Has the SPF concept gone too far?

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In the development of new treatments for human diseases, mice are the most commonly used animal model before drugs are tested in humans. However, results from animal experiments often lack reproducibility, and findings in mice frequently differ significantly from those observed in humans. This presents both a costly and health-related challenge for drug development, as well as for the ethical issue of wasting animal lives. One possible explanation is that specific pathogen free (SPF) mice are raised in highly controlled, ultraclean environments, resulting in a lack of essential gut bacteria and exposure to infections that are critical for the proper development of their immune systems. Consequently, their immune systems differ significantly from those of wild mice and humans, who have been exposed to common 'childhood diseases'. Additionally, gut bacterial composition varies depending on the breeder. While it is well known that different mouse strains can yield varying results in identical experimental setups, differences in gut bacteria can also contribute to these inconsistencies. Despite this, inter-individual microbial differences in mice are rarely considered in final data analyses. The current reproducibility crisis highlights the need for strategies that prevent the loss of valuable insights from animal research and improve the translation of results to human contexts.

Recent studies have demonstrated that wild mice and SPF mice exposed to certain microbial stimuli that are otherwise absent in SPF facilities, develop immune systems more closely resembling those of adult humans. These 'dirty' mice better mimic human responses to drugs and vaccines, and exhibit less variability compared to 'clean' SPF mice, enhancing reproducibility and reducing group sizes. However, introducing disease-causing microbes into animal facilities raises concerns about animal welfare, increased mortality, zoonotic transmission, and experimental bias. To address this, we are currently developing a system in which SPF mice receive gut bacteria from uninfected wild-caught mice or injections of inactivated pathogens. This approach aims to simulate the immune development seen in wild mice that have encountered the 'childhood diseases', without causing disease or risk of infections within the facility, and we hope to develop a new 'dirty' but safe mouse that exhibit more human-like responses to established treatments compared to untreated SPF mice.