Mammalian Genome (2027) 38:2
https://doi.org/10.1007/s00335-026-10295-4

The MMRRC as translational infrastructure for biomedical research and the integration of new approach methodologies

Terry Magnuson[1] · Stephen A. Murray[2] · Cathleen M. Lutz[2] · Lorin Roiphe[2] · James Amos-Landgraf[3] · Amy Yokoyama[4] · K. C. Kent Lloyd[4,5]

Received: 30 July 2026 / Accepted: 12 November 2026
© The Author(s) 2026

Abstract

The central challenge in translational research is aligning each biological question with the model system best suited to answer it. Mouse models are particularly powerful when research questions require mammalian physiology, developmental timing, neuroimmune and cardiometabolic interactions, pharmacology, longitudinal assessment, and other system-wide phenomena. Yet no single mouse model fully recapitulates a human disease, just as no single new approach methodology (NAM) captures the complexity of human pathobiology in vivo. Translational advances therefore depend on integrating complementary experimental systems and comparative cross-species analysis. Within this ecosystem, the NIH-funded Mutant Mouse Resource and Research Center (MMRRC) provides essential infrastructure for translational biomedical research by preserving and providing unique strains, ensuring genetic and microbial quality control, maintaining a reversible cryoarchive, standardizing data and documentation, supporting in vivo phenotyping, and ensuring equal and equitable public access and availability. Recent studies demonstrate how MMRRC-distributed models contribute to mechanistic insights observed from human-based studies, and vice versa. The MMRRC's expanding human pluripotent stem cell collections and informatics capabilities offer further opportunities to integrate human-derived systems with genetically-engineered mouse models. By supporting rigorous, accessible, and increasingly human-informed experimental research, the MMRRC strengthens discovery, improves reproducibility, supports the 3Rs (replacement, reduction, refinement), and enables the integration of complementary models in translational science.

Keywords Mutant mouse resource and research center · MMRRC · Translational research · New approach methodologies · Mouse models · Reproducibility · NAMs

Introduction

Mouse models are foundational to biomedical research because they combine in vivo mammalian physiology with experimental tractability. Their short generation time, fecundity, defined genetics, and amenability to precise genome engineering enable direct testing of causal hypotheses in vivo (Gurumurthy and Lloyd 2019). Advances in mouse genetics have further strengthened translational relevance by enabling orthologous disease modeling, patient-variant knock-in alleles, conditional and inducible systems, and increasingly sophisticated genetically humanized models in which human alleles are incorporated into the mouse genome (Birling et al. 2021; Gurumurthy and Lloyd 2019).

At the same time, well-documented limitations in animal-to-human translation have highlighted challenges to preclinical research (Seok et al. 2013). These challenges

✉ K. C. Kent Lloyd
kclloyd@ucdavis.edu

1 Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

2 The Jackson Laboratory, Bar Harbor, ME, USA

3 Department of Veterinary Pathobiology and Integrative Biomedical Sciences, College of Veterinary Medicine, University of Missouri, Columbia, MO, USA

4 Mouse Biology Program, University of California, Davis, CA, USA

5 Department of Surgery, School of Medicine, and Informatics, Coordination and Service Center, Office of Research, University of California, Davis, CA, USA

Published online: 20 November 2026

involve two related but distinct issues: reproducibility and translatability. Reproducibility failures can arise from avoidable problems, including inadequate study design, incomplete phenotyping, insufficient reporting, and unrecognized effects of genetic background or microbiota. In contrast, translational failures can result from suboptimal model selection and misalignment between the model and the clinical disease target (van der Worp et al. 2010; Perrin 2014; Ericsson and Franklin 2021; Pardo-Manuel de Villena et al. 2026). Nevertheless, such limitations do not diminish the value of animal model systems but highlight the need to improve how they are selected, validated, standardized, and used in translational studies. Genetically and microbiologically quality-controlled models, standardized documentation, and access to comparable biological resources can address these avoidable sources of uncertainty. Although improved reproducibility does not necessarily establish human relevance, it increases confidence in the experimental findings used to evaluate translatability. When deployed properly and integrated with other experimental paradigms, mouse models provide key biological insights and can offer important predictive information from a systemic, whole-organism perspective.

The U.S. public mouse model repository system

Within this context, the Mutant Mouse Resource and Research Center (MMRRC) program serves a distinct translational value. Established by the NIH in 1999, the MMRRC consortium has evolved into the premier U.S. public repository system for mutant mouse models, with four repository centers and an Informatics, Coordination, and Service Center that together acquire, validate, cryopreserve, maintain, characterize, and distribute genetically altered mouse strains and related materials. The scale and impact of this infrastructure are substantial. A recent consortium report noted that the MMRRC maintains resources for nearly 65,000 unique mutant alleles and has fulfilled more than 20,000 orders from over 13,000 investigators at more than 8,000 institutions worldwide (Agca et al. 2024). A bibliometric analysis identified more than 4,000 publications potentially associated with MMRRC resources, 1,761 of which reported using MMRRC mice (Piekniewska et al. 2025). These numbers demonstrate the extent to which the MMRRC serves as an active and essential national resource.

The translational impact of the MMRRC is amplified by advances in the development of new technologies. New approach methodologies (NAMs), also known as novel alternative methods, including human cell-based systems, organoids, microphysiological systems, and computational models, are rapidly expanding the experimental toolbox (Avila et al. 2020). While increasing experimental capabilities, these approaches do not eliminate the need for rigorous in vivo human biology-relevant systems when the research question involves organismal physiology, developmental timing, tissue-tissue communication, pharmacokinetics and pharmacodynamics, host-microbe interactions, immunological responses, pleiotropy, reproductive biology, aging, or complex behavior. Translational progress is therefore best achieved through the coordinated use of complementary models rather than substitution of one platform for another (Lloyd 2025). In that context, the MMRRC functions as a critical bridge, ensuring that in vivo mouse studies are robust, reproducible, and maximally informative for human biology and medicine (Fig. 1).

