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The Future of Microbiome Research

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The Overview

Kyle Emerson

In the spring of 2022, a group of ten graduate students from Duquesne University signed up for an Advanced Topics course titled, "The Future of Microbiome Research," run by Dr. Wook Kim. While this topic fit squarely within the scope of some student's dissertation research, most of the class had minimal exposure to the exponentially growing microbiome field. This collection of wide-ranging research interests proved to be more beneficial than originally hypothesized, as we all quickly understood how integrated the microbiome is into many aspects of experimental biology.

The microbiome consists of microorganisms (bacteria, fungi, archaea, protists, viruses) that make up a specific community, whether that community resides in or on an organism (plant, animal), or as part of the environment. Our first class provided a crash-course overview lecture on the microbiome and the current state of the field from Dr.

Barbara Methe, Director of the Center for Medicine and the Microbiome at the University of Pittsburgh. From there, we were tasked with critically evaluating the state of microbiome research ourselves by choosing and analyzing recent primary literature. The next three weeks were dedicated to one topic of microbiome research: 1) Health and Disease, 2) Applications of the Microbiome, and 3) The Unknown: Investigating the 'Forgotten' Microbes. Each class consisted of three graduate students each selecting and presenting one paper relevant to the weekly topic, which divulged into a thoughtful class discussion. Taking what we had learned from each paper and topic, the overarching goal of the course was to determine relevant future courses of action to push the microbiome field forward. This proved to be a lofty mission in a short five-week span, as much research is correlational due to the vastness of the microbiome and the ambiguity that comes with trying to understand and interpret it. Here, we present our findings on the current state of the microbiome field and our collective suggestions on how to move microbiome research forward.

The papers chosen to discuss our first weekly topic, Health and Disease, provided a great snapshot of how microbiome research is conducted and presented (**See:** **Module 1: Health and Disease**). Among our key takeaways were that relative changes in large phyla/genera/families alone isn't insightful to implicate a specific effect of gut microorganisms, which was a consistent theme in our class discussions. We also discussed the importance of using proper models for microbiome research, as our first paper discussion illuminated the difficulty of implementing proper controls when conducting a microbiome

experiment on humans. In what may be our main suggestion for the future of microbiome research, we discovered the value of collaboration. Because the microbiome field is so large, experiments can fall under many different fields of experimental biology. Collaborating with experts in fields where microbiome research can be applied will improve experimental design, data collection and data interpretation.

Because much of microbiome research is conducted in the context of biomedical research, our second weekly topic, Applications of the Microbiome, tried to investigate some alternative ways in which microbiome research can be conducted and applied (**See:** **Module 2: Applications of the Microbiome**). Our key takeaways included the pitfall that many microbiome experiments can experience, which is that mechanisms generalized in one model system may not be applicable within another model system. We also discussed how the microbiome can be used in bioremediation, the use of biological organisms to remediate polluted sites, which is a promising ecological conservation tool. Unfortunately, we found that challenges remain regarding implications of explicit mechanisms. We also found that questions remain regarding the natural consequences of manipulating environmental microbial communities and how transient those changes can be. Lastly, our theme of collaborations came up once again as we discussed a paper that incorporated multiple models, multiple approaches (transcriptomics the study of all RNA transcripts in the community and metabolomics to look at all metabolites within the community), and was able to implicate

microbes on the species level that have a relative abundance that influences effectiveness of cancer treatment.

Our third week of discussion focused on the under-evaluated area of the microbiome, investigating the mycobiome and viriome (**See:** **Module 3: The Unknown**). While this section had less papers to choose from due to the lack of research into the fungi and viruses of the microbiome, we were able to gain an appreciation of just how far microbiome research has come. Among our takeaways was the need to universalize language, as we spent quite a few minutes discussing if it was 'virome' or 'viriome'. Since the field is inherently ambiguous, consensus building within the language of the field is a great place to start to aid in presentation and interpretation of microbiome research. We also as a class discovered that bacteria, viruses, and fungi all interact and compete for resources. As most papers focus solely on bacteria, we questioned how much of the host phenotype, the physical aspects of an organism, is driven by these unknown microbes 1) in the presence of a diverse microbiota (microorganisms) and 2) in the absence of a diverse microbiota? Being able to disentangle these complex mechanisms is a major avenue for future microbiome research, which very well may cause us to go back and re-evaluate some of the foundational microbiome studies.

