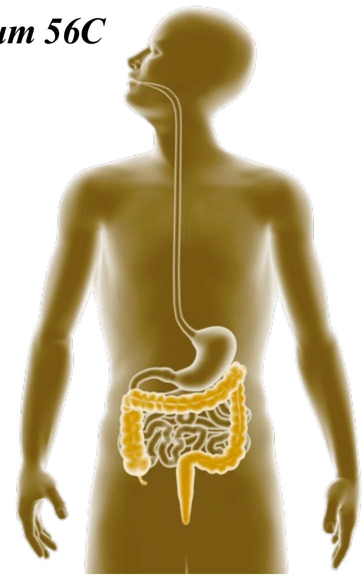
HEB 114: Gut Microbiome & Human Health

Discussion: Wednesdays 12:45-2:45, Peabody Museum 52H
Labs: Mondays 9:00AM-noon or 3:00PM-6:00PM, Peabody Museum 56C



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Course description

Microorganisms residing in the human gastrointestinal tract are as numerous as our own cells and together encode at least 150 times as many unique genes. In this research seminar, we explore gut microbial contributions to human physiology in states of health and disease. We consider how the human gut is colonized, the factors shaping the structure and function of the gut microbiome, and the pivotal roles of the gut microbiome in digestion, energy regulation, immunity, development, drug metabolism, and behavior. We evaluate fast-growing evidence for the gut microbial modulation of metabolic syndrome, cardiovascular disease, cancer, and neurodevelopmental and neurodegenerative disorders, and discuss microbiome-targeted approaches for the prevention and treatment of human disease. The weekly three-hour lab will introduce students to experimental, bench and computational techniques used to investigate the gut microbiome, enabling students to collaborate on a novel research project that dovetails with topics discussed in seminar.

Course structure

Each week, we will meet to discuss selected readings that introduce the diverse functions of gut microbial communities and their consequences for human health. Because we have limited time to explore such a broad field, it is imperative that you read and reflect on these readings **before** the meeting for which they are assigned. In addition, each student will sign up to present and lead discussion of one supplementary reading during the term. Please note that because research into the gut microbiome is advancing rapidly, we will likely replace some readings on the syllabus over the course of the semester.

In addition to the discussion section, there will also be a weekly lab where you will have the opportunity to learn and apply techniques enabling you to study a novel problem in microbiome research. This year, we will be studying how the gut microbiome affects maternal energy allocation during pregnancy! Our work each week in lab will build on the progress made in prior weeks, therefore it is imperative that you are prepared and present for all labs.

Your written assignments for this course will encourage you to think critically about the primary literature and apply what you have learned in preparing a research paper of your own. The mid-term paper will review and critique a primary research paper: Smits SA et al. (2017) Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. *Science* 357: 802-806.

The final paper will communicate your research findings in lab. It should be written in the style of a journal article with the following content: abstract, background and hypotheses, methods, results (plus figures and/or tables), discussion, and references. We will discuss the paper format in class, and you will have an opportunity to confer with classmates and course staff about your findings and interpretations.

Course requirements

- Informed, engaged, and thoughtful participation in class and lab (40%)
- Presentation and directed discussion of supplementary paper – 1 per student (10%)
- Mid-term critique of published paper, due Wednesday, October 16 by 11:59 PM (20%)
- Final paper, due Friday, December 13 by 11:59PM (30%)

Required readings are indicated under the weekly headings below. All readings will be made available on the course website and must be reviewed in advance of the meeting for which they are assigned. Papers listed under "presentation options" will be presented by class members on a sign-up basis and are not required reading for the entire class.

The course will be graded based on achievement, not by curve.

Class policies

Collaboration

In this class, we will be working together on a novel problem in microbiome research, so we should consider ourselves a research team! In line with this team effort, you are encouraged to discuss class topics, readings, assignments, and analyses outside of class. In addition, because you will be working in small research groups on your final project, it is acceptable for your group to have common hypotheses, predictions, figures, and to share any code used in your analyses. However, your contributions in class discussions and the written work that you submit for evaluation must reflect your own efforts. To ensure the proper use of sources while at the same time recognizing and preserving the importance of discussion and collaboration, the Faculty of Arts and Sciences has adopted the following policy:

> "It is expected that all homework assignments, projects, lab reports, papers, theses, and examinations and any other work submitted for academic credit will be the student's own. Students should always take great care to distinguish their own ideas and knowledge from information derived from sources. The term "sources" includes not only primary and secondary material published in print or online, but also information and opinions gained directly from other people.
> Quotations must be placed properly within quotation marks and must be cited fully. In addition, all paraphrased material must be acknowledged completely. Whenever ideas or facts are derived from a student's reading and research or from a student's own writings, the sources must be indicated." (Except from the Student Handbook)

Generative artificial intelligence

Certain assignments in this course may be conducive to the use of generative artificial intelligence (GAI) tools such as ChatGPT. However, such use is disallowed unless otherwise stated. Any use of GAI tools must be appropriately acknowledged and cited. Violations of this policy will be considered academic misconduct. Notably, different classes at Harvard could implement different GAI policies, and it is the student's responsibility to conform to expectations for each course.

Attendance

You are expected to attend all discussion and lab meetings, except in extraordinary circumstances. If you cannot attend a meeting due to illness or an emergency, you must notify both the professor and TF. You may be offered the opportunity to receive participation credit for a missed discussion by completing an opinion piece that will be shared with the class and graded for quality. In order to ensure timely progress of the research project, any missed lab sessions must be made up within 6 days, by arrangement.

WEEKS 1-5: INTRODUCTION TO THE GUT MICROBIOME

Week 1 (9/4) – Introductions and overview

***** Confirmation of lab section assignments this week *****

Questions

- What is the gut microbiome?
- Why is the microbiome receiving so much attention lately?
- What aspects of human biology are influenced by the gut microbiome?
- Why is the microbiome important for our understanding of human evolution, and vice versa?

Readings

Pollan (2013) Some of my best friends are germs. *New York Times Magazine*. Available at: http://www.nytimes.com/2013/05/19/magazine/say-hello-to-the-100-trillion-bacteria-that-make-up- your-microbiome.html.

Lynch and Pedersen (2016) The human intestinal microbiome in health and disease. *New England Journal of Medicine* 375: 2369-2379.

Dominguez Bello et al. (2018) Preserving microbial diversity. *Science* 362: 33-34.

Amato and Carmody (2023) Gut microbial intersections with human ecology and evolution. *Annual Review of Anthropology* 52: 295-311.

Week 2 (9/11) – Origins of the human gut microbiome

Questions

- How are we colonized?
- How can we consider the interactions between mother, baby, and microbes?

Readings

Yong (2016) Breast-feeding the microbiome. *The New Yorker*. Available at: http://www.newyorker.com/tech/elements/breast-feeding-the-microbiome.

Amato et al. (2024) Host-gut microbiota interactions during pregnancy. *Evolution, Medicine, and Public Health* 7-23

Ferrati et al. (2018) Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host & Microbe* 24: 133-145.

Marcobal et al. (2011) *Bacteriodes* in the infant gut consume milk oligosaccharides via mucus-utilization pathways. *Cell Host & Microbe* 10: 507-514.

Week 3 (9/18) – The human gut microbiome across time

*** Sign-up for supplementary paper presentation slots this week on Canvas ***

Questions

- How does the gut microbiome change as we age?
- How has the gut microbiome changed over evolutionary time?

Readings

Yatsunenko et al. (2012) Human gut microbiome viewed across age and geography. *Nature* 486: 222-227.

Walter and Ley (2011) The human gut microbiome: ecology and recent evolutionary changes. *Annual Review of Microbiology* 65: 411-429.

Moeller et al. (2014) Rapid changes in the gut microbiome during human evolution. *PNAS* 111: 16431-16435.

Example – Supplementary paper presentation (NOT ASSIGNED READING)

Wibowo et al. (2021) Reconstruction of ancient microbial genomes from the human gut. *Nature* 594: 234-263.

Week 4 (9/25) – Factors shaping the gut microbiome

Questions

- What factors influence gut microbial composition and function?
- How do we assess the relative importance of these factors?

Readings

Foster et al. (2017) The evolution of the host microbiome as an ecosystem on a leash. *Nature* 548: 43-51.

Goodrich et al. (2014) Human genetics shape the gut microbiome. *Cell* 159: 789-799.

Blaser (2016) Antibiotic use and its consequences for the normal microbiome. *Science* 352: 544-545.

Carmody et al. (2015) Diet dominates host genotype in shaping the murine gut microbiota. *Cell Host & Microbe* 17: 72-84.