Current strengths and limitations of MMRRC models

A major strength of MMRRC-distributed models is that they enable investigators to test physiological and disease mechanisms in an intact mammalian organism. This matters because most complex disease processes are synergistic manifestations of interacting systems rather than the additive effects of isolated cell types. Neuroimmune signaling, endocrine feedback, cardiac remodeling, tissue repair, metabolism, fertility, developmental patterning, and therapeutic response often depend on multicompartment physiology that cannot be fully recapitulated in vitro, in chemico, or in silico. Therefore, the value of a mouse model does not depend on whether it reproduces every feature of a human disease, but on the extent to which it is useful to interrogate the relevant pathobiological mechanism, susceptibility state, cell population, circuit, or therapeutic target for a defined context of use. Accordingly, a mouse model can be highly translational even when the overt mouse phenotype only partially recapitulates a human syndrome (van der Worp et al. 2010; Perrin 2014).

The value of this approach depends on the quality, definition and accessibility of the models themselves. This is where the MMRRC provides critical added value. By enforcing rigorous genetic and microbial quality control, preserving alleles on defined or well-documented backgrounds, and maintaining cryopreserved reference stocks, the MMRRC ensures that investigators are working with stable and well-characterized reagents (Agca et al. 2024). Standardized nomenclature, metadata, and strain documentation further enable appropriate model selection and interpretation, while centralized distribution reduces redundancy and minimizes the propagation of poorly defined lines or genetic drift across laboratories (Agca et al. 2024). Equally

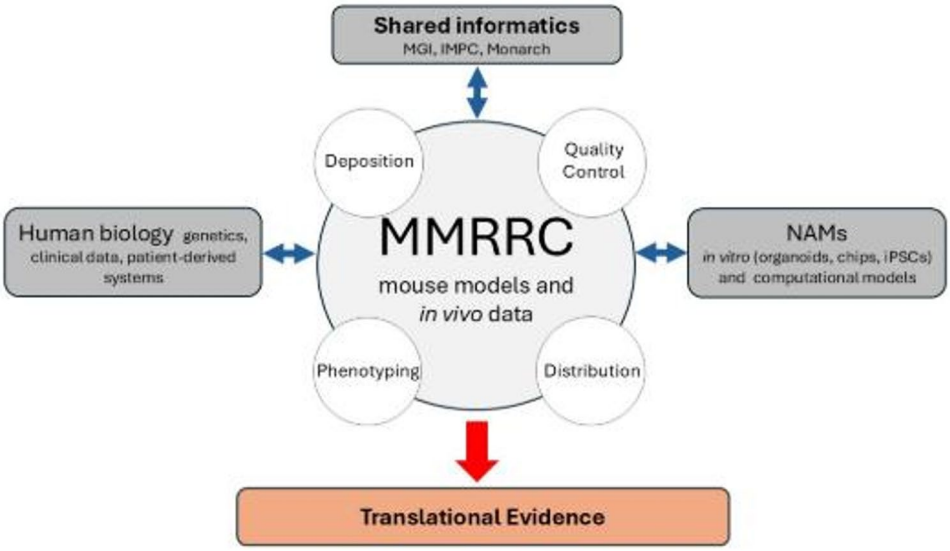


Fig. 1 The MMRRC as translational infrastructure for integrated model-based biomedical research. The MMRRC provides publicly accessible, quality-controlled, and reproducible mouse models and associated in vivo data that support the integration of human biology, new approach methodologies (NAMs), and functional genomics for modern translational research. Bidirectional interactions among human genetic and clinical data, mouse models, and in vitro NAMs and computational models enable complementary investigation of disease mechanisms. The MMRRC facilitates these studies through strain deposition, preservation, genetic quality control, phenotyping, standardized documentation, and distribution, while shared informatics resources, including Mouse Genome Informatics (MGI), the International Mouse Phenotyping Consortium (IMPC), and the Monarch Initiative, support integration and cross-species comparison of genetic and phenotypic information. Together, these complementary resources enable model selection, mechanistic validation, interpretation of concordant and discordant findings, and bidirectional translation between experimental systems and human disease, strengthening the reliability and human relevance of translational evidence

important, the MMRRC facilitates reproducibility and cross-study comparability. Access to common, validated strains allows independent groups to test related hypotheses in comparable biological systems, while consistent documentation supports integration with human datasets and other model platforms. In this way, the MMRRC helps shift mouse-based research from isolated, laboratory-specific efforts toward a more cumulative, translational science.

Repository-level quality control directly addresses major sources of irreproducibility in animal research. Incoming strains are genotype-verified, background-checked, monitored for pathogens, cryopreserved, and documented in standardized Strain Detail Sheets (Agca et al. 2024). MMRRC centers also support recovery, breeding, phenotyping, pathology, and other technical services. The use of MiniMUGA, an array-based high-density single nucleotide polymorphism (SNP) genetic quality control platform (Morgan et al. 2015; Sigmon et al. 2020), is particularly important because background strain and substrain effects can materially alter phenotypes and undermine interpretation if left undocumented (Sigmon et al. 2020; Pardo-Manuel de Villena et al. 2026). Similarly, growing recognition of microbiome-dependent phenotype variation means that microbial context is not a husbandry afterthought but a translational variable. The MMRRC's attention to genetic quality control, environmental conditions, microbiome data, and reproducibility troubleshooting, among other features, is a major strength of its support for the biomedical research enterprise (Ericsson and Franklin 2021; Agca et al. 2024).

An additional and often underrecognized strength of the MMRRC is its concentration of expertise in comparative medicine and comparative pathology. These are disciplines whose specialized expertise is increasingly difficult to access in many biomedical research settings but remain essential for the rigorous translational use of mouse models (Lloyd 2026). That expertise helps investigators choose the most informative tissues, time points, endpoints, and controls, and it improves interpretation by distinguishing background lesions, husbandry- or microbiome-related effects, and species-specific biology from findings that are truly relevant to the modeled disease process. In practical terms, comparative interpretation of this kind makes mouse studies biologically coherent, more clinically informed, and better suited for evaluating their relevance to human disease.

Despite these advantages, no mouse model is a perfect human phenocopy, just as no organoid or computer model recapitulates a human disease. Human disorders are shaped by genetic diversity, environmental exposures, long time scales, social context, clinical care, and other factors that cannot be fully captured in any experimental system.