With our evaluation of our three weekly topics completed, our final class period was designed to evaluate how to turn correlational studies into causation studies in the microbiome field. While I do not have an explicit answer to that question, nobody does; I instead decided to review the main takeaways from the course and give some suggestions as

to what future microbiome research studies can implement to accurately assign causation. While I have covered most of that in the paragraphs above, I will leave you with some final thoughts about the microbiome field. A common critique is that it is too association-based to divulge anything meaningful. While many papers have main takeaways regarding the relative abundance of bacterial phyla, genera, or families that alone may not be able to assign causation, they provide pieces to the puzzle, nonetheless. Further, the foundational microbiome studies that get published in the most impactful journals often begin investigating how changes to the gut microbiome are associated with changes in host phenotype, which is a common question in microbiome studies regardless of the journal or reception of the study. This tells us the questions most microbiome studies are asking are valid, but as we will discuss in this document, there is more researchers can be doing to improve our chances of assigning causation.

While five weeks was only long enough to scratch the surface, as a class we were able to appreciate the work that has gone into getting the microbiome field to where it is today. I believe I speak for all of us when I say that we look forward to seeing how the microbiome field continues to advance and how it will impact all of our wide-ranging areas of research and expertise.

Module 1: The Microbiome Health and Disease

Anna Manges, Bethann Wilson, Lili Macharashvili

As young scientists, our goal is to learn how to interpret and dissect primary research so that we may repeat or contribute to experiments that affect the world. The interactions and

communities of bacteria that make up the gut microbiome in animals is a complex, poorly understood web. While technology continues to improve experimental techniques, from describing changes in microbiota (microorganisms), metabolomics (metabolites within a community), proteomics (proteins within a community), etc., it is extremely difficult to interpret these, and the real impact of these studies are limited in this way.

General scale changes, such as introducing a new food to a diet, can have multiple downstream effects, which produce little information, or, frustratingly, too much information to dissect. For instance, **Corona-Cervantes et al.** described a study in which *Opuntia cacti* (Nopal) was supplemented in women's diets due to historical cultural use of the plant to determine the effects on weight loss and changes in fecal microbiota were assessed. Among the most notable findings of the study was the decreased prevalence of the *Ruminococcaceae* family following a month of nopal supplementation. However, describing how such complex supplementations affect large and diverse families of bacteria does little to enlighten us or provide any meaningful interpretation of what the shift in community organization means to overall health.

Microbiome studies also have the ability to focus on more specific additions, such as only one chemical to a diet with results slowly becoming more defined. This interaction may not be reproducible in all mammals, but the information gathered from these experiments is more specific compared to that of the general food addition approach. For instance, **Callejón-Leblic et al.** measured both metabolite and microbiota changes as a result of selenium

supplementation in microbiota depleted mice. Selenium is a trace element that is necessary for proper function of the immune system. Interestingly, they observed altered metabolites and metabolic routes consistent with known effects of selenium on lipid metabolism. In addition to this, Callejón-Leblic et al. noticed significant decreases in both *Lachnospiraceae* and *Ruminococcaceae* after selenium supplementation. Although these results were more widely meaningful, there is still a disconnect in the ability to determine anything besides significant correlations and associations, which highlights the gap in the current understanding of the microbiome in human health.

One clinically relevant application of gut microbiome research is reducing the difference between the gut microbiota of healthy individuals and that of patients with certain medical conditions. **Duan et al.** demonstrated this approach by using mice colonized with gut microbiota of alcoholic hepatitis patients, a condition of liver inflammation due to alcohol use, that had an increased presence of cytolysin-positive *E. faecalis*, a microorganism, compared to healthy individuals. The *E. faecalis* was targeted by phage therapy, the use of viruses that infect specifically bacteria, which led to a marked decrease in ethanol-induced (alcohol-induced) liver disease in the mice. While further research is necessary to determine whether this approach is feasible in humans, and whether it is applicable to other medical conditions with a less pronounced difference in gut microbiota composition, the marked difference in outcomes for treated and non-treated mice makes this an interesting and promising area of study.

