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Evolution of FMT – From early clinical to standardized treatments

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ABSTRACT

Faecal microbiota transplantation (FMT) is widely reported to be an effective treatment against recurrent *Clostridioides difficile* infections. Recent clinical studies support the therapeutic use of FMT for several other pathologies including inflammatory bowel disease, several types of cancer, and other functional or metabolic disorders. Initial guidelines are now available to overcome some of the technical and logistical issues for establishing a non-standardized treatment into clinical practice with proper safety and governance. To aid the improvement of guidance and standardization requirements for FMT, the International Alliance for Biological Standardization (IABS) and the BIOASTER Microbiology Technology Institute hosted a joint online workshop in May of 2021. The goal of the webinar was to provide a multi-disciplinary perspective of the ongoing efforts to develop FMT guidelines including technical, regulatory, and standardization requirements. Recognized experts gave insights into state-of-the art approaches and standards developed by international organizations and institutions.

1. Introduction

The recognition of faecal microbiota transplantation (FMT) as a therapeutic intervention strategy has been growing steadily over the past couple of decades. This is largely due to the advancement of metagenomic technologies that have supported research into the role of the gut microbiome in health and disease. An increasing number of researchers are investigating the link between the gut microbiome and a wide array of conditions from autism to allergy to diabetes [1]; however, currently FMT is mostly used clinically for treatment of recurrent *Clostridioides difficile* infections (rCDI). Despite the promising research from clinical, academic, and industry laboratories, there are still several challenges with respect to technical and logistical issues in establishing a non-standardized treatment into clinical practice with proper safety and governance. Towards this end, the IABS/BIOASTER webinar provided a multi-disciplinary perspective of the ongoing efforts to develop FMT guidelines that include technical, regulatory, and standardization requirements. Representatives from national metrology organizations, academic researchers, and biopharmaceutical experts provided insights into state-of-the art approaches and standards developed by international organizations and institutions.

2. Developing global standards for the microbiome field

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Kingdom (NIBSC), discussed the challenges of developing standards (reference reagents) for complex biological systems like the microbiome. Dysbiosis of the gut microbiome has been linked with numerous diseases [2], and thus numerous efforts to develop therapeutic strategies targeting the gut microbiome are ongoing. One of the hurdles faced by this field is the complex workflow and variability across methodologies at each step in the workflow. This can include everything and anything from sample collection and storage [3,4] to the bioinformatics pipeline for determining the microbiome composition [5,6]. To address this challenge, NIBSC launched the microbiome program in 2016, to investigate the needs and requirements of World Health Organization (WHO) reference reagents for emerging microbiome therapeutics. As a result NIBSC is leading 18 projects endorsed by the WHO Expert Committee on Biological Standardization (ECBS) to establish international reference reagents for six distinct microbiome sites in the human body (gut, lung, oral cavity, nasopharynx, skin and vagina); prominent among these are standards for the gut microbiome. The majority of microbiome characterizations rely heavily on metagenomic analyses, and thus there is a critical need for reference reagents to support this type of measurement. The biggest challenge for reference reagent development is the numerous step microbiome characterization pipeline which can be broken down into three parts: (1) Sample collection and storage, (2) DNA extraction, and (3) sequencing and bioinformatics. Each step will introduce a difference type of bias. NIBSC has chosen to start from the end of the workflow, beginning with reagents that will focus on providing quality control for step 3, sequencing and bioinformatics. Unlike the development of other reference reagents where the constituents are obvious, composition of this material is less clear. The gut microbiome contains up to 1000 species, many of which are unknown and vary widely between individuals. As a starting point, NIBSC has chosen to develop DNA mock communities for key microbiome sites, including the gut microbiome, with strains most commonly found in each body site. Each NIBSC gut microbiome reagent is comprised of 20 strains (5 Phyla, 13 families, 16 genera, 19 species). In addition to supplying the reagent, NIBSC has developed four key reporting measures for data generated using metagenomic sequencing (MGS) assays: (1) Sensitivity (2) False Positive Relative Abundance, (3) Diversity, and (4) Similarity (based on Bray-Cutis). A proof of concept was published in 2020 demonstrating the combined utility of the reference reagents and the reporting metrics to evaluate the MGS pipelines [7]. This analysis exposed one of the major hurdles to MGS characterization of microbiome samples. By running these standards, researchers can understand the limitations of their analyses, for example, whether a platform is prone to massively overestimate the number of strains present or underestimate the diversity. Another important finding was that reagents of lower complexity had higher measures of sensitivity and similarity, and thus may not fully challenge the pipelines. Therefore, it is crucial to consider the complexity and the composition of the specific microbiome sample of interest in order to determine if a reference reagent is fit -for -purpose, as taxonomic dependent differences in performance have been observed. The genomic DNA reference reagents and guidance are now available from NIBSC, and they are continuing this effort with the development of the next reference reagent which will look to tackle the step up-stream of sequencing and bioinformatics: the DNA extraction. In order to tackle the bias introduced at this step, the material must be comprised of whole cells with intact cell walls to adequately challenge the DNA extraction process. In contrast to DNA, the accurate quantification of whole bacterial cells is still difficult to achieve and NIBSC is working to overcome this challenge. The DNA and whole cell reference reagents can be used together as complementary reagents to evaluate and challenge microbiome analytical pipelines at different steps in the process. These reagents can be used to validate and standardize existing MGS assays and DNA extraction kits and to determine the bias introduced at the different steps of the process and whether they are fit for purpose for studying the microbiome, prior to being tested for reproducibility on clinical material. Wide spread adoption of these reference reagents will provide a baseline for assessing reproducibility, robustness, replicability and generalizability of microbiome analysis [8] important concepts for the validity of microbiome data and support the development of new and improved pipelines.