Important limitations of mouse models include species-specific differences in immune responses, metabolism, gene regulation, disease progression, and therapeutic susceptibility. Furthermore, the use of relatively homogeneous genetic backgrounds, standardized environmental conditions, and restricted age ranges can limit representation of the heterogeneity observed in human populations. Some of these limitations can be mitigated through improved genetic modeling, experimental design, and comparative interpretation, but others reflect biological differences that cannot be eliminated through high-level quality control alone. Some questions are better addressed first in human cells or patient-derived tissues, especially when species-specific biology is central. These realities do not negate the translational value of mouse models. Instead, they define the conditions and parameters by which a model should be used for translationally-relevant research. Importantly, the MMRRC helps address many of these variables by reducing avoidable sources of genetic drift, microbial contamination, and poor documentation of provenance. But this support does not obviate the need for thoughtful model selection and rigorous study design.

Better genetic representation of human disease

To improve translatability, the first priority is to strengthen the genetic alignment between mouse models and human disease. The most informative translational models are often those built around human genetics, which in some cases requires functional knockouts or deletion alleles, knock-ins of suspected pathogenic variants, allelic series, conditional models that capture tissue or temporal specificity, and humanized loci when species differences in sequence or regulation are important (Melo et al. 2021; Shankar et al. 2022). Advances in genome engineering now make these strategies far more feasible than in earlier eras of mouse genetics (Gurumurthy and Lloyd 2019; Modzelewski et al. 2018). The MMRRC provides the platform through which genetically humanized models can be preserved, validated, and disseminated broadly after their initial creation.

The MMRRC is also well positioned to capitalize on large-scale functional genomics efforts. The International Mouse Phenotyping Consortium (IMPC) and related knockout resources have produced standardized in vivo information on thousands of genes, creating a framework for systematic genotype-to-phenotype discovery and prioritization of clinically relevant mouse models (Birling et al. 2021; Lloyd 2024). By serving as a primary archive and distribution point for many of these resources, the MMRRC assists the field from ad hoc model generation toward a more strategic, human genetics-informed translational pipeline.

Finally, the MMRRC contributes to the management of mouse genetic diversity. Much mouse research still relies on a limited number of inbred backgrounds, whereas human disease unfolds across diverse, outbred genomes. Expanding deposition and use of models on sensitized, mixed, or intentionally diverse backgrounds would better capture modifier effects and variable penetrance. To that end, the MMRRC provides mouse models from the Collaborative Cross (Threadgill et al. 2011) and Diversity Outbred (Morgan et al. 2015) projects. Investigators have expressed particular interest in these strains, submitting 325 orders for them over the last 5 years. A centralized repository is critical as these tools are most useful as recombinant inbred strain panels and genetically diverse outbred populations, respectively, and because such models are especially vulnerable to drift, contamination, and loss if dispersed across multiple local colonies.

Although genetically diverse mouse resources provide important opportunities to investigate modifier effects and variable disease penetrance, their use can be limited by the expense and logistical complexity of maintaining such types of colonies. However, these barriers are more likely to be overcome by providing centralized access to genetically diverse panels, together with coordinated breeding, phenotyping, and experimental services. Similarly, improved characterization of environmental exposures, microbiota, and other relevant biological variables could help to clarify and distinguish gene-related effects from non-genetic responses.

Integration of human-relevant biology

Translational research is improved when mouse studies are explicitly linked to human data rather than interpreted in isolation. Increasingly, these types of investigations proceed bidirectionally. Human genetics, patient-derived cells, organoids, and computational analyses can identify candidate, disease-associated mechanisms, while mouse models can test the extent to which those mechanisms are causal in an intact organism. Conversely, discoveries made in mice can be challenged in human tissues or human cell systems to define where pathways are conserved or where they diverge. Equally important is back-translation in which observations from human genetics, clinical studies, or therapeutic responses can be used to generate new experimental hypotheses and refine existing models. Patient-associated variants, unexpected treatment responses, or newly identified disease pathways can be investigated using genetically humanized mouse models, while the resulting in vivo findings can be

compared back to patient-derived cells, organoids, and other human-relevant systems.

Quality-controlled in vivo data can also be used to support the development and evaluation of NAMs. For example, findings from organoids, microphysiological systems, or computational models can be compared with those obtained from genetically characterized mouse models for mechanistic alignment and concordance and to identify missing physiological interactions. Where NAMs are intended to predict defined outcomes, such comparisons with in vivo systems can also be used to estimate predictive performance. Importantly, however, concordance with a mouse model is not by itself evidence of human relevance. Interpretation requires consideration of the strengths and limitations of each experimental system and, whenever possible, benchmarking against independent human biological or clinical evidence. Formal NAM validation therefore differs from mechanistic comparison and biological contextualization across experimental systems. Whereas formal validation requires systematic evaluation of a NAM's performance, reliability, and predictability for a defined application, mechanistic comparison examines concordance or divergence in biological mechanisms, and contextualization determines how findings from reductionist systems are influenced by the physiological complexity of an intact organism.

This is the context in which mouse models and NAMs most clearly strengthen one another. Human cell-based systems may offer stronger species relevance for certain questions about how cells behave in isolation and can support higher-throughput perturbation, whereas mouse models add organism-level context, longitudinal physiology, and therapeutic testing under conditions that involve multiple tissues and feedback loops. For gene therapy, small molecules, immunotherapies, or neuromodulatory interventions, cell systems may help identify candidate mechanisms, but in vivo mouse studies often remain necessary to assess biodistribution, tissue specificity, durability, systemic toxicity, and whole-organism efficacy.

Recent MMRRC-associated studies in gene therapy and heart failure illustrate the translational value of these resources (Guo et al. 2025; Cools et al. 2025). For example, MMRRC-linked models have been used to evaluate AAV9/SLC6A1 gene therapy in a mouse model of neurodevelopmental disease and to define early hippocampal circuit dysfunction in the 3xTg model of Alzheimer's disease (Guo et al. 2025; Michaud et al. 2024). In cardiovascular and metabolic biology, MMRRC resources have supported work on hypertension-induced cardiac remodeling, candidate therapy for heart failure, anti-obesity ketone metabolism, and mechanisms of vasoconstriction (Duse et al. 2024; Cools et al. 2025; Moya-Garzon et al. 2025; Zhang et al. 2025). Other studies illustrate the breadth of translational questions enabled by MMRRC resources. In immunology, cancer, and developmental biology, MMRRC-associated strains have been used to study mucosal immune trafficking, glioblastoma microenvironments, immunotherapy resistance in prostate cancer, cranial neural crest specification, and mechanisms contributing to androgenetic hydatidiform moles (Ocón et al. 2024; Matsuzaki et al. 2025; Barnada et al. 2024; Rezaei et al. 2024).

