“Born to be Wild - Wildlings a novel translational research model for human diseases".

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Mouse models are paramount for research. However, they suffer from major shortcomings like irreproducible results rooted in divergent microbiota among institutions and the fact that the transition from studies in mice to bedside practice in humans rarely works. A vast body of literature shows that lab mice have not only misdirected clinical approaches consuming trillions of euros (1), but also caused fatal outcomes in human trials (2, 3). The imperative question is: How can we solve these problems!?

Microbiome research may help to answer this question. Even tough, the microbiome plays a vital role in every aspect of physiology. Till recently, the limited translational value of the lab mouse was primarily attributed to differences in genetics between mice and humans. However, paradigm-shifting work has shown that lab mice are too far removed from natural conditions to faithfully mirror the physiology of free-living mammals like humans. Mammals and their immune systems evolved to survive and thrive in a microbial world and behave differently in a sanitized environment. This distorts how the immune system of ultra-clean lab mice develops and functions, leading to false assumptions of how the human immune system works.

To improve mouse models, three concepts were proposed. The “rewilding approach” houses lab mice in diverse seminatural-environments, the “dirty mouse approach” exposes lab mice to pathogens that may or may not represent natural exposure, and the “natural microbiota approach” implants embryos of lab mice into wild mice to create “wildlings”. Wildlings more closely resemble the natural mammalian metaorganism of humans with co-evolved microbes and pathogens while preserving the genetics of lab mice (4, 5).

Indeed, in preclinical trials, where rodent and non-human primate models failed to predict the human response to harmful drug treatments (2, 3), wildlings accurately phenocopied humans and could have prevented these catastrophically failed human trials (5). Further, the microbiome of wildlings was stable over multiple generations and highly resilient against environmental challenges thereby providing an excellent model for long-term work and reproducible experimentation (4, 5).

In summary, such models may open up a promising window of opportunity and facilitate the discovery of treatments that cannot be found in lab mice, increase the safety and success of bench-to-bedside efforts, reduce costs and the number of animals needed, and accelerate the development of disease treatments for the benefit of human health.

References:

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