Despite this valuable information, targeting individual bacterial species leads us back to the original dilemma: understanding the complex web of interactions that all organisms play in such an environment, and determining how those within each community affect each other. Thus, we are brought back to: how does the removal of a single type of organism affect the total microbiota, and even further, the host organism's health? Future technologies may assist in simulating what changes may occur with the addition or subtraction of different chemicals or organisms to each specific environment, as well as more effectively predict the overall health effect of these changes. However, before this can happen, we must first elucidate the meaningful changes associated with microbiome research in the most well-rounded way possible.

Perhaps this is best demonstrated by the almost-random selection of the three primary research articles mentioned above. As a graduate student class, we recognized that some of the microbiota changes observed from nopal addition were consistent with that of selenium supplementation. With a quick Google search, we realized that nopal has approximately 0.7µg of selenium per 100g, and hypothesized that those microbiome changes the authors attributed to the fiber-richness of nopal could actually be a result of increases in selenium to the diet. This demonstrates one last final conclusion: in order for microbiome research to provide real and insightful outcomes and conclusions, there must be a push for collaborative work between professionals of various disciplines.

Module 2: Application of the Microbiome

Meghan Wells, Marisa Guido, Anna Vietmeier

The microbiome has recently become one of the more popular areas of research in basic science with almost every environmental system looking for the effects of microbes and their composition. Initial 16S rRNA sequencing studies, a commonly used microbiology technique to identify which microbes are present, have been used to identify microbes that are common to an environment and provided spaces for more in-depth studies to be performed. Common goals for microbiome-based interventions involve either 1) identifying microbes associated with a specific phenotypic change in the environment, 2) clarifying a role of the microbiome in development, or 3) modifying the microbes present to achieve a desired result. Application of the microbiome includes a variety of uses such as those in human health and environmental health. Applications involve modulations in the gut microbe of mosquitos to limit the transmission of malaria, the diagnosis and treatment of cancer, and bioremediation of polluted sites such as petroleum contamination. Application of the microbiome and its constituents can be at the large scale with considerations of the entire community, or considerations of individual members within the community. Modifications of the microbiome to harness and study its potential include the uses of biostimulation/prebiotics, bioaugmentation/prebiotics, fecal microbiota transplants, antibiotics, and germfree/sterile experiments. Amendments with specific nutrient sources have been correlated with changes in the microbiome such as the addition of nitrogen or short chain fatty acids. The lack of a microbiome in germ-free or alteration of a microbiome in antibiotic or sterilized conditions have been shown to impact organism development.

When designing these studies to determine the implications of the microbiome and how it can be managed, all variables should be considered, including those that are biotic (with life) and abiotic (without life).

Alterations of the human microbiota is not the only area where microbiome interventions are focused. Vector-borne disease, where the disease is encoded on a mobile piece of DNA, is a major cause of morbidity and mortality, and insect disease vectors are spread across the globe. The concept of modifying the microbial composition of arthropods known to disseminate disease is not new. In **1997, Durvusala et al.** introduced the concept of paratransgenesis, the modification of the microbiome using genomic techniques to then infect their host species as a way to prevent the transmission of the parasite that causes Chagas' disease, which results in fever, eyelid swelling, and potentially heart failure if untreated. This technique has spread to malaria prevention. The identification of cytoplasmic incompatibility caused by strains of *Wolbachia* has long been a target for mosquito microbiome manipulation in the hopes of reducing the mosquito population or reducing arbovirus and *Plasmodium* transmission. Recently, **Coon et al.** identified that mosquitoes lacking any microbiota were incapable of completing their larval development, but could be "rescued" by reintroducing a single bacterial species. This study highlights the opportunities available for mosquito microbiome modification. Identifying bacteria present within several mosquito life stages can provide a target for modification, or that introducing a new component to the mosquito midgut microbiome can drastically alter the vector lifecycle and

parasite disease outcomes. Despite these advances, there are still several unknowns regarding any introduction of modified or nonnative microbes into a field setting, and these questions need to be answered both on a scientific and public basis to ensure clear communication and trust between researchers and their communities.

