Researchers call for genetically diverse models to drive innovation in drug discovery

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A stylized icon of the mouse and human connection created by JAX Creative. Credit: The Jackson Laboratory

Researchers at The Jackson Laboratory (JAX) have unveiled a new approach to drug discovery that could revolutionize how we understand and treat diseases. Their commentary in the Aug.14 issue of *Nature Biotechnology* explains the limitations of studies using traditional mouse models and proposes using genetically diverse mice and mouse and

human cells to better predict human responses to drugs and diseases.

For decades, scientists have relied on inbred mice to study human diseases and test new drugs. However, these mice often fail to accurately replicate human conditions, especially for complex diseases like cancer and diabetes. The FDA's recent decision to allow alternatives to animal testing through the Modernization Act 2.0 highlights the urgency of finding more reliable solutions.

JAX Mammalian Genetics Scientific Director Nadia Rosenthal, Ph.D., F.Med.Sci, and colleagues make a bold claim: it's not the mice that are the problem, but the lack of genetic diversity in the models used. Reliance on a single inbred strain can lead to inconsistent and often unreliable results, creating unnecessary obstacles to finding better therapies for a variety of diseases.

A new, more accurate approach

The researchers propose an integrative solution: combine the use of genetically diverse mouse models with cell-based assays to more accurately match data from mice and humans. This approach takes full advantage of the rich genetic resources already available in diverse mouse and human populations to create more accurate and relevant disease models.

"Using diverse mouse models has already shown remarkable improvements in mimicking human diseases," said Rosenthal. "This method could revolutionize our understanding of disease progression and patients' responses to different treatments."

Real-world impact

Studies using diverse mice have already provided valuable insights into diseases like heart disease, cancer, and diabetes. For example, recent research on chemotherapy side effects identified genetic factors that influence how patients respond to treatment, leading to more personalized and effective therapies for cancer patients.

And heart attacks in humans can lead to variable severity and different kinds of damage to the heart, such as scarring or dilation, driven by complex genetics that a single inbred mouse strain is unable to replicate. A genetically diverse mouse panel showed a human-like variety of outcomes, however.

This new framework stresses the importance of combining mouse and human data. While human cell-based tests are useful, they often fall short in capturing the full complexity of human diseases. Cells from genetically diverse mouse models help fill this gap, ensuring that findings are directly applicable to real-world patients.

A call to action

The authors advocate for a new, balanced approach that respects ethical concerns while maximizing scientific benefits. They urge the community to embrace experimental designs that account for genetic diversity and environmental factors, moving away from standardized but limited mouse and cellular models.

By combining the strengths of both in vitro and in vivo systems, researchers will be able to develop more effective, humane methods for studying human diseases and testing new treatments.

More information: Improving the predictive power of mouse models, *Nature Biotechnology* (2024). DOI: 10.1038/s41587-024-02349-2

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