A particularly relevant example is provided by Lyu et al. (2025) who used an MMRRC-distributed *Spp1*-EGFP reporter mouse to investigate mechanisms of immunotherapy resistance in prostate cancer. By integrating single-cell analyses of human tumors, genetically defined mouse models, in vitro T-cell suppression assays, and therapeutic interventions in vivo, the investigators identified SPP1-high tumor-associated macrophages as mediators of immune suppression and resistance to checkpoint blockade. These findings illustrate how MMRRC resources can provide mechanistic and physiological context for observations derived from human tissues and cell-based experimental systems, strengthening the translational interpretation of complementary approaches.

Outcomes such as these could only be carried out in studies using experimental approaches capable of modeling complex biological systems in vivo. Further, these examples reinforce the point that MMRRC resources are already contributing to translational research across therapeutic areas, from target discovery and disease mechanism to therapeutic testing. Although these studies do not necessarily represent formal validation of NAM platforms, they illustrate the value of well-characterized in vivo models and data that can be used for mechanistic comparison and evaluation across complementary experimental systems.

Enhanced phenotyping and data standardization

In addition to genotype, model quality depends also on the depth of phenotype and quality of metadata. One reason translation fails is that preclinical phenotypes are sometimes too shallow, too narrow, or too poorly contextualized to support clinical inference. The MMRRC can provide standardized phenotyping, longitudinal assessment, and rich documentation of variables such as sex, age, genetic background, microbiome, husbandry, and environmental exposures.

The existing MMRRC Strain Detail Sheet structure links genotype, background, husbandry, genotyping methods, cryorecovery protocols, and availability in a way that supports authentication and reuse (Agca et al. 2024). This is strengthened further through the adoption of RRIDs, FAIR

data principles, ARRIVE 2.0 reporting standards, and newer laboratory animal genetic reporting frameworks such as Laboratory Animal Genetic Reporting (LAG-R) (Bandrowski and Martone 2016; Wilkinson et al. 2016; Percie du Sert et al. 2020; Teboul et al. 2024) which is a framework for standardized reporting and comparison of laboratory animal genetic information. Standardized metabolic and physiologic phenotyping through operational relationships with complementary NIH resources such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored Mouse Metabolic Phenotyping Centers (MMPC) *Live* program also enhances the ability of the MMRRC to contribute to translational comparability, especially for cardiometabolic and endocrine models (Laughlin et al. 2024). In parallel, systematic links to IMPC data help investigators interpret whether an observed phenotype is robust, background-specific, or part of a broader genotype-phenotype pattern (Lloyd 2024).

These data resources also provide a foundation for comparing mouse studies with NAM-derived findings. Genotype, genetic background, phenotype, experimental conditions, and biological endpoints can be used to identify appropriate in vivo comparators and interpret concordance or discordance across platforms. For example, matching a molecular perturbation in a human cell-derived system to the corresponding genetic alteration in a mouse model can help determine which effects are cell intrinsic and which depend on interactions among tissues or organ systems.

Integration into a functional genomics ecosystem

One-to-one phenotypic matching is not the focus of model validity (Robinson et al. 2008). A more productive approach is comparative and mechanism-centered (Haendel et al. 2015). Does the model perturb the same gene network, cell state, developmental process, or therapeutic pathway as in human disease? Can phenotypic commonalities and differences be mapped explicitly across species? Are discordant findings informative about context dependence rather than grounds for dismissing the model outright?

The MMRRC is especially valuable in this setting because its resources are already linked to broader informatics databases, including MGI, OMIM, IMPC, and the Monarch Initiative, which supports phenotype-driven, cross-species computational analysis (Agca et al. 2024; Putman et al. 2024). The MMRRC continually works to expand these connections to deepen its integration into external research resources. Cross-species comparison can help investigators move beyond simplistic "mouse versus human" debates and instead ask whether a conserved mechanism is present, whether a therapeutic target behaves similarly across contexts, and what additional experiments are needed when it does not.

Improved rigor, reproducibility, and accessibility

Translational research depends on more than scientific creativity alone. It relies on the persistent availability of well-characterized reagents. In that sense, the MMRRC is a necessity, not a mere convenience. A mouse model cannot serve as a scientific standard if it disappears when a laboratory closes, drifts genetically over time, accumulates undocumented microbial differences, or is distributed only through informal exchanges that lack robust quality control. Centralized repositories were created to solve these problems, and they remain critical for doing so (Donahue et al. 2012; Lloyd 2015).

Public repositories also serve the 3Rs (replacement, reduction, refinement) by reducing unnecessary duplication. Re-creating a model *de novo* because the original is inaccessible wastes time, money, and animals. Similarly, reusing a validated, cryopreserved line is both more efficient and more rigorous. The MMRRC's cryoarchiving, recovery, pathogen control, and disaster planning efforts have direct translational consequences by preserving scientific investments, enabling independent replication, and increasing confidence that results obtained across laboratories are being generated with the same underlying biological reagent (Agca et al. 2024).

Leveraging emerging technologies

The translational value of the MMRRC will only increase as technologies improve. Rapid CRISPR-based genome engineering, including more efficient editing workflows, allows investigators to build mouse models around patient-derived variants, noncoding regulatory elements, combinatorial genotypes, and more precise disease architectures than were previously practical (Gurumurthy and Lloyd 2019; Modzelewski et al. 2018). This makes repository-based archiving even more important, because the number and complexity of useful models will continue to grow.

At the same time, emerging phenotyping technologies can make MMRRC resources more informative. Molecular phenotyping, single-cell and spatial transcriptomics, quantitative imaging, digital pathology, telemetric physiology, advanced behavioral analysis, and AI-assisted phenotyping can reveal subtle or distributed phenotypes that conventional phenotyping approaches might not detect. Longitudinal

multi-omic characterization may be especially valuable for pre-symptomatic disease states, therapeutic response, and modifier effects. The MMRRC contributes to the application of these technologies by providing well-characterized, quality-controlled mouse models for advanced phenotyping and facilitating the interpretation and comparison of findings across experimental systems. Recent studies illustrate how MMRRC-distributed mouse models are being used with advanced phenotyping technologies to investigate disease mechanisms. These include quantitative MRI and histopathological characterization of Alzheimer's disease (Perera et al. 2024), spatial single-cell transcriptomic analysis of disease-associated microglia in Alzheimer's disease (Barahona et al. 2025), and integrated genetic lineage tracing and spatial transcriptomic characterization of *DICER1*-associated sarcoma, including comparisons with human tumors (Kommoss et al. 2026).