Presentation options

David et al. (2014) Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505:559-563.

Vangay et al. (2018) US immigration westernizes the human gut microbiome. *Cell* 175: 962-972.

Rothschild et al. (2018) Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555: 210-215.

Asnicar et al. (2021) Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nature Medicine* 27: 321–332.

Week 5 (10/02) – Debates

Questions

- Why do different studies reach different conclusions?
- How do we reconcile opposing findings in the literature?

Readings

Dominguez Bello et al. (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *PNAS* 107: 11971–11975.

Chu et al. (2017) Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. *Nature Medicine* 23: 314-326.

Sonnenburg and Sonnenburg (2019) The ancestral and industrialized gut microbiota and implications for human health. *Nature Reviews Microbiology* 17: 383–390.

Carmody et al. (2021) Gut microbiota through an evolutionary lens. *Science* 372: 462-463.

Presentation options

Ayeni et al. (2018) Infant and adult gut microbiome and metabolome in rural Bassa and urban settlers from Nigeria. *Cell Reports* 23: 3056-3067.

Aagaard et al. (2014) The placenta harbors a unique microbiome. *Science Translational Medicine* 6:237

de Goffau et al. (2019) Human placenta has no microbiome but can contain potential pathogens. 572: 329-334

WEEKS 6-13: HUMAN-MICROBIAL INTERACTIONS

Week 6 (10/9) – Nutrient digestion

Questions

- How does the gut microbiota assist in nutrient digestion?
- Why do gut microbes serve this function?

Readings

Cummings and Macfarlane (1997) Role of intestinal bacteria in nutrient metabolism. *Clinical Nutrition* 16: 3-11.
Hehemann et al. (2010) Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature* 464: 908-912.
Sonnenburg et al. (2016) Diet induced extinctions in the gut microbiota compound over generations. *Nature* 529: 212-215.
Carmody et al. (2019) Cooking shapes the structure and function of the gut microbiome. *Nature Microbiology* 4: 2052-2063.

Presentation options

Muegge et al. (2011) Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* 332: 970-974.
Semova et al. (2012) Microbiota regulate intestinal absorption and metabolism of fatty acids in the zebrafish. *Cell Host & Microbe* 12: 277-288.

Week 7 (10/16) – Energy regulation

***** Midterm paper due today by 11:59 PM *****

Questions

- What factors shape microbial contributions to energy regulation?
- How do microbial contributions revolutionize the traditional model of energy metabolism?

Readings

Carmody and Bisanz (2023). Roles of the gut microbiome in weight management. *Nature Reviews Microbiology* 21: 535–550.
Bäckhed et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. *PNAS* 101: 15718-15723.
Ridaura et al. (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 341: 1241214.
Cox and Blaser (2015) Antibiotics in early life and obesity. *Nature Reviews Endocrinology* 11: 182-190.

Presentation options

Liou et al. (2013) Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. *Science Translational Medicine* 27: 178ra41.
Depommier et al. (2019) Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nature Medicine* 25: 1096–1103.
Koren et al. (2012) Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* 150: 470-480.

Week 8 (10/23) – Immunity and inflammation

Questions

- How does the gut microbiota interact with the immune system?
- Why might immune maturation depend on exposure to specific microbial strains?

Readings

Zheng et al. (2020) Interaction between microbiota and immunity in health and disease. *Cell Research* 30: 492-506.

Chung et al. (2012) Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* 149: 1578-1593.

Cani et al. (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 57: 1470-1481.

Chassaing et al. (2015) Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 519: 92-96.

Presentation options

Devkota et al. (2012) Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in $Il10^{-/-}$ mice. *Nature* 487: 104-108.

Simpson et al. (2022) Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome. *Nature Medicine* 28: 2344–2352.

Week 9 (10/30) – Early life influences

Questions

- Why do host-microbial interactions in early life have an outsized impact on human biology?
- If early life is a critical window, how might we change our approach to pediatric health care?

Readings

Tamburini et al. (2016) The microbiome in early life: implications for health outcomes. *Nature Medicine* 22: 713-722.

Cox et al. (2014) Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* 158: 705-721.

Kimura et al. (2020) Maternal gut microbiota in pregnancy influences offspring metabolic phenotype. *Science* 367: eaaw8429.

Markle et al. (2013) Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science* 339: 1084-1088.

Presentation options

Gomez de Agüero et al. (2016) The maternal microbiota drives early postnatal innate immune development. *Science* 351: 1296-1302.

