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Resilient Microbiome

Building Innate Warfighter Resiliency Against Environmental Exposures Via the Gut Microbiome

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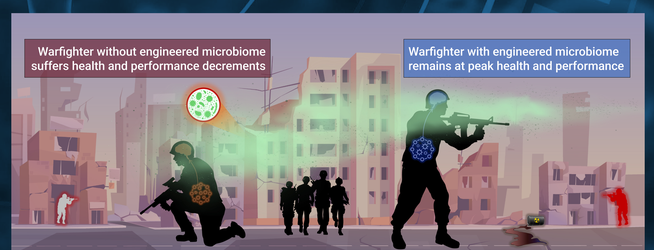

Our hypothesis: the gut microbiome can be engineered to mitigate health and performance decrements from environmental/occupational exposures

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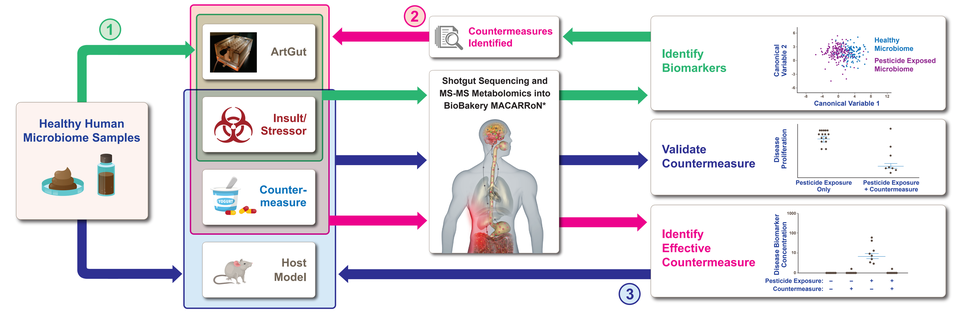
Introduction

- The gut microbiome is a complex, individualized ecosystem shaped by genetics and environmental factors such as diet, stress, and antibiotics
- A diverse microbiome promotes resilience, whereas dysbiosis is linked to inflammation, metabolic disorders, and diseases such as colon cancer
- Understanding both microbial composition and metabolic function is essential to study responses to environmental and chemical exposures
- Traditional models poorly replicate the gut environment, limiting ex vivo microbiome research
- We developed a 3D-printed in vitro system that mimics the colon oxygen gradient for high-throughput microbiome analysis (ArtGut)
- Using the ArtGut platform, a chemical exposure expected to disrupt microbial function was spiked into human gut microbiome samples and cultured 24 hours to assess metabolic impacts and potential resilience of supplemental tryptophan as a countermeasure

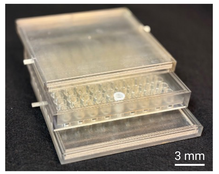
Pipeline to Validate Novel Microbial Biomarkers

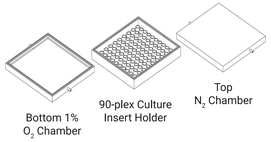


*Pipeline, combining ArtGut culture with downstream analysis, enables iterative process of identifying biomarkers and validating countermeasures using an open-source metabolome-analysis program, MACARRoN (https://huttenhower.sph.harvard.edu/macarron)**

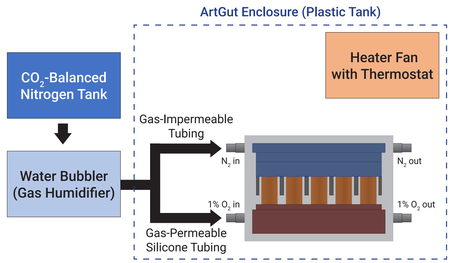
Method and Materials

- 90-plex 3D-printed ArtGut capable of parallel culture of human gut microbiome samples, with disposable gas-permeable inserts for each microbiome sample that emulate radial oxygen gradient in the colon
- Benchtop device operation is carried out in a plastic tank enclosure with a humidified gas source split into two feeds to generate the oxygen gradient across the samples and a heater fan with a thermostat to maintain the cultures at 37°C
- Environmental exposure impacts on microbiome assessed by whole genome sequencing and metabolite profiling

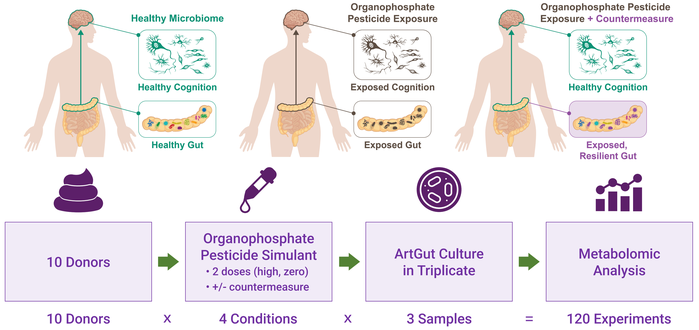




ArtGut Platform



Experimental Design

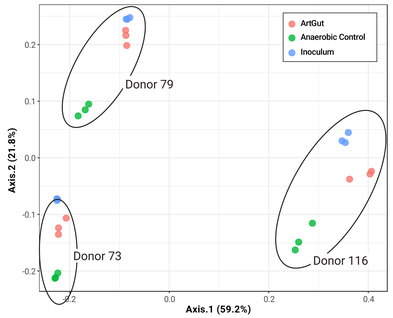


Evaluation of an organophosphate pesticide simulant (demeton-S-methyl) in human gut microbiome samples derived from fresh frozen stool samples and cultured for 24 hours in the ArtGut platform in the presence/absence of L-tryptophan countermeasure

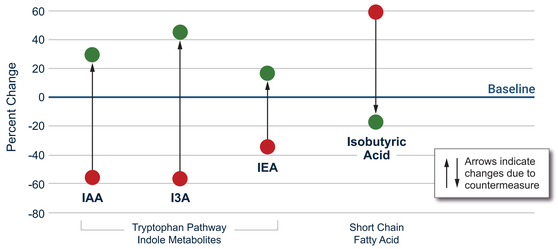
Results

- Microbial composition of samples cultured in ArtGut closer in composition to initial inoculum than anaerobic control
- Addition of prophylactic L-tryptophan provides microbiome resiliency by reversing the effects of Demeton-S exposure for several key metabolites in the tryptophan indole degradation pathway
- Although whole genome sequencing showed minimal taxonomic shifts between the baseline control (untreated) and exposed microbiome samples cultured 24 hours in the ArtGut, metabolic pathway analysis using MACARRoN revealed an upregulation of pathways associated with tryptophan catabolism and the production of NAD+, a key co-enzyme for cellular energy production and resistance to chemical challenges

Maintaining Microbial Diversity With ArtGut



Adding L-Tryptophan Countermeasure Reverses Metabolite Change Caused by High (1:10 Rat LD50) Organophosphate Simulant Demeton-S Exposure



Discussion and Conclusions

- The ArtGut high-throughput platform has clear utility for modeling complex patient-derived microbial communities for screening exposures and countermeasures under controlled in vitro conditions
- The platform allows simultaneous modeling of multiple donor-derived microbiomes that retain their individual characteristics representative of the host they were derived from, even after experimental conditions are introduced
- Using an organophosphate as a model of an acute chemical challenge to human fecal microbiome samples, shifts in microbial function and key metabolites were observed, and supplementation with tryptophan appears to promote resiliency by restoring or preventing perturbations to microbial function

Collaborate with us! **thorsen@ll.mit.edu**