3. Current and emerging indications of FMT: can it really be a standardized treatment

Professor Harry Sokol, of the Gastroenterology department at Saint Antoine Hospital (APHP, Paris, France) spoke on three topic areas: the success and advances in FMT in the treatment of CDI, emerging indications for FMT treatment, and the challenges of trying to standardize a complex therapy like FMT. There is currently only one indication for FMT in clinical practice; the treatment of recurrent CDI. Since the seminal study published in 2013 by Van Nood and colleagues the efficacy of FMT for treatment of recurrent CDI has been: confirmed in several studies, supported by the presentation of reassuring safety data, and undergone evaluation for alternative delivery methods such as delivery by capsule [9]. Additionally, the field has seen publication of some guidelines regarding FMT and the success of this treatment has led to the development of stool banks and the use of frozen stool. The successes observed in FMT treatment for recurrent CDI and the evidence of gut dysbiosis in other disease states has led to exploratory efforts into the use of FMT for other indications. Two promising indications are inflammatory bowel disease, including ulcerative colitis and Crohn's Crohn's disease, and as an adjuvant to immune checkpoint inhibitor therapy. The Sokol group designed the IMPACT study to evaluate the combined therapy of immune modulation followed by FMT to treat Crohn's disease. Overall, the results were promising and in fact upon close examination of responders and non-responders to FMT treatment the Sokol group observed that individuals with successful engraftment and maintenance/colonization with healthy microbiota saw remission. In comparison, individuals where the healthy microbiota was unable to colonize behaved more similarly to the sham group. This observation led the group to suggest that additional criteria need to be considered when evaluating FMT therapy for other indications. Simply comparing clinical outcome of the sham group to the treatment group may not be a sufficient end point. Rather than the conclusion that the FMT isn't an effective treatment, a more accurate conclusion was the FMT is not always successful at altering the recipient's microbiota. In cases where the microbiota is unchanged, no therapeutic effect is derived from the FMT. These findings highlight the importance of monitoring the gut microbiota of recipients and potentially shed light on the mechanism of action for treatment of some diseases. Other groups have been examining the efficacy of FMT in the treatment of IBD. Three out of four recent randomized clinical trials showed positive data for therapeutic efficacy in ulcerative colitis; however, it's worth noting that there is a high degree of heterogeneity between the study design [10–13]. Unlike CDI, IBD are not a purely microbiota driven diseases which may explain why the response to FMT has been less clear and less dramatic than that observed for treatment of CDI. Prof. Sokol, emphasized the need to consider recipient factors in addition to the donor. To-date much of the focus has been on evaluating the suitability of the donor, but the donor isn't everything. As evident from the IMPACT study, while the composition of the donor didn't appear to be associated with success or failure of the FMT, there were significant associations between the recipient profiles and failure to colonize. The importance of understanding the recipient, and the impact of immune system (e.g. antimicrobial peptides and antibodies), resident microbiota, and/or diet on the donor microbiota was a theme that came up throughout the webinar.