Olm et al. (2022) Robust variation in infant gut microbiome assembly across a spectrum of lifestyles. *Science* 376: 1220-1223.

Zhou et al. (2023) Effects of vaginal microbiota transfer on the neurodevelopment and microbiome of cesarean-born infants: a blinded randomized controlled trial. *Cell Host & Microbe* 31: 1232-1247.

Week 10 (11/06) – Neurodevelopment, neurodegeneration, and behavior

Questions

- How strong is the evidence for a microbial influence on neurodevelopment and behavior?
- Do microbial influences on neural function challenge our views of human cognition?

Readings

Sampson and Mazmanian (2015) Control of brain development, function, and behavior by the microbiome. *Cell Host & Microbe* 17: 565-576.

Vuong et al. (2020) The maternal microbiome modulates fetal neurodevelopment in mice. *Nature* 586: 281-286.

Hsaio et al. (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155: 1451-1463.

Sampson et al. (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167: 1469-1480.

Presentation options

Diaz Heijtz et al. (2011) Normal gut microbiota modulates brain development and behavior. *PNAS* 108: 3047-3052.

Braniste et al. (2014) The gut microbiota influences blood-brain barrier permeability in mice. *Science Translational Medicine* 6: 263ra158.

Sordillo et al. (2019) Association of the infant gut microbiome with early childhood neurodevelopmental outcomes. *JAMA Network Open* 2: e190905.

Week 11 (11/13) – Xenobiotic metabolism, therapeutic drugs

Questions

- Through what mechanisms can the gut microbiota transform therapeutic compounds?
- How can we leverage this information to design more effective treatments for disease?

Readings

Spanogiannopoulos et al. (2016) The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. *Nature Reviews Microbiology* 14: 273-287.

Haiser et al. (2013) Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. *Science* 341: 295-298.

Wallace et al. (2010) Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. *Science* 330: 831-835.

Maini Rekdal et al. (2019) Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. *Science* 364: eaau6323.

Presentation options

Zimmermann et al. (2019) Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* 570: 462-467.

Forslund et al. (2015) Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 528: 262-266.

Week 12 (11/20) – Chemical transformation of diet-derived compounds

Questions

- How does the gut microbiota transform diet-derived bioactive compounds?
- How can we leverage this information to design more effective dietary interventions?

Readings

Tang et al. (2013) Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *New England Journal of Medicine* 368: 1575-1584.

Mabrok et al. (2012) Lignan transformation by gut bacteria lowers tumor burden in a gnotobiotic rat model of breast cancer. *Carcinogenesis* 33: 203-208.

Humblot et al. (2007) β-glucuronidase in human intestinal microbiota is necessary for the colonic genotoxicity of the food-borne carcinogen 2-amino-3-methylimidazo[4,5-*f*]quinoline in rats. *Carcinogenesis* 28: 2419-2425.

Zheng et al. (2013) Melamine-induced renal toxicity is mediated by the gut microbiota. *Science Translational Medicine* 5: 172ra122.

Presentation options

Koeth et al. (2013) Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature Medicine* 19: 576-585.

Wang et al. (2015) Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell* 163: 1585-1595.

Week 13 (11/27) – Happy Thanksgiving!

Week 14 (12/04) – Toward microbiome-targeted medicine

Questions

- What microbiome-targeted therapies are on the near-term horizon?
- When is fecal transplantation a viable treatment?
- How effective are prebiotics/probiotics/synbiotics/postbiotics?
- Could the next big drug come from the gut microbiota?

Readings

Waller et al. (2021) An update on fecal microbiota transplantation for the treatment of gastrointestinal diseases. *Journal of Gastroenterology and Hepatology* 37: 246-255.

Cunningham et al. (2021) Shaping the future of probiotics and prebiotics. *Trends in Microbiology* 29: 667-685.

Donia and Fischbach (2015) Small molecules from the human microbiota. *Science* 349: 1254766. Kuntz and Gilbert (2017) Introducing the microbiome into precision medicine. *Trends in Pharmacological Sciences* 38: 81-91.

Presentation options

Zeevi et al. (2015) Personalized nutrition by prediction of glycemic responses. *Cell* 163: 1079-1094.

Javdan et al. (2020) Personalized mapping of drug metabolism by the human gut microbiome. *Cell* 181:1661-1679.

Final Paper (12/13) – 11:59PM