Research team introduces new tool to boost battle against childhood undernutrition

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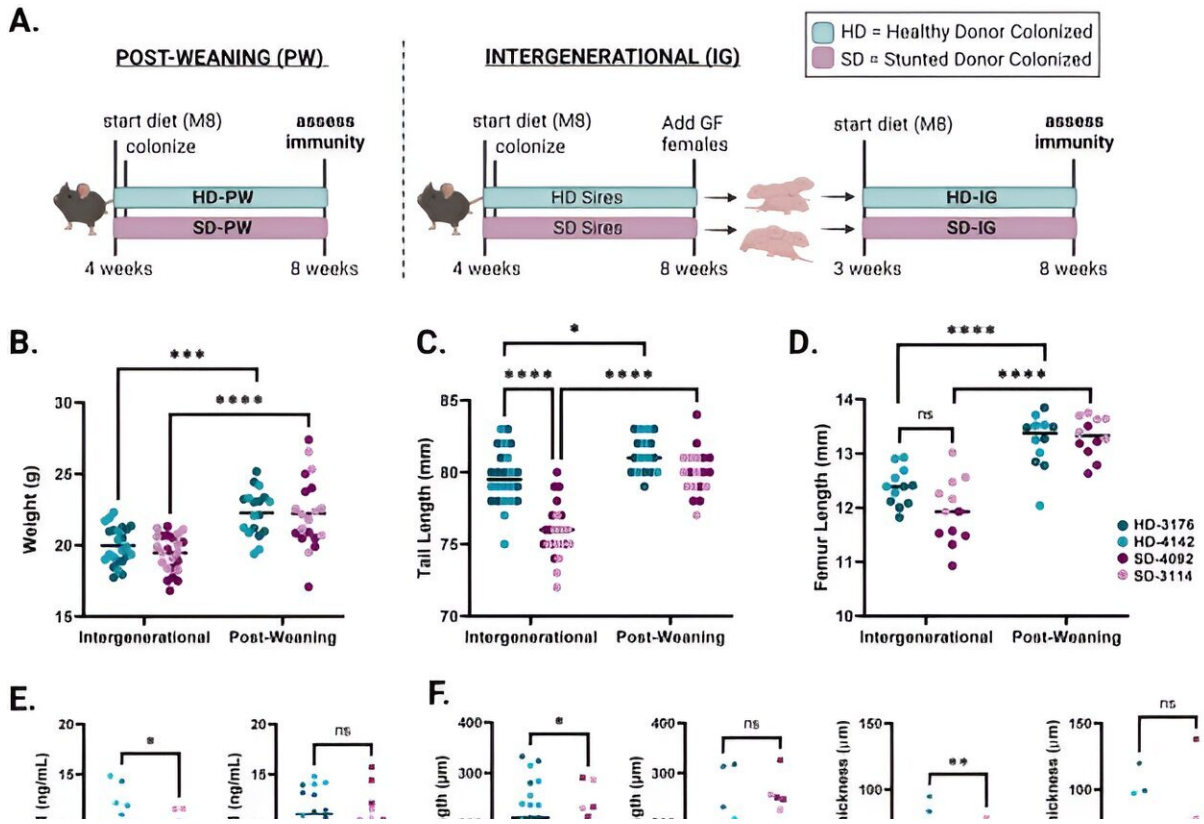

Development of a murine model of intergenerational undernutrition. **A** Schematic of experimental design (created with Biorender.com). Both HD and SD pups in the PW model are maintained on the M8 diet from 4–8 weeks of age. HD and SD pups in the IG model are likewise weaned onto the M8 diet at 3 weeks of age. **B** Absolute weight of animals at the time of euthanasia**. C** Tail length. **D** Femur length. **E** Measurement of IGF-1 in liver tissue of IG and PW mice. (**F**) Representative histological images of H&E stained ileal tissue from IG mice. **G** Quantification of villus length and muscularis thickness in IG and PW

mice. Data shown pooled between healthy donor colonized mice (3176 and 4142) and stunted donor colonized mice (4092 and 3114) at 8 weeks of age. Each point represents an individual animal. **B-D** * $p \leq 0.05$, **** $p \leq 0.0001$ by Two-Way ANOVA with Šídák's multiple comparisons test. **B-C** $n = 24$/group [12 per donor] for IG groups, $n = 18$-20/group [8-10 per donor] for PW groups. **D** $n = 12$/group [6 per donor] for all groups in all conditions (**E**) $n = 16$/group [8 per donor] for all groups. **F-G** $n = 18$-22/group [7-12 per donor] for IG groups, $n = 18$-20/group [8-10 per donor] for PW groups. **E-G** * $p \leq 0.05$, ** $p \leq 0.01$ by Mann-Whitney U test. Credit: *Microbiome* (2024). DOI: 10.1186/s40168-024-01783-3

A new tool developed at the University of Virginia School of Medicine is expected to help doctors and scientists better understand and overcome childhood undernutrition that contributes to almost half of all deaths of children under 5.

The research model created by UVA's Carrie A. Cowardin, Ph.D., and colleagues provides a more sophisticated way to study the effects of undernutrition on the microbiome, the microbes that naturally live inside the gut, and in turn, on growth and the immune system.

The paper is published in the journal *Microbiome*.

Scientists routinely study the many complex interactions within the microbiome by taking samples from the human microbiome and moving them into lab mice. But Cowardin and colleagues found that they could significantly improve the effectiveness of that model by introducing the microbes when the mice were very young, before they had been weaned. This new model of "intergenerational colonization," they determined, better mimicked the effect of undernutrition during early childhood.

"We believe this new model will help us investigate many of the major

challenges facing undernourished children, including higher rates of infection and changes in cognitive development," said Cowardin, part of UVA's Department of Pediatrics. "Our current studies are using this system to identify specific microbes that impact development, with the goal of using these microbes as therapies to promote healthy growth. "

Undernutrition and the microbiome

Using Cowardin's new model, the researchers found that unweaned mice that were given microbes derived from children with impaired growth also suffered stunted growth. Further, the young mice developed immune system responses similar to those seen in human children. But when the microbes were given to mice later in life, the effects were much less similar to what was seen in humans.

That suggests Cowardin's new approach offers a better way to study childhood undernutrition. Further, the results align nicely with prior research suggesting that infancy is a critical period that shapes the health and strength of the immune system throughout life, the researchers say.

The new model, Cowardin said, should help scientists better understand the underlying biological causes of stunted growth and other harmful effects of undernutrition in developing countries. That understanding will advance efforts to develop new approaches to prevent those effects and help children live longer, healthier lives.

"We hope this work also allows us to answer fundamental questions about how the microbiome interacts with our own cells to shape the course of development," Cowardin said. "Growth stunting due to undernutrition is a really difficult problem facing global child health, and the lessons we learn will likely apply to many other conditions as well."

More information: Yadeliz A. Serrano Matos et al, Colonization during a key developmental window reveals microbiota-dependent shifts in growth and immunity during undernutrition, *Microbiome* (2024). DOI: 10.1186/s40168-024-01783-3