4. Commercial scale fecal microbiota transfer

Herve Affagard, the CEO and co-founder of MaaT Pharma, introduced the field of commercial scale FMTs. MaaT Pharma is a patient-centric, oncology-focused microbiome company with two full-

ecosystem live biotherapeutic programs in clinical development. Affagard's talk transitioned from traditional FMT to the use of commercially produced fecal microbiota. In addition to MaaT Pharma, there are numerous microbiome biocompanies working to develop commercialized microbiome products including: Rebiotix (USA), Finch (USA), and Seres Therapeutics (USA) to name a few. Commercial launch from Rebiotix is expected soon and will be the first commercial option of its kind. Unlike MaaT Pharma, Finch and Rebiotix products are being developed for treatment of CDI, whereas MaaT Pharma is focused on another indication for FMT: Graft-vs-Host-Disease (GvHD).

Affagard's presentation provided a detailed look into the commercialization of FMT, which includes the development of a drug discovery platform. This discovery and data science platform known as GutPrint combines data from patients (per indication), healthy donors and the literature, then employs screening, biomarker identification and microbiome community selection processes. Data mining is followed by validation *in vitro/in vivo* and finally a microbiome ecosystem product candidate is selected for manufacturing and clinical testing. All modalities are focused on ecosystem development not selection of individual species. With respect to the development of the current pipeline, Affagard emphasized the importance investigator led studies in providing the foundational work and the numerous collaborations that were leveraged to develop the current pipeline. An early collaboration with Institut National de Recherche en Agriculture (INRA) led to the creation of the first GMP platform developed in Europe for the generation of FMT enemas. Subsequent collaborations have resulted in the development of cultured microbiota (BIOASTER) and development of oral products (Biocodex).

In addition, the MaaT Pharma portfolio demonstrated the breadth one might expect for the next generation FMT products. For example, MaaT Pharma's approach to FMT development can be broken into two broad categories: (1) native FMT and (2) fermented. Their native production process begins with vetting over 1000 potential donors, selecting 10 healthy donors, pooling material from 4 to 8 healthy donors, and final formulation for delivery by either enema or capsule. The production pipeline began with the design of a proprietary collection device to protect samples from oxygen and a proprietary cryoprotectant. All material is evaluated and characterized by the parameter of richness as a reported by the number of OTUs. Maat Pharma reports that pooling of material results in the ability to achieve greater richness and a reduction in variability seen with a single donor. One potential benefit of starting with a higher richness pool may be the ability to maintain richness even after selection that likely occurs in the recipient. MaaT Pharma is also working towards developing a cGMP fermentation process, a full ecosystem fermentation technology. This begins with the culture of native fecal microbiota using conditions for enrichment and depletion of targeted species followed by co-fermentation of the final full ecosystem. The benefits of this method compared to the native process are it is donor independent, designable, and highly scalable. MaaT Pharma has several ongoing clinical trials with the native formulations and is in preclinical testing with one of the fermented products. The presentation by MaaT Pharma demonstrated the immense strides being made towards commercialization of a very complex biotherapeutic, and gives a glimpse at a potential future of this field of medicine.