In the article by **Sarkar et al. 2016**, the native microbial population was successfully used to bioremediate petroleum pollution and remediation was successfully improved through the amendments of nitrogen to increase metabolism. The paper demonstrated the use of stimulating microbial populations with either nitrogen in the form of nitrate or phosphorus compared to the original community and contamination levels and a community that was allowed to naturally attenuate without amendments. Overall, communities supplemented with nitrate were able to remove more petroleum than those that were not. The authors also theorized based on previous literature, individuals identified through 16S rRNA sequencing that may be involved in the biogeochemical cycling, the cycling of chemical species by microbes, and used primers to confirm the presence of specific genes involved in biogeochemical cycling. They used the data collected to generate a potential model showing the relationships within the mixed community to metabolism and biogeochemical cycling. Although this paper was able to show a change in remediation capability, they mostly made correlations between the community, its changes in composition, and remediation, but failed to identify specific microbes and their metabolic mechanisms involved in remediation.

Another recent article by **Huang J, et al.** explores the application of the microbiome in cancer treatment. The paper aimed to bridge this gap in knowledge by exploring the effects of the combined treatment of anti-Programmed Death 1 (PD-1) antibodies and a component of a common Asian medicinal plant, Ginseng polysaccharides (GPs). They initially found that combined treatment decreased tumor weight and volume in mice. To understand the mechanism behind this, the authors performed a series of experiments involving transcriptomics, metabolomics, and immunology techniques. They found that combined treatment increased abundance of *muribaculum* in the gut lumen, leading to upregulation of epithelial protection genes, changes in metabolite levels, and changes in immune cell abundance. In summary, they show that combined treatment alters the gut microbiota, leading to a change in metabolite levels, which travel through the blood to ultimately enhance the immune response against tumor cells. The remainder of the paper involved studying human patients who either responded or did not respond to PD-1 antibody treatment. Responders had increased levels of *Bacteroides vulgatis* in their gut microbiota. A fecal transplant was performed from human non-responders into germ-free mice, and the mice were then treated with GPs and PD-1 antibodies. Consistent with their previous results, the authors found that combined treatment reinstated the gut microbiota to that of a responder, leading to the same patterns in metabolite and immune cell abundance, ultimately resulting in tumor suppression. Two main conclusions were drawn from this data:

1) gut microbiota composition can be used as an indicator to predict the effectiveness of PD-1 antibody immunotherapy, and 2) GPs are able to sensitize a patient's response to cancer treatment when combined with PD-1 antibodies through modulation of the gut microbiota.

As a class, we found this paper to be a good representation of the potential future directions of microbiome research. Unlike other microbiome literature we had come across, this paper was able to identify microbes at the genus and species level and directly link changes in abundance to an increased efficacy of cancer treatment. Additionally, this paper explored the mechanisms behind how the gut microbiota can affect cancer treatment by using a range of approaches including transcriptomics, metabolomics, and immunology techniques in addition to 16S sequencing. Microbiome research would be strengthened by taking a mechanistic approach rather than trying to find meaningful patterns in 16S sequence data alone.

However, we also discussed as a class whether this paper is a solid representation of successful microbiome research or if it is simply luck. The paper was able to identify specific alterations in the gut microbiota and link these changes to a clear outcome, but can this approach be applicable to all microbiome research? If the authors simply got lucky to choose a model in which they were able to identify microbiota changes at the species level, is this paper a good representation of the future of microbiome research? Another topic we discussed was about the amount of work that goes into a successful microbiome paper. From what we have found, the better papers involved many authors. Was this paper only successful

because of the amount of time, money, and effort that was put into it? Overall, we concluded that while this paper seems to be an ideal outcome in microbiome research, not all microbiome topics can be approached in the same way.