Collaborative and translational ecosystem

The future translational role of the MMRRC is best understood as a critical component in the broader translational research ecosystem. In most cases, no single model system is sufficient to translate experimental findings into clinical applications. Mouse repositories, human tissue resources, organoid and chip platforms, computational biology, clinical genetics, phenotyping centers, and disease-focused consortia all contribute different forms of evidence. The MMRRC occupies a distinctive place in that ecosystem because it provides the publicly accessible, reusable in vivo component of biomedical research that relies on the use of mouse models.

That role includes at least four translational functions. *First*, MMRRC resources support mechanistic investigation of genes and pathways for the discovery and validation of novel drug targets. *Second*, the MMRRC enables rigorous and reproducible preclinical studies through the distribution of in vivo model systems. *Third*, the MMRRC accelerates translational research by facilitating access to advanced models of human disease and state-of-the-art in vivo services. *Fourth*, MMRRC mouse models can be used to corroborate, challenge, and contextualize findings from orthogonal NAM systems. In this context, MMRRC mouse models complement NAMs to refine the understanding of disease mechanisms and preclinical outcomes.

Finally, the MMRRC's collaborative value is amplified by its connections to complementary NIH and international infrastructures. Its links to IMPC, MMPC*Live*, phenotype ontologies, and cross-species knowledge systems such as Monarch make it possible to compare model features systematically using well-defined genetic and phenotypic criteria (Agca et al. 2024; Lloyd 2024; Laughlin et al. 2024; Putman et al. 2024). Together, these complementary resources provide an integrated framework for comparative studies that strengthen the biological relevance and translational value of experimental findings.

The MMRRC's distinctive contribution to integrated translational research is not the development of individual NAM platforms, but the provision of standardized, genetically defined, and publicly accessible in vivo resources and associated expertise. As NAM technologies become more widely used, these functions provide an increasingly important foundation for appropriately designed comparative studies.

Future opportunities for integrated model research

The MMRRC is well positioned to expand its role in integrated translational research as advances in genetic engineering, human cell-based systems, computational biology, and phenotyping provide new opportunities to investigate human disease. The MMRRC is modernizing its informatics infrastructure to improve strain discovery, expand connections with external biological databases, and support the integration of data generated across experimental models. These efforts include the development of NAM-ready catalog enhancements, improved access to genotype and phenotype information, and the application of machine learning and artificial intelligence to facilitate resource discovery and reproducibility. Such enhancements are intended to improve the identification of mouse models and associated data suitable for comparison with human cell-based, organoid, and computational systems. These improvements should enable investigators to identify genetically and mechanistically related models across platforms and select experimental systems appropriate to their specific biological questions and hypotheses.

Recently, the MMRRC expanded into the archiving and distribution of human pluripotent stem cells, including iPSCs, which are now available through its online catalog. As new collections are added, these and other human-derived resources can be integrated with genetically defined mouse models. For example, human iPSCs can be subjected to in vitro phenotyping to study the cellular and molecular consequences of specific human genetic variants. Mice genetically engineered to express the corresponding humanized alleles can then be used for in vivo phenotyping of tissue function, interorgan communication, development, immune responses, and other systemic pathophysiological processes that are beyond the resolution of isolated, cell-based systems. Conversely, observations in humanized mouse models

can guide further investigation in patient-derived iPSCs and related NAM platforms.

Further opportunities exist to improve the representation of human genetic and biological diversity in translational studies using MMRRC mice. Expanded access to coordinated breeding, phenotyping, and experimental services can help to address questions related to genetic modifiers, variable penetrance, and differential responses to experimental interventions. Similarly, improved characterization of microbiota, environmental exposures, and other biological variables can assist investigators better understand how genetic and environmental factors influence disease phenotypes and therapeutic responses. These capabilities also can provide more informative in vivo comparators for NAMs developed to represent human biological heterogeneity.

Finally, the MMRRC is also expanding its education and training activities to support the appropriate selection, use, and interpretation of complementary model systems. These efforts can help investigators determine when human cell-based systems, mouse models, or combinations of approaches are most appropriate for addressing a specific biological question or hypothesis. This includes recognizing the limitations of individual experimental platforms, designing studies in which evidence from different systems can be integrated, and interpreting concordant and discordant findings. For example, NAMs can be informative for identifying cell-intrinsic mechanisms, whereas genetically defined mouse models can establish whether those findings are relevant in the context of in vivo physiology. Differences in genetic background, developmental stage, tissue environment, exposure, or experimental endpoint can be examined to resolve discrepancies, make necessary adjustments to the models to improve biological relevance, and/or identify the more appropriate model system for the question at hand.

Conclusion

The MMRRC contributes to translational research in a way that is both practical and conceptual. Practically, it preserves, validates, documents, and distributes mouse models under conditions that improve rigor, accessibility, and reproducibility. Conceptually, it supports a more mature view of translation. It is not just a source for a single perfect model, but a disciplined effort to align model systems with mechanisms of disease. In this context, the MMRRC is a necessary resource for translational research. Without public mouse repositories, valuable models would be lost, distributed unevenly, or used under poorly controlled conditions that undermine confidence in downstream findings. In the absence of high-quality in vivo mammalian resources, many questions involving integrated physiology, development, behavior, immunity, and therapeutic response would be left incompletely answered. If mouse results couldn't be compared against human cell systems, organoids, computational models, and other organisms, translation would be weaker, not stronger.

Mice should not displace NAMs, nor should NAMs displace mice (Lloyd 2025). On the contrary, translational science is strongest when these approaches are used together. In that integrated framework, the NIH-funded MMRRC program serves as a critical translational bridge by preserving community access to rigorous in vivo models, enabling mechanism-based experimentation, and helping convert biological insight into knowledge that is more reproducible, more comparable across systems, and more relevant to human health.

Acknowledgements The authors would like to thank all the staff, scientists, students, and technicians at their respective Centers for their outstanding efforts that contribute to ensuring the continuing success of the MMRRC Program.