5. New strategies for stratification and longitudinal monitoring of microbiota

The final speaker of the session was Vincent Thomas, PharmD.; Ph. D., the head of the Microbiome Program at the BIOASTER Technology Research Institute. Dr. Thomas presented work on technology development for longitudinal monitoring of the microbiota. Current analysis is mainly performed using sequencing; a multiple step, time consuming process, where each step introduces bias ultimately resulting in data that can be difficult to interpret. Thus, there is a pressing need for additional technologies that can measure important microbiota parameters that have been linked to health status. These parameters include traditional metrics such as richness and diversity as well as additional indicators including bacterial load, bacterial viability, proportion of Gram-positive bacteria, bacterial species level identification, identification of additional microbes (e.g. fungi, yeast), simple functional analysis (e.g. enzymatic activity), and longitudinal analysis (e.g. multiple analyses over a specified time course from the same source/sample). This talk focused on the development of a new method to assess several of the parameters listed above in the context of monitoring the gut microbiota composition during administration of immune checkpoint inhibitor (ICI) therapies. In 2018, Gopalakrishnan et al. published an article showing that patients with more "favorable" microbiomes are more likely to respond to treatment with ICI compared to those with a dysbiotic gut microbiome [14]. Subsequently, several groups have published on the effect of FMT to improve response in refractory patients (patients whose cancer is non-responsive to ICI treatment) [15,16]. These publications highlighted the need to monitor the gut microbiota composition at various stages of treatment. As outlined by McQuade et al. this could include measuring the patient microbiota before therapy to stratify or select patients; during therapy to assess function and/or engraftment; and long term to determine durability of engraftment and/or to identify key contributors to successful outcomes. To answer the call for longitudinal monitoring, Dr. Thomas and colleagues at BIOASTER, have been working on developing flow cytometry as a tool for microbiome monitoring. A proof-of -concept study was done in conjunction with Cynbiose to monitor the gut microbiota of non-human primate receiving antibiotic treatment. Flow cytometry used to analyze the stool samples of animals, before during and after treatment, revealed dramatic changes in microbiota composition. These findings were consistent with the 16S sequencing data on the samples. Published and on-going studies further demonstrate how flow cytometry can be combined with sequencing data to adjust relative abundance based on total bacterial burden and to link the flow cytometry dot plots to bacterial relative abundance data [17]. In addition to overall composition analysis, Dr. Thomas and colleagues demonstrated the potential of flow cytometry to assess bacterial viability in stool samples (described in detail in Ref. [18]). As part of this project, flow cytometry was also used to monitor the proportions of Gram-positive and Gram-negative bacteria. Building upon previous work, the group is now focusing on developing species-specific flow cytometry using detection with species-specific antibodies. Once the antibodies have been validated, they can be combined with live-dead staining to monitor the composition of different stool samples in greater detail. In summary, BIOASTER has developed and validated a series of staining methods compatible with flow cytometry analysis enabling the exploration of fecal microbiota composition at various levels of precision. Flow cytometry has the potential to become a fast and cost-effective tool for microbiota profiling including comparisons such as decreased bacterial load, decrease viable bacterial fraction, changes in bacterial diversity, and loss of species of interest. The ultimate goal for this technology would be the generation of plots that enable patient stratification and longitudinal monitoring based on multiparametric flow cytometry data analysis.

6. Discussion: how can we begin to implement standards in FMT?

The webinar concluded with a panel discussion on implementation of standards for FMT basic and clinical research. The panel featured the four speakers, joined by two experts at the forefront of FMT clinical research; Dr. Jennifer Wargo, Professor of surgical Oncology and Genomic Medicine at the University of Texas MD Anderson Cancer Center, and Dr. Gary Wu, Professor in Gastroenterology at the University of Pennsylvania Perelman School of Medicine.

Panelists discussed best practices to standardize donor selection and assay donor material to ensure optimal safety and efficacy. Among the specific criteria that were outlined for safety standards, the need for

specific pathogen free (SPF) testing, and virome composition (including phage) were cited as important considerations. Dr. Wargo also emphasized that effects of diet, medication, and other variables should be considered in donor selection, with the possibility of prescribing specific diets for donors. In addition, Dr. Wargo discussed the challenge of standardizing the donor selection process beyond the basic safety criteria, specifically the more complex issue of identifying the optimal donor for efficacious treatment. One major challenge in characterizing the optimal donor sample is that selection is constrained by the current technologies and their limited ability to provide the complete composition of donor material. A recurring theme throughout the webinar was the need to identify the "dark matter" that comprises FMT donor material, such as microbial components that are yet unidentified but may play a critical role in the efficacy of the treatment. In addition to potential gaps in the composition analysis, there is also a need for standardized functional analyses, which could vary by diagnosis.

Dr. Wu concurred that donor selection criteria are needed, and emphasized that overall the field has done a good job in screening and preventing the transfer of pathogens; however, the question of how to predict if you are transferring something beneficial has been more elusive. Dr. Wu reiterated that the issue really lies with the technology and the complexity of the samples and pipelines used for FMT measurements. As an example, Dr. Wu discussed the inherent heterogeneity of stool and the incredible variability of collection and sampling methods. Stool texture and water content will vary and can impact results, as well as whether the sample was from the stool surface or a core sample. All these factors will affect what is going into the recipient and are not necessarily well controlled. These parameters should be considered when standardizing donor material.