Similar recurring issues can be noted across the wide variety of microbiome applications in science. There are several unknowns associated with modifying microbes in environmental settings, and the impact of these modifications. We have yet to discover how long these modifications persist, and if they transfer into unintended hosts. It is unknown what changes may occur as a result of modifying microbes to secrete nonnative proteins, and if these changes on the whole microbiome impact their host of the environment. Will immediate interventions lead to later problems, such as removing fixed carbon from the environment and increasing atmospheric CO_2? These unknowns are arguments against the immediate field trials of transgenic microbes, but provide further areas of study in microbiome research. We are unable to account for the long term applications of some of these microbiome approaches until they have been tested for extended periods of time and will require longitudinal studies. A drawback we have noted is the unintentional altering of the microbiome through the use of antibiotics, which wipes out current microbial populations within the gut. Additionally, the long term use of antibiotics has resulted in the increase of antibiotic resistant microbes, raising the question of how and if we can account for these alterations of microbiome. Future applications of the microbiome will most likely entail identification of specific microbes

involved in the desired or undesired outcomes and lower taxonomic levels as well as determination of the mechanism that produces this outcome.

Module 3: The Unknown - The Virome

Jessica Packard & Joseph Heath

The human virome is defined as the assembly of viruses associated on and within the human body, and is often identified by metagenomic sequencing, the sequencing of all genes within a community. For example, a person who is not infected with herpes simplex virus type 1 does not have the same virome as someone who does. Therefore, the virome is specific to each individual. Based on the literature presented during this session, it is clear that the virome and microbiome interact with one another, beyond simply existing within or on the same organism.

The first paper discussed by **Liang et al.** explores the virome of newborn infants during the first few months of life. In this study, the authors found that infants that are breastfed have a higher accumulation of bacteriophages, viruses that specifically infect bacteria, in their virome. Inversely, infants that were formula fed contained a higher proportion of viruses that infect human cells. The authors subsequently identified the bacterial strains that were present in these children based on the dramatic abundance of bacteriophages in their initial experiments, and how these populations are modified between birth, two months, and four months of age. One finding that interested the class was that 80% of bacterial strains isolated produced a virus-like particle following mitomycin C treatment. This indicates that the majority of the bacterial populations in newborn children are latently infected by

bacteriophages. One criticism that the class had was it lacked a substantial conclusion, and could have delved deeper into what the specific bacterial populations influence the biology of these children.

The second paper discussed in this module, by **Bradley et al.**, made a connection between the microbiome and immune functionality. The data presented implicates the microbiome in modulating the interferon profile in lung epithelial cells, such that the immune system is primed and prepared to fend off respiratory viruses. This paper provides a mechanistic understanding of how interferon signaling levels function, and finds that having an interferon signaling active upon initial infection increases the ability to fight influenza infection. The authors conclude this paper by infecting microbiome depleted mice with influenza, and observing the interferon response and infection characteristics. This builds on previous publications, which indicate that germ-free mice are more susceptible to viral infection. Overall, these findings indicate that an unknown microbial signal stimulates an interferon response, which results in an increased ability to reduce viral infection and the associated symptoms. The authors use these results to caution the overuse of antibiotics, as depleting bacterial populations can increase susceptibility to viral infection. Though this study makes a mechanistic, causative claim about the microbiome and steps beyond correlation, the class found that the microbiome component of the paper is very broad. Most of the results presented are immunology based, and the microbiome work only scratched the surface of what is needed to understand this phenomenon. While future work will likely expand upon

these findings in an authentic way, using the microbiome to wrap up a story without specific population experiments did not provide the depth necessary for a satisfying conclusion.

Through both of the papers, as well as those that appeared in our searches, we found that a unique trend of virome research is that viruses can be implicated in or affected by a variety of human and bacterial processes. Perhaps one reason that virome research is not studied as well as the microbiome is that viruses do not contain a conserved genomic region, regions of genetic code that are conserved across evolution, like the 16S rRNA gene used to classify bacteria. Perhaps, this is because the viral genomic material can be a small proportion of the total nucleic acids in samples, and/or there is not a viral gene that is well-conserved enough to conduct a broad viral screen. It is apparent that a system needs to be established to classify viral populations, which could be made possible by newer sequencing methods. Though virome research does exist, PubMed searches found that 261 papers were published with the key phrase "Human Virome", while 21,484 papers were published with the phrase "Human Microbiome". As indicated by the articles discussed in this module, there is a direct interplay between viral and bacterial populations, further highlighting the need to better understand the virome.