Author contributions All authors (T.M., S.A.M., C.M.L., L.R., J.A-L., A.Y., K.C.K.L.) contributed to the conception and drafting of the manuscript. K.C.K.L. prepared the initial draft and coordinated revisions. All authors reviewed, edited, and approved the final manuscript.

Funding The authors received funding from the National Institutes of Health, Division of Program Coordination, Planning, and Strategic Initiatives, Office of Research Infrastructure Programs, Division of Comparative Medicine to TM (U42OD010924), SM, CL, and LR (U42OD010921), JA-L (U42OD010918), AY (U42OD012210), and KL (U42OD010983 and U42OD012210).

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that they have no competing interests.

Ethical approval Ethics approval was not required for this article because no new studies involving human participants or animals were conducted.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

Agca Y, Amos-Landgraf J, Araiza R, Brennan J, Carlson C, Ciavatta D, Clary D, Franklin C, Korf I, Lutz C, Magnuson T, Pardo-Manuel de Villena F, Mirochnitchenko O, Patel S, Port D, Reinholdt L, Lloyd KCK (2024) The mutant mouse resource and research center (MMRRC) consortium: the US-based public mouse repository system. Mamm Genome 35:524–536

Avila AM, Bebenek I, Bonzo JA, Bourcier T, Davis Bruno KL, Carlson DB, Dubinion J, Elayan I, Harrouk W, Lee SL, Mendrick DL, Merrill JC, Peretz J, Place E, Saulnier M, Wange RL, Yao J, Zhao D, Brown PC (2020) An FDA/CDER perspective on nonclinical testing strategies: classical toxicology approaches and new approach methodologies (NAMs). Regul Toxicol Pharmacol 114:104662

Bandrowski AE, Martone ME (2016) RRIDs: A Simple Step toward Improving Reproducibility through Rigor and Transparency of Experimental Methods. Neuron 90:434–436

Barahona RA, Kwang NE, Kono-Soosaipillai AR, Rubio Salgado G, Tran KM, Lu YH, Reddy S, da Cunha C, Velazquez-Rivera E, Crapser JD, Xu X, Hohsfield LA, Green KN (2025) Aggrecan protects against plaque accumulation and is essential for proper microglial responses to plaques. Cell Rep 44:116064

Barnada SM, Giner de Gracia A, Morenilla-Palao C, López-Cascales MT, Scopa C, Waltrich FJ Jr, Mikkers HMM, Cicardi ME, Karlin J, Trotti D, Peterson KA, Brugmann SA, Santen GWE, McMahon SB, Herrera E, Trizzino M (2024) ARID1A-BAF coordinates ZIC2 genomic occupancy for epithelial-to-mesenchymal transition in cranial neural crest specification. Am J Hum Genet 111:2232–2252

Birling MC, Yoshiki A, Adams DJ, Ayabe S, Beaudet AL, Bottomley J, Bradley A, Brown SDM, Bürger A, Bushell W, Chiani F, Chin HG, Christou S, Codner GF, DeMayo FJ, Dickinson ME, Doe B, Donahue LR, Fray MD, Gambadoro A, Gao X, Gertsenstein M, Gomez-Segura A, Goodwin LO, Heaney JD, Hérault Y, de Angelis MH, Jiang ST, Justice MJ, Kasparek P, King RE, Kühn R, Lee H, Lee YJ, Liu Z, Lloyd KCK, Lorenzo I, Mallon AM, McKerlie C, Meehan TF, Fuentes VM, Newman S, Nutter LMJ, Oh GT, Pavlovic G, Ramirez-Solis R, Rosen B, Ryder EJ, Santos LA, Schick J, Seavitt JR, Sedlacek R, Seisenberger C, Seong JK, Skarnes WC, Sorg T, Steel KP, Tamura M, Tocchini-Valentini GP, Wang CL, Wardle-Jones H, Wattenhofer-Donzé M, Wells S, Wiles MV, Willis BJ, Wood JA, Wurst W, Xu Y, Teboul L, Murray SA, International Mouse Phenotyping Consortium (IMPC) (2021) A resource of targeted mutant mouse lines for 5061 genes. Nat Genet 53:416–419

Cools JMT, Goovaerts BK, Feyen E, Van den Bogaert S, Fu Y, Civati C, Van Fraeyenhove J, Tubeeckx MRL, Ott J, Nguyen L, Wülfers EM, Van Berlo B, De Vries AAF, Vandersickel N, Pijnappels DA, Audenaert D, Roderick HL, De Winter H, De Keulenaer GW, Segers VFM (2025) Small-molecule-induced ERBB4 activation to treat heart failure. Nat Commun 16:576

de Pardo-Manuel F, Amos-Landgraf JM, Bell TA, Blanchard MW, Brennan J, Carlson C, Ciavatta DJ, Cotney PA, Ferris MT, Hock P, Korf I, Lloyd KCK, Lutz C, Lynch RM, Magnuson T, Murray SA, Patel S, Reinholdt LG, Sigmon JS, Willis B, Xenakis JG (2026) Improve genetic quality control to increase rigor and reproducibility of mouse research. Science 392:698–700

Donahue LR, Hrabe de Angelis M, Hagn M, Franklin C, Lloyd KCK, Magnuson T, McKerlie C, Nakagata N, Obata Y, Read S, Wurst W, Hörlein A, Davisson MT (2012) Centralized mouse repositories. Mamm Genome 23:559–571

Duse DA, Schröder NH, Srivastava T, Benkhoff M, Vogt J, Nowak MK, Funk F, Semleit N, Wollnitzke P, Erkens R, Kötter S, Meuth SG, Keul P, Santos W, Polzin A, Kelm M, Krüger M, Schmitt J, Levkau B (2024) Deficiency of the sphingosine-1-phosphate (S1P) transporter Mfsd2b protects the heart against hypertension-induced cardiac remodeling by suppressing the L-type-Ca2 + channel. Basic Res Cardiol 119:853–868

Ericsson AC, Franklin CL (2021) The gut microbiome of laboratory mice: considerations and best practices for translational research. Mamm Genome 32:239–250

Guo W, Rioux M, Shaffo F, Hu Y, Yu Z, Xing C, Gray SJ (2025) AAV9/SLC6A1 gene therapy rescues abnormal EEG patterns and cognitive behavioral deficiencies in Slc6a1−/− mice. J Clin Invest 135:e182235

