

The Microbiome: *Getting to Products That Benefit People*



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Overview

- Where we are so far: 30,000 foot view
- What seems like it works, doesn't always, and what seems safe, sometimes is not.
- Observations and causation
- Unique conceptual issues in microbiome manipulation and their implications, including parallels to ecosystems
- Unique aspects of potential microbiome related products
- Points to consider in thresholds for and design of clinical trials of microbiome targeted, or informed, interventions
- Mapping out a development pathway - working together to move forward

Where do things seem to be?

- Major conceptual breakthrough in terms of understanding microbes as part of, influencing and influenced by, the human organism
- Tremendous data explosion triggered by both conceptual shift and technology
- Legitimate excitement and enthusiasm
- Many gaps such as those identified at this meeting, such as understanding what is “normal” and what is not, dynamics of change and in connecting the inventory of various microbiome states to functional status and host effects
- Many disease associations being reported in humans
- Some animal data suggest that microbiome related manipulations can impact disease or risk factors, favorably or unfavorably
- Successful intervention in refractory human *Clostridium difficile* antibiotic induced colitis, promise also seen in diverse areas such as atopy, acute diarrhea, prevention of NEC
- Other potential implications/utility in predicting disease/disease risk and in modulating response to drugs or vaccines

But...what seems likely safe and effective, or to predict safety and effectiveness, or to be “simple” may not be when subjected to scrutiny...or to reality.....

- Selected examples
 - Autologous BMT for breast cancer
 - Suppression of PVCs to prevent sudden death
- And in the realm of the biologics, product safety a particular concern
 - Horse named Jim
 - Disease transmission by transplantation
 - Death from “safe” Staph strain utilized as “interference therapy”
- And healthy biology, particularly with respect to immunity and inflammation, is a balance of modulating factors, providing resilience to new challenges – yet many medical interventions are blunt
 - E.g. there is a reason we have TNF and blocking it too much gives us PML, TB, histoplasmosis, and lymphoma – or that we don’t clot too much or too little
 - Altering the microbiota may, or may not, allow more nuanced, balanced intervention
 - **Can we get the porridge “just right”?**



Observation and causation

- Considerations in weighing observational data (e.g. associations as opposed to data from controlled interventions) with respect to causation include well known factors such as strength of association, temporality, dose-response, biologic “plausibility”, reproducibility.
- Key omnipresent problem with observational data is confounding (e.g. failure to recognize/account for factor(s) other than the variable of interest that affect outcome)
- Confounding can itself lead to reproducible results, and even dose-response and temporality findings (e.g. at an extreme - presence of Starbucks in neighborhoods results in higher income)
- If there was ever an observational area subject to confounding, the microbiome is it!
 - A complex and dynamic “state” subject to numerous exogenous influences
 - Factors such as diet, genetics, changes with time, SES (e.g. on antibiotic use), drug and other unmeasured environmental exposures
 - For microbiome, as for many such complex endpoints, all potential confounders are not known and so cannot be corrected for, and
 - Systems biology and multiplicity of measures and assays allow one to infer and believe in “plausibility” for almost anything
- For microbiome interventions, these factors will make RCTs particularly important

Unique issues in microbiome manipulation and implications, including parallels to ecosystems

- A number of issues are reminiscent of complex ecosystem issues – yet on reflection are also seen quite commonly in other human disease domains. These have implications for basic and clinical studies and include that:
 - States of health and disease may not be binary and their establishment or treatment may require a multi-step process
 - Late in the course of disease, an intervention which could have been effective earlier, may not be effective (e.g. damage has been done, or resilience needed to heal is lost)
 - Interventions, and/or their effects, may or may not persist depending on other system factors (immune system, other organisms, environment, disease state)
 - Unpredictable effects may occur through unsuspected networks and systems
 - The most important outcomes, whether positive or negative, may be long-term (e.g. chronic disease endpoints and long-term safety, an issue raised by the very invocation of the microbiome as a determinant of chronic health and disease)

- For other aspects of an ecosystem view see also [Lemon KP, Armitage GC, Relman DA, Fischbach MA. Sci Transl Med 2012 Jun 6;4\(137\):Microbiota-targeted therapies: an ecological perspective.](#)



Unique aspects of microbiome related products and their characterization

- Need for defined, characterized products
- More science needed to define relative need for and dose of specific organism(s) (or their targeting) vs. defined mixtures and their complexity. Balancing subtle, dynamic effects of entire microbiota vs. specific organisms
- Potential for adventitious agents and for non-pathogens to be pathogenic based on host or other factors, or to transmit antimicrobial resistance
- Genotype vs. phenotype: understanding what is important for desired effect
- Stability of organisms, mixtures, both genotypic and phenotypic
- Stability and fate at target site after administration (more a “clinical” than product related measure)
- Based on these types of issues, FDA typically seeks information for organisms on source, history, genotype/phenotype, antibiogram, stability, “purity”, “potency” and related assays
- Risk based approach includes considering known experience in other domains (e.g. foods), and stage of clinical development/patients treated
- Investigators should consider scale up and reproducibility early
- FDA guidances e.g. on live bacterial products, may be helpful, but guidances are just that, alternative approaches can be proposed
- Consult FDA/CBER early with proposed approaches – we encourage discussion where routine requests/approaches are not felt to be feasible – one size does not fit all and living organisms are not small molecules

