalents to human organoids (e.g. as developed by industry), or equivalent comparative models (e.g. rat – more commonly used in metabolic studies) that are less easily supported / justified through other funding routes

- **fundamental physiology** – recognizing the limitations of mouse models applied to some diseases (e.g. schizophrenia), nevertheless whole animal models can increasingly be considered as tools for deep interrogation of mechanism to understand normal physiology, for example tissue-specific, temporally-controlled perturbations of protein function to explore neural circuitry and behaviour phenotypes, or changes to metabolism.

Experimental design

The network / MLC presents opportunities for improving best practice:

- **economies of scale** - minimizing wastage of tissue, e.g. in multi-morbidity research
- **standards and reproducibility** – the network can lead the way nationally in setting and maintaining and aligning standards and QC, and to address clinical and industry concerns and requirements, for example in behaviour assays and QC (e.g. in phenotyping and data capture), or for genotyping (e.g. resequencing a large genome)
- **moving animals or moving humans** – transfer of animals across the network presents key challenges for best practice (experimental design, animal welfare etc.). For example, centralising stocks for comparative phenotyping at the MLC to ensure QC, reproducibility, versus the need for proximity to on-site model and phenotyping expertise. The network may facilitate these decisions for example through catalysing developments in remote monitoring, or opportunities for support for ‘mobile’ early career researchers (e.g. utilizing Harwell campus ‘hotel’ facilities) to bring in appropriate expertise
- **licensing** - opportunity to engage with the Home-Office and address 3Rs agenda (e.g. tissue-sharing) to streamline some licensing requirements, using the centralized MLC facilities, and across the network / clusters to standardise licences.

Experimental readouts

Key opportunity to support more sophisticated approaches such as moving away from ‘end-point’ based research to continuous, multi-modality monitoring (imaging and phenotyping), with ramifications for data volume management, and better experimental design / best practice:

- **non-invasive remote monitoring** technologies, capitalising on strengths of the MLC e.g. to understand environmental influences on neurological disease, from early in development through to later neuro-degeneration
- **cost-effective support for readouts from complex protocols** – such as life-course / aging studies allowing multi-user access to continuously monitored models to efficiently phenotype the aging mouse, e.g. for cardiovascular / neuro-degenerative diseases, or across development / senescence
- **integrated phenotyping and imaging across scale** – e.g. from molecular / cellular through neural circuits, sub-regions of the brain to whole organism behaviour aligned to current UKRI priority areas in understanding multi-scale and dynamic biological systems, and improved integration between mouse and human disease phenotypes

Data and bioinformatics

The network will need to support large data outputs (e.g. from continuous monitoring) and facilitate state-of-the-art bioinformatic approaches to integrate experimental and clinical research, and to capitalise on the existing trove of molecular, morphological and phenotypic data for complex models and human disease cohorts. Ways in which this can be facilitated include:

- **support data portal(s) / cloud-based systems** – need to be discoverable and simple to use
- **better data sharing** - for the academic community e.g. for complex cross-disciplinary discovery research such as immune-system and susceptibility to infections or cancer.
- **promote integration of multiple data sources** – e.g. multi-scale imaging to build data sets, visual graphics etc.

- **best practice** – delivering excellence in bioinformatics approaches and stringent data regulatory requirements to engender effective and trusting interactions with the clinic and industry e.g. through sharing of data resources to link to specialised patient databases
- **data repositories for mouse models** – for example between normal / wild-type / outbred in metabolic studies
- **effective linkage to centralised infrastructure** – particularly for data heavy activities such as imaging and molecular pathology including databases, data storage, data integration technologies
- **network management and coordination** – the MLC will play a key role but should also be support for a distributed network approach to ensure reproducibility.

Training and knowledge exchange

The network / MLC offers opportunities for training (e.g. new students) and KE, for example through initially bringing together cluster expertise in specific models to capitalise on centralised regulatory licensing and training expertise (QC, phenotyping etc.) at the MLC's newly designed 'Advance Training Centre', to then develop more sophisticated models / deeper phenotyping approaches that can be rolled out across the national network.

Technology pipeline

The network can provide a better platform to support the technology development pathway:

- **discovery research** – bringing together critical diverse expertise and forging key collaborations to ensure best support of cutting-edge technology developments (e.g. advances in genome engineering, phenotyping, imaging, data management, and underpinning technologies such as single-cell 'omics)
- **sharing, scale-up and national dissemination** – advocating a culture of sharing and proactive dissemination, capitalising on MLC capabilities across the network and clusters to make available tools, technologies and methodological developments as national assets

Infrastructure and equipment

The network could foster more equitable access and training for key facilities, e.g. C3 lab equipment (e.g. FACS) for cluster partners and external users that don't have these facilities. It may also help access cross-cutting finances (e.g. from other funders or industry) as they arise, to capitalise on excellent existing national (and networked) infrastructure and developing new initiatives.

National visibility

The network should engage outwards, setting the standards for better models, data integrity and management, open-access (e.g. distribution of developed tools and technologies) etc. with network leads acting as advocates and setting standards (e.g. for Boards assessing response-mode grants) across all mouse-based research.

Network needs

Communications and engagement

The network and clusters once established should be nationally inclusive avoiding 'winners and losers' and reaching out to all research active institutes. MRC Harwell / MLC will play a strong role in continuous national engagement, e.g. through training. All network members will have the responsibility of communicating both nationally and beyond (UK, EU, worldwide). By being advocates for best practice and ambassadors for the mouse as a model organism, this will help to leverage other funding opportunities, add value to existing investments and drive retaining state-of-the-art mouse facilities in UK universities. The network should ensure integration with key complementary national activities such as Genomics England and the MRC-supported Genome Editing Mice for Medicine (GEMM) programme, and to forge connections with international research and mouse facility communities to capitalise on the

existing UK-international connections to further develop technologies, models, data sharing etc. Ways to facilitate this could include:

- **network and MLC forum** – sign up to share contact details and receive updates
- **annual UK conference** – bringing together clusters and externally, drawing in key stakeholders
- **international partnership** – including the EU to help develop consortia
- **championing the network** – identify nationwide channels for disseminating information on licensing / home office legislation, experimental best practice and training, data management etc.