Gurumurthy CB, Lloyd KCK (2019) Generating mouse models for biomedical research: technological advances. Dis Model Mech 12:dmm029462

Haendel MA, Vasilevsky N, Brush M, Hochheiser HS, Jacobsen J, Oellrich A, Mungall CJ, Washington N, Köhler S, Lewis SE, Robinson PN, Smedley D (2015) Disease insights through cross-species phenotype comparisons. Mamm Genome 26:548–555

Kommoss FKF, Zhang JYH, Lynch BJ, Chen SY, Senz J, Moscovitz Y, Hill LA, Ma D, Scott RW, Bush J, Chen KS, Roth A, von Deimling A, Foulkes WD, Morin GB, Underhill TM, Wang Y, Huntsman DG (2026) Spatial single cell transcriptomic analysis informs tumor developmental hierarchy of DICER1 syndrome related sarcoma. Nat Commun 17:4608

Laughlin M, McIndoe R, Adams SH, Araiza R, Ayala JE, Kennedy L, Lanoue L, Lantier L, Macy J, Malabanan E, McGuinness OP, Perry R, Port D, Qi N, Elias CF, Shulman GI, Wasserman DH, Lloyd KCK (2024) The mouse metabolic phenotyping center (MMPC) live consortium: an NIH resource for in vivo characterization of mouse models of diabetes and obesity. Mamm Genome 35:485–496

Lloyd KCK (2015) Use mouse biobanks or lose them. Nature 522:151–153

Lloyd KCK (2024) The International Mouse Phenotyping Consortium: high-throughput in vivo functional annotation of the mammalian genome. Mamm Genome 35:537–543

Lloyd KCK (2025) Why simply ending animal testing is not the answer in biomedical research. Nature 643:1191

Lloyd KCK (2026) Restoring comparative expertise to improve translation of animal models. Dis Model Mech 19:dmm053172

Lyu A, Fan Z, Clark M, Lea A, Luong D, Setayesh A, Starzinski A, Wolters R, Arias-Badia M, Allaire K, Wu K, Gurunathan V, Valderrábano L, Wei XX, Miller RA, Van Allen EM, Fong L (2025) Evolution of myeloid-mediated immunotherapy resistance in prostate cancer. Nature 637:1207–1217

Matsuzaki H, Kai K, Komohara Y, Yano H, Pan C, Fujiwara Y, Yamada R, Iwauchi A, Fukasawa N, Tanaka T, Shimoda M, Watanabe H, Maruyama T, Takeo T, Mikami Y, Mukasa A (2025) Abnormal vessels potentially accelerate glioblastoma proliferation by inducing the protumor activation of macrophages. Cancer Sci 116:897–909

Melo US, Bonner D, Kent Lloyd KC, Moshiri A, Willis B, Lanoue L, Bower L, Leonard BC, Martins DJ, Gomes F, de Souza Leite F, Oliveira D, Kitajima JP, Monteiro FP, Zatz M, Menck CFM, Wheeler MT, Bernstein JA, Dumas K, Spiteri E, Di Donato N, Jahn A, Hashem M, Alsaif HS, Chedrawi A, Alkuraya FS, Kok F, Byers HM (2021) Biallelic UBE4A loss-of-function variants cause intellectual disability and global developmental delay. Genet Med 23:661–668

Michaud F, Francavilla R, Topolnik D, Iloun P, Tamboli S, Calon F, Topolnik L (2024) Altered firing output of VIP interneurons and early dysfunctions in CA1 hippocampal circuits in the 3xTg mouse model of Alzheimer's disease. eLife 13:RP95412

Modzelewski AJ, Chen S, Willis BJ, Lloyd KCK, Wood JA, He L (2018) Efficient mouse genome engineering by CRISPR-EZ technology. Nat Protoc 13:1253–1274

Morgan AP, Fu CP, Kao CY, Welsh CE, Didion JP, Yadgary L, Hyacinth L, Ferris MT, Bell TA, Miller DR, Giusti-Rodriguez P, Nonneman RJ, Cook KD, Whitmire JK, Gralinski LE, Keller M, Attie AD, Churchill GA, Petkov P, Sullivan PF, Brennan JR, McMillan L, Pardo-Manuel de Villena F (2015) The mouse universal genotyping array: from substrains to subspecies. G3 (Bethesda) 6:263–279

Moya-Garzon MD, Wang M, Li VL, Lyu X, Wei W, Tung AS, Raun SH, Zhao M, Coassolo C, Islam H, Oliveira B, Dai Y, Spaas J, Delgado-Gonzalez A, Donoso K, Alvarez-Buylla A, Franco-Montalban F, Letian A, Ward CP, Liu L, Svensson KJ, Goldberg EL, Gardner CD, Little JP, Banik SM, Xu Y, Long JZ (2025) A β-hydroxybutyrate shunt pathway generates anti-obesity ketone metabolites. Cell 188:175-186.e20

Ocón B, Xiang M, Bi Y, Tan S, Brulois K, Ayesha A, Kunte M, Zhou C, LaJevic M, Lazarus N, Mengoni F, Sharma T, Montgomery S, Hooper JE, Huang M, Handel T, Dawson JRD, Kufareva I, Zabel BA, Pan J, Butcher EC (2024) A lymphocyte chemoaffinity axis for lung, non-intestinal mucosae and CNS. Nature 635:736–745

Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen OH, Rawle F, Reynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Würbel H (2020) The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. PLoS Biol 18:e3000410

Perera C, Cruz R, Shemesh N, Carvalho T, Thomas DL, Wells J, Ianuș A (2024) Non-invasive MRI of blood-cerebrospinal fluid-barrier function in a mouse model of Alzheimer's disease: a potential biomarker of early pathology. Fluids Barriers CNS 21:97

Perrin S (2014) Make mouse studies work. Nature 507:423–425

Piekniewska A, Roelandse M, Lloyd KCK, Korf I, Voss SR, de Castro G, Magnani DM, Varga Z, James-Zorn C, Horb M, Grethe JS, Bandrowski A (2025) Do organisms need an impact factor? Citations of key biological resources including model organisms reveal usage patterns and impact. PLoS One 20:e0327344