Module 3.5: The Unknown – The Mycobiome

William King

The mycobiome, or the fungal microbiota, is a key aspect of the multi kingdom microbial community that inhabits the human body. While a majority of microbiome studies focus primarily on bacterial compositions, the fungal contribution is an area which should not

be ignored. The mycobiome has already been associated with several disease states and been shown to affect the host immune response. The commensal fungi, *Candida albicans*, also secretes the quorum sensing molecule, farnesol, which has been shown to affect neighboring bacteria like *Staphylococcus aureus*. With these contributions, the mycobiome role must be considered when thinking about the totality of the microbiome.

The paper discussed by **Li et al.** explores the role of mycobiome, and specifically *Candida albicans*, in inflammatory bowel disease (IBD). The study identified a notable increase in the genus *Candida* in patients with IBD, and further experiments showed an increase of the species *C. albicans.* The paper continued to show that *C. albicans* can trigger the host's immune response in a mouse model. However, when isolating *C. albicans* species from the patients with IBD, they discovered a large range of genetic diversity. This diversity led to a variety of ranges of host immune responses in a strain-dependent manner. They continued to try to characterize the mechanism which *C. albicans* contributed to the host immune response identifying the secreted peptide, candidalysin, as a contributor to this response. The paper eventually established a correlation between the severity of the patients IBD symptoms and strain specific induction of the cytokine IL-1β by *C. albicans*.

Through the discussion of this paper, we began to discuss how individual species can affect the host microbiome and affect disease states. We specifically began to hypothesize that diseases like IBD, which have been shown to be affected by both bacteria and fungi, may be affected by individual species in a case specific manner. We postulated in cases of IBD where

specific species of *C. albicans* is not affecting the host immune response as strongly there might be increased contribution from bacteria species that is leading to IBD symptoms. We discussed established strategies through which fungi and bacteria have been shown to interact, and concluded that these interactions must be considered when exploring the microbiome.

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Kyle Emerson. Correlation vs Causation: The Wrap Up.
https://docs.google.com/presentation/d/14ovMqlP1ckwbAcpeE-znmJJndQiR08FUV2D06Mg1YmM/edit?usp=sharing

Marisa Guido. Predaceous Toxorhynchites Mosquitoes Require a Living Gut Microbiome to Develop.
https://drive.google.com/file/d/18orI4hfz8DolFrm9e3voSVRMPTCUrQob/view?usp=sharing

Joseph Heath. Microbiota-Driven Tonic Interferon Signals in Lung Stromal Cells Protect from Influenza Virus Infection
https://drive.google.com/file/d/1_OFccuX2sSpGOtFpuonBVQ4fFtnbkrlL/view?usp=sharing

William King. Immune regulation by fungal strain diversity in inflammatory bowel disease.
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Lili Macharashvili. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease.
https://docs.google.com/presentation/d/1e6CPSMgw73DsvKDlzpzQYCXflod1jLvd/edit?usp=sharing&ouid=113692440948239755400&rtpof=true&sd=true

Anna Manges. Physical and Dietary Intervention with Opuntia ficus-indica (Nopal) in Women with Obesity Improves Health Condition through Gut Microbiota Adjustment.
https://docs.google.com/presentation/d/19esaTc4rw1C4K5asGJcsUq30N2rrT5phmDO560guMKY/edit?usp=sharing

Jessica Packard. The stepwise assembly of the neonatal virome is modulated by breastfeeding. https://docs.google.com/presentation/d/1tyNHKoOOwDxcf-kn7ENh3IJTCCwapeF6wBWfgXb -ukU/edit?usp=sharing

Anna Vietmeier. Biostimulation of Indigenous Microbial Community for Bioremediation of Petroleum Refinery Sludge. https://docs.google.com/presentation/d/1Dy57aLwDQlRsrKlJmE6Q_t6pH2WdlZUM/edit?usp=sharing&ouid=112204661815042840870&rtpof=true&sd=true

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Bethann Wilson. Untargeted Gut Metabolomics to Delve the Interplay between Selenium Supplementation and Gut Microbiota https://docs.google.com/presentation/d/1LIjJoacjDZFBQ3GY3O3xZvFxnepTfudsHWhWMW27XOQ/edit?usp=sharing

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