

Revolutions in Biotechnology

Microbiome

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Human Microbiota







Human Microbiota

- Mass of micro-organisms in your body: 3 pounds
- Intestinal tract: 100 trillion microbes
- $10^{11} 10^{12}$ cells/mL in the colon, the highest density recorded for any microbial habitat







Human Microbiota

"Humans are superorganisms with two genomes, the genetically inherited human genome (25,000 genes) and the environmentally acquired human microbiome (over 1 million genes)."

– Liping Zhao, Microbiologist







Microbiome Links to Parkinson's

- Constipation years before onset of neurological symptoms Park et al. Parkinsonism Relat. Discord. (2015)
- Human fecal transplants triggered Parkinson's symptoms in mice Sampson et al. *Cell.* (2016)
- Microbiome diversity much different in Parkinson's, especially in mucus Sampson et al. *Cell.* (2016)
- Microbe-synthesized short chain fatty acids (SCFA) lower in Parkinson's patients, which affect the blood-brain barrier Unger et al. Parkinsonism. Relat. Discord. (2016) Al-Asmakh et al. Tissue Barriers. (2015)









How Relationship between Parkinson's and Microbiome Is Studied Now

Current gut-brain axis studies lack the spatial-temporal resolution required or do not take into account the myriad of chemical and gaseous gradients present in the gut







Why Is This Difficult? Microbiome Is Complex



- 100s of different bacterial species (biodiversity)
- Bacteria stratify themselves to reduce competition for resources (biogeography)
- Current *in vitro* systems lose this complexity
- Gradients in gut critical to microbial complexity





LL Microbiome Testing R&D: ArtGut







ArtGut Goal: Improve throughput, predictive power, ease-of-use, and resolution of microbiome R&D

LINCOLN LABORATORY

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ArtGut System Requirements

	Technical Requirement	System Design
Trends in Biotechnology CelPress Enabling Microfluidics: from Clean Rooms to Makerspaces David 1. Walsh III ¹ ,* David S. Kong, ¹ Shashi K. Murthy, ^{2,3} and Peter A. Carr ¹ **	• Oxygen gradient from 2.5%–0% outside of anaerobic chamber	 Device geometry and materials passively control gas diffusion
	Persistent, realistic mucus layer	Continuous and controllable mucus feed
	 Fed-batch culture with multiple sampling and sensor ports 	 Single-feed input port with multiple sampling output ports
	 Sufficient sample volume for various testing (e.g., sequencing, mass spec) 	Sample chamber volume of 2.5 mL
	 Robust and low-cost fabrication No highly specialized skills or equipment required for fabrication 	 Composed entirely of low-cost thermoplastic, adhesive, membrane, and rubber materials





Integrated ArtGut System (Fabrication)



- Expanded and integrated oxygen gradient with mucus and microbiome sample
- Performed systems-level analysis of materials, fabrication strategy, and user requirements along with modeling
- Final system enables us to tackle real-world problems (e.g., Parkinson's)





ArtGut Would Replace Current Microbiome Models

The Artificial Gut system will enable researchers to study a variety of toxins on healthy patients and potential therapeutic probiotics on Parkinson's patients





Insult

Therapy





FY18 ArtGut Project

Microbiome - 12

CRC 03/06/18

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Meaningful collaborations shepherded by Lincoln Laboratory create an integrated strategy to study Parkinson's



Summary and Next Steps

- Microbiome critical part of health; however, current tools to study the microbiome are inadequate
- An approach combining computational and experimental analysis is required to develop new tools
- MIT Lincoln Laboratory is paving the way for future microbiome research through high-throughput *in vitro* models



Future work: Incorporate immune and nervous system model components into ArtGut





ArtGut Contributors and Sponsors

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