Infrastructure planning

To help deliver ambitions on better access to infrastructure, and leveraging potential parallel dedicated infrastructure investments across the network, there is an early opportunity to:

- **compile an inventory / database** of existing key equipment (imaging, mass spectrometry, NMR, MRI etc.) across different institutes and infrastructure (e.g. access requirements)
- **survey existing animal facilities** – to identify regions / areas that are underpowered (and drawing lessons learnt from closed facilities such as the Wellcome Sanger Institute)

MLC capabilities

Key capabilities that the MLC can bring to the network, and discussed at the workshop included:

- high quality / high volume resource for breeding, mouse line generation and genetics
- 'one stop shop' for mouse line archives, and frozen sperm collection;
- centralized point and interface between clusters, providing uniform expertise and use of facilities for high demand / prioritized techniques;
- focal point for exchange of expertise and training (e.g. through the new Advanced Training Centre), with flexible opportunities for 'hoteling', e.g. to support logistics for minimising animal movement, or early career researcher training;
- high quality phenotyping resource, including for network needs in remote continuous monitoring – and with ambitions to increase capacity for high-end experimentation, more complex and controlled conditions;
- setting standards for animal welfare and distribution, to support best practice in training across the network, efficient management of animal licensing, home office inspections and legislation;
- hub to the network for data capture and dissemination and open source sharing of samples, publications etc.;
- hub for upscaling network technology discoveries to the national level;
- access point for network to broader Harwell campus resources;
- portal to internationally recognized mouse research and facilities e.g. JAX, Taconic and EMMA.

Also, it was recognized that whilst partnerships with MLC will be key, there may also be advantages to accessing local resources and infrastructure.

Cluster needs

The added value of clusters will be through bringing together key Institutions to deliver challenge-led research through innovation, knowledge exchange and technical developments, and having a significant footprint at MLC at Harwell to share expertise (e.g. for model development or QC). Clusters should not be insular / siloed but engage and identify new people / groups to build cohesion. For example, clusters can bring together expertise to catalyse technology developments (e.g. phenotyping), with the network / MLC subsequently supporting upscaling. Other areas discussed as criteria for cluster proposals included:

- **staffing strategy** - dedicated cluster project managers
- **benefits to broader network** – clusters should engage e.g. smaller ROs / labs that will benefit from the network, but can also contribute, e.g. through specialist technologies

- **benefits of MLC and wider Harwell campus** – as well as MLC, clusters should consider opportunities with resources offered by the bigger Harwell infrastructure investments (Rosalind Franklin Institute; Nucleic Acid Therapy Accelerator: NATA; Diamond Light Source, Research Complex at Harwell etc.)
- **providing resources to the community** – clusters should provide open access to tools, technologies, data etc. not just to academics, but also e.g. SME biotechs

A key measure of the success of the network (added value, economies of scale, interconnectivity etc.) will be that cluster investments, once up and running, will unlock access to further external funding (national and international), through supporting research excellence, best practice etc. to bring in new ambitious and high-quality research programmes.

4. Conclusions

The community inputs to the workshop identified a range of areas where the new network investment could add value and deliver above and beyond current funding mechanisms to drive forward ambitions to capitalise on developments in mouse models as experimental tools applied to human disease, and on cutting-edge technologies and data-rich outputs from human / clinical genetics. Areas discussed included ways in which the network, and the core expertise and facilities of the MLC hub, could support:

- developing more sophisticated mouse models and genome editing / engineering technologies, as a platform for planned new research clusters to address more complex, or hitherto less tractable disease challenges;
- opportunities for efficient exploitation of technology discoveries and developments to the national benefit;
- centralisation for training and effective regulatory compliance at the MLC;
- open research approaches through sharing of tools, technologies, methodologies and data;
- better reproducibility and experimental design, and to drive efficiencies to forge best practice and to deliver against the 3Rs agenda.

The network investment should also pave the way for maximising benefits of interacting national investments (for example in data or infrastructure platforms, and major institutes), and to help support sustainability of the research clusters, including to unlock access to other funding sources across UKRI and beyond, and to forge partnerships with key stakeholders such as the pharmaceutical industry to support needs for more sophisticated and fit-for-purpose models of human disease.

Annex 1 – Workshop agenda

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Agenda

Time	Item
09:45	Log in and arrival
10:00	Professor Paul Kaye – Welcome, Background & Workshop objectives (10 mins)
10:10	Plenary presentations 1 (25 mins) <ul style="list-style-type: none"> • Professor Owen Sansom – Network Vision • Dr Sara Wells – Mary Lyons Centre
10:35	Breakout 1 – (45 mins) – ‘how network vision and opportunities will support a challenge theme’
11:20	Reconvene to share ideas & raise questions (30 mins)
11:50	Lunch break (50 mins)
12:40	Plenary presentations 2 (30 mins) – institute, industry & clinical perspectives <ul style="list-style-type: none"> • Professor Fiona Powrie • Dr Simon Barry • Professor Andy Copp
13:10	Breakout 2 – (45 mins) - ‘what does a cluster need to function (key components, ways to engage, partnerships?)’
13:55	Reconvene to share ideas & raise questions (30 mins)
14:25	Wrap-up - consolidating key messages and next steps
15:00	End