Clinical Trials and Microbiome

- Determining whether to do clinical trials - a risk/benefit assessment of all evidence
 - Is there strong evidence of causality and/or a mechanism of action that supports the proposed intervention?
 - Is there evidence for safety and efficacy of the intervention in a model and/or in humans?
 - Can the therapy be reproduced in the future so the results can be meaningful?
 - What are the known risks? What are possible worst case scenarios, short and longer term? Has everything reasonable been done to reduce risks?
 - What is the evidence to support any benefit?

Specific Issues Raised by Microbiome Manipulation in Clinical Studies

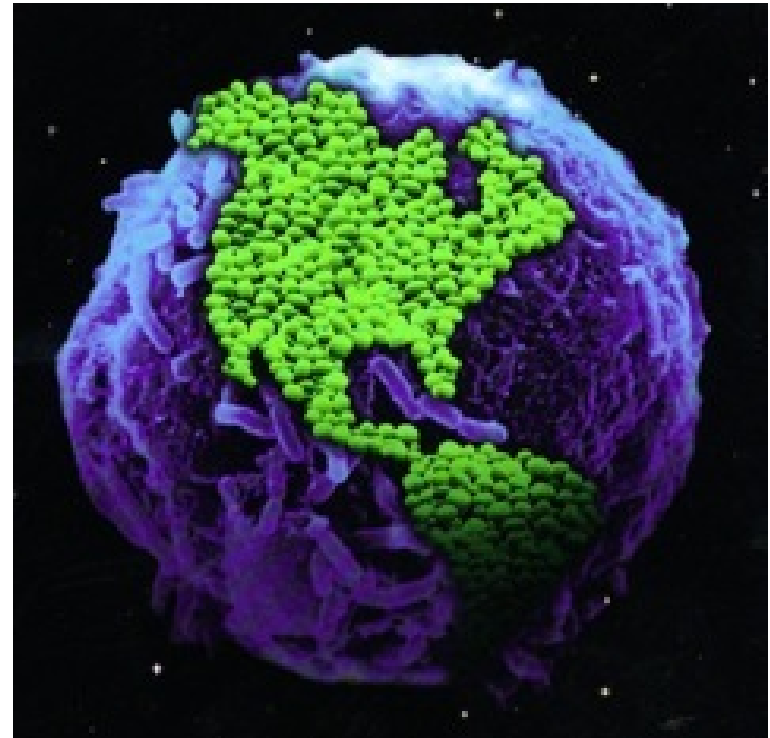
- Fine tuning intervention (add/subtract specific organism(s) vs. reproducing “nature”)
- Sufficient product characterization to reproduce/understand results
- Typical clinical trial design stages generally relevant to microbiome interventions, e.g. initial tolerability and dose defining experience in small studies followed by larger controlled trials for clinical endpoints
- Challenges in population selection (e.g. target dysbiotic subgroup?)
- Monitoring of effects on microbiome for dose-response and/or as an intermediate endpoint, and for development of biomarkers, raises complexity and importance of appropriate sampling, assays, measurements, and need for data analysis plans
- Actual clinical disease endpoints likely similar to others defined for disease stats: increasing general interest in patient functional status
- Biomarker and related diagnostic R and D unique - data collection may provide disease insights: e.g. organisms, metabolism, measurement of putative organism-related disease/health mediators
- Potential importance of long term follow-up of microbiota and host
- Considerations of issues like unrelated antimicrobial use

Mapping Out a Successful Development Pathway Targeting the Microbiome

- Define and prioritize specific candidate patient populations and indications
- Ensure ability to reproducibly produce and characterize relevant product/intervention
- Study in relevant disease models, if available
- Carefully consider potential safety issues and their monitoring
- Design staged clinical trials and relevant endpoints: consider sampling and assays for candidate biomarkers
- Early interaction with FDA encouraged, even pre-IND
- FDA very supportive of NIH efforts in this area
- Emerging science that we all can and should learn from

Thanks!

- We are, ourselves, complex ecosystems, with both vulnerabilities and resilience
- The promise of recognizing this reality, much like recognition of our broader global ecosystem and environment, and the need to support its balance, offer great potential benefits to human health and quality of life
- Manipulating the microbiome must be based on the best science, with a healthy respect for the complexity of nature
- We are optimistic about the impact of microbiome science on medicine and welcome your input and engagement going forward, to bring better health and new products to people in need...



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Figure: <http://www-personal.umich.edu/~jsemrau/Welcome.html>
by Prof. Jeremy Semrau, Univ. Michigan