'Wildling' mice could help translate results in animal models to results in humans

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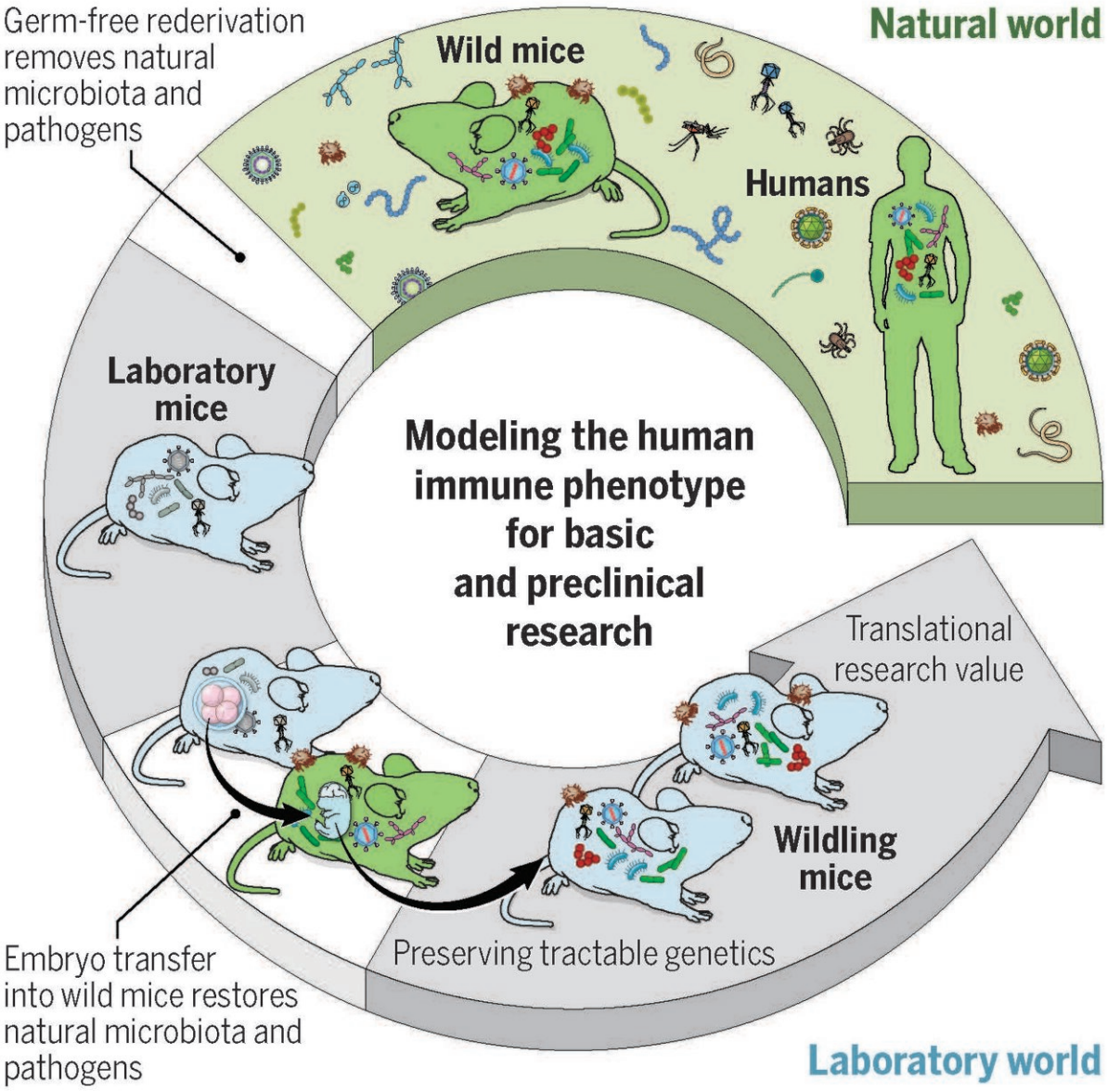