Putman TE, Schaper K, Matentzoglu N, Rubinetti VP, Alquaddoomi FS, Cox C, Caufield JH, Elsarboukh G, Gehrke S, Hegde H, Reese JT, Braun I, Bruskiewich RM, Cappelletti L, Carbon S, Caron AR, Chan LE, Chute CG, Cortes KG, De Souza V, Fontana T, Harris NL, Hartley EL, Hurwitz E, Jacobsen JOB, Krishnamurthy M, Laraway BJ, McLaughlin JA, McMurry JA, Moxon SAT, Mullen KR, O'Neil ST, Shefchek KA, Stefancsik R, Toro S, Vasilevsky NA, Walls RL, Whetzel PL, Osumi-Sutherland D, Smedley D, Robinson PN, Mungall CJ, Haendel MA, Munoz-Torres MC (2024) The Monarch Initiative in 2024: an analytic platform integrating phenotypes, genes and diseases across species. Nucleic Acids Res 52:D938–D949

Rezaei M, Liang M, Yalcin Z, Martin JH, Kazemi P, Bareke E, Ge ZJ, Fardaei M, Benadiva C, Hemida R, Hassan A, Maher GJ, Abdalla E, Buckett W, Bolze PA, Sandhu I, Duman O, Agrawal S, Qian J, Vallian Broojeni J, Bhati L, Miron P, Allias F, Selim A, Fisher RA, Seckl MJ, Sauthier P, Touitou I, Tan SL, Majewski J, Taketo T, Slim R (2024) Defects in meiosis I contribute to the genesis of androgenetic hydatidiform moles. J Clin Invest 134:e170669

Robinson PN, Köhler S, Bauer S, Seelow D, Horn D, Mundlos S (2008) The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. Am J Hum Genet 83:610–615

Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, Finnerty CC, López CM, Honari S, Moore EE, Minei JP, Cuschieri J, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Jeschke MG, Klein MB, Gamelli RL, Gibran NS, Brownstein BH, Miller-Graziano C, Calvano SE, Mason PH, Cobb JP, Rahme LG, Lowry SF, Maier RV, Moldawer LL, Herndon DN, Davis RW, Xiao W, Tompkins RG, Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 110:3507–3512

Shankar SP, Grimsrud K, Lanoue L, Egense A, Willis B, Hörberg J, AlAbdi L, Mayer K, Ütkür K, Monaghan KG, Krier J, Stoler J, Alnemer M, Shankar PR, Schaffrath R, Alkuraya FS, Brinkmann U, Eriksson LA, Lloyd K, Rauen KA (2022) Undiagnosed Diseases Network. A novel DPH5-related diphthamide-deficiency syndrome causing embryonic lethality or profound neurodevelopmental disorder. Genet Med 24:1567–1582 Erratum in: Genet Med. 2022;24(10):2207

Sigmon JS, Blanchard MW, Baric RS, Bell TA, Brennan J, Brockmann GA, Burks AW, Calabrese JM, Caron KM, Cheney RE, Ciavatta D, Conlon F, Darr DB, Faber J, Franklin C, Gershon TR, Gralinski L, Gu B, Gaines CH, Hagan RS, Heimsath EG, Heise MT, Hock P, Ideraabdullah F, Jennette JC, Kafri T, Kashfeen A, Kulis M, Kumar V, Linnertz C, Livraghi-Butrico A, Lloyd KCK, Lutz C, Lynch RM, Magnuson T, Matsushima GK, McMullan R, Miller DR, Mohlke KL, Moy SS, Murphy CEY, Najarian M, O'Brien L, Palmer AA, Philpot BD, Randell SH, Reinholdt L, Ren Y, Rockwood S, Rogala AR, Saraswatula A, Sassetti CM, Schisler JC, Schoenrock SA, Shaw GD, Shorter JR, Smith CM, St Pierre CL, Tarantino LM, Threadgill DW, Valdar W, Vilen BJ, Wardwell K, Whitmire JK, Williams L, Zylka MJ, Ferris MT, McMillan L, Manuel de Villena FP (2020) Content and performance of the MiniMUGA genotyping array: a new tool to improve rigor and reproducibility in mouse research. Genetics 216:905–930

Teboul L, Amos-Landgraf J, Benavides FJ, Birling MC, Brown SDM, Bryda E, Bunton-Stasyshyn R, Chin HJ, Crispo M, Delerue F, Dobbie M, Franklin CL, Fuchtbauer EM, Gao X, Golzio C, Haffner R, Hérault Y, Hrabe de Angelis M, Lloyd KCK, Magnuson TR, Montoliu L, Murray SA, Nam KH, Nutter LMJ, Pailhoux E, Pardo Manuel de Villena F, Peterson K, Reinholdt L, Sedlacek R, Seong JK, Shiroishi T, Smith C, Takeo T, Tinsley L, Vilotte JL, Warming S, Wells S, Whitelaw CB, Yoshiki A, Pavlovic G, RRRC- Rat Resource and Research Center (2024) Improving laboratory animal genetic reporting: LAG-R guidelines. Nat Commun 15:5574

Threadgill DW, Miller DR, Churchill GA, de Villena FP (2011) The collaborative cross: a recombinant inbred mouse population for the systems genetic era. ILAR J 52:24–31

van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, Macleod MR (2010) Can animal models of disease reliably inform human studies? PLoS Med 7:e1000245

Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, Blomberg N, Boiten JW, da Silva Santos LB, Bourne PE, Bouwman J, Brookes AJ, Clark T, Crosas M, Dillo I, Dumon O, Edmunds S, Evelo CT, Finkers R, Gonzalez-Beltran A, Gray AJ, Groth P, Goble C, Grethe JS, Heringa J, 't Hoen PA, Hooft R, Kuhn T, Kok R, Kok J, Lusher SJ, Martone ME, Mons A, Packer AL, Persson B, Rocca-Serra P, Roos M, van Schaik R, Sansone SA, Schultes E, Sengstag T, Slater T, Strawn G, Swertz MA, Thompson M, van der Lei J, van Mulligen E, Velterop J, Waagmeester A, Wittenburg P, Wolstencroft K, Zhao J, Mons B (2016) The FAIR guiding principles for scientific data management and stewardship. Sci Data 3:160018

Zhang X, Cheng Y, Lu Y, Xu N, Guo Z, Wu M, Lin G, Yao M, Yang Y, Lin Y, Peng J, Shen A (2025) DAPK1 acts as a positive regulator of hypertension via induction of vasoconstriction. Clin Sci 139:667–681

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.