Researchers harnessed natural microbiota and pathogens to address shortcomings of current mouse models. Credit: Reprinted with permission from Rosshart et al., *Science* 365:eaaw4361 (2019)

Researchers at the National Institutes of Health developed a new mouse model that could improve the translation of research in mice into advances in human health. The mouse model, which the scientists called "wildling," acquired the microbes and pathogens of wild mice, while maintaining the laboratory mice's genetics that make them more useful for research. In two preclinical studies, wildlings mirrored human immune responses, where lab mice failed to do so. Led by scientists at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the study published online in *Science*.

"We wanted to create a mouse model that better resembles a mouse you'd find in the wild," said Barbara Rehermann, M.D., chief of the Immunology Section in NIDDK's Liver Diseases Branch and senior author on the study. "Our rationale was that the immune responses and microbiota of wild mice and humans are likely shaped in a similar way—through contact with diverse microbes out in the real world."

Microbiota refers to the trillions of tiny microbes, such as bacteria, fungi, and viruses, that live in and on the bodies of people and animals and play a critical role in keeping immune systems healthy. Unlike squeaky clean lab mice raised in artificial settings, wild mice have developed symbiotic relationships with microbes they have encountered in the outside world—just as people have done.

Rehermann and Stephan Rosshart, M.D., the study's lead author and NIDDK postdoctoral fellow, have long sought to improve animal models of complex diseases in humans. In 2017, they led research showing that

transferring wild mice gut microbiota into lab mice helped the mice survive an otherwise lethal flu virus infection and fight colorectal cancer.

The image depicts the transfer of natural microbiota from the “Natural World” to the “Laboratory World.” Credit: National Institutes of Health

In the current study, they transplanted embryos of the most commonly used strain of laboratory mice for immune system research into female wild mice, who then gave birth to and raised wildlings. The researchers and their collaborators compared the microbiota of the wildlings, wild mice and lab mice. They found that the wildlings acquired the microbes and pathogens of wild mice and closely resembled wild mice in their bacterial microbes present at the gut, skin, and vagina, as well as in the number and kinds of fungi and viruses present.

"A healthy microbiome is important not only for the immune system, but also for digestion, metabolism, even the brain," said Rosshart, who recently completed his fellowship in NIDDK and will open a new lab in Germany. "The wildling model could help us better understand what causes diseases, and what can protect us from them, thus benefitting many areas of biomedical research."

The researchers also tested the stability and resilience of the wildlings' microbiota and found the microbiota was stable across five generations and resilient to environmental challenges. For example, when the mice were given antibiotics for seven days, the lab mice's gut microbiota changed and did not recover, while the wildlings' microbiota fully recovered. Further, when the mice were fed a 10-week high-fat diet, the microbiota of the lab mice changed significantly and never returned to baseline. The wildlings' microbiota changed only mildly and recovered shortly after the diet ended. The authors suggest that the stability and resilience of wildlings, if the model is used widely, could improve the validity and reproducibility of biomedical studies.

Finally, the researchers tested how well the wildlings could predict human immune responses. To do so, they drew from two studies where drugs used to target immune responses were successful in treating lab mice in preclinical trials but consequently failed to have therapeutic effects in humans. In the current study, the researchers treated wildlings and lab mice with the same drugs. The wildlings, but not the lab mice, mimicked the human responses seen in clinical trials.

"We always strive for effective ways to shorten the gap between early lab findings and health advances in people, and the wildling model has the potential to do just that," said NIDDK Director Griffin P. Rodgers, M.D. "By helping to predict immune responses of humans, the wildling model could lead to important discoveries to help treat and prevent disease, and ultimately, improve human health."

More information: S. Rosshart el al., "Laboratory mice born to wild mice have natural microbiota and model human immune responses," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aaw4361

S.P. Nobs el al., "Walk on the wildling side," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aay2864

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