Dr. Affagard commented on the need to ensure reproducibility from optimal donors, especially if the donor ecosystem is expanded ex vivo in fermenters. This challenge spurred several follow-up questions into donor material comparisons between commercial FMT products and more traditional FMT donor banks. For its part, MaaT Pharma invested 4 years in the development of the fermentation process which included testing multiple culture conditions to control or promote specific bacteria and maintain proper pH and oxygen levels. These processes are monitored using Bray-Curtis similarity indexes, viability measurements, and monitoring of a core bacterial consortia that was selected from the literature. Affagard explained that MaaT Pharma is focused on microbial ecosystem development, not single species therapeutics, and therefore from a biomanufacturing point of view, co-culturing the mixture is more convenient that starting from the ground up and trying to combine 100s of organisms. While some argued that having pooled donors could increase safety concerns, the material is still screened for pathogens as are the donors of the original material limiting the additional risk seen by pooling which Affagard reasons is outweighed by the potential benefit of increased diversity and richness.

Expanding upon the idea that optimal FMT material may be synthetic communities defined by a high degree of richness and diversity, the panel discussed why donor material diversity matters. Dr. Sokol made the point that healthy donor ecosystems are diverse, but synthetic communities developed *in vitro* may not have the same functions as a diverse ecosystem that has evolved in the natural environment of the human GI tract. The question of why diversity of donor material matters further supports the need for improved understanding of the functional aspects of the GI microbiota, in addition to its composition. It is possible that the metric of diversity actually reflects functional redundancy, thus a more diverse microbiome can fill holes in the functional repertoire of the gut microbiota and is therefore more resilient to perturbation. From the discussion the consensus was FMT therapy will not be a one size fits all approach. Traditional FMT, commercially derived FMT, pooled ecosystems, and even consortia built from individual microbes are all plausible approaches for developing live biotherapeutic strategies. However, more basic research is needed to identify the key microbial contributors and host molecular signatures that could define successful approaches.

Several other topics were covered only briefly during the discussion, including route of delivery for the FMT, the potential role of probiotics, and the role of FMT in the treatment of other indications such as the aging process. While the discussion covered a range of FMT topics, several key themes emerged: (1) current limitations of metagenomic methodologies and technologies limit confidence in the FMT measurement pipeline (2) recipient screening is critical to understanding FMT engraftment, and how to measure it is critical to understanding efficacy (3) in addition to SPF screening and diversity metrics, basic safety criteria for donor selection should be expanded to include things like metatranscriptomics, metabolomics, proteomics, diet and other environmental exposures (4) formation of working groups or a larger consortia comprised of FMT subject matter experts is a promising path forward to address these challenges.

The discussion concluded with some final thoughts from the panel members, each of which touched on a recurring theme. Dr. Thomas reiterated the importance of considering other contributing factors such as diet, and how the diet of the donor as well as the post-transplant recipient is important. Regarding the use of FMT donors from non-industrial populations, Dr. Thomas commented that FMT of material derived from donors in developing countries into patients consuming industrialized, western diets may lose their efficacy, as beneficial metabolites (or other factors) from native diets will not necessarily be produced in the recipient.

Dr. Wu highlighted several outstanding questions for the field to contemplate: (1) Is engraftment important for outcome? (2) Should engraftment be measured in the stool or at the mucosal surface? (3) What is happens to the structure and function of the donor material once it's in the FMT recipient (4) What is the biological basis for a successful FMT?

Herve Affagard noted that to date much of the work on FMT has been conducted in silos. Collaborations between pharma, biotech, and research institutes could go a long way toward helping address remaining challenges. He recommended a common goal of defining engraftment, defining guidelines for how to monitor engraftment, and how to communicate this to regulators.

Dr. Sokol reminded the audience that we talk about the microbiota like it is one entity, with one mode of action but it's not. Plenty of modes of action plenty of difference effects, as all the disease are not related to the same impairment, it makes sense some donor might be more prone to induce therapeutic effects in some disease but not in others; "Not one stool fits all."

Along the same lines, Dr. Wargo asked the audience to consider where the bar for each indication resides. The bar appears very low for CDI and immune check point-associated colitis since these patients typically have a very dysbiotic gut microbiome with low diversity of microbiota and a healthy donor FMT may result in therapeutic benefit in many cases. The bar is higher for IBD and some of the more complex diseases, where there are likely many other variables contributing. With so many challenges, Dr. Wargo suggested a path forwards through convening as a group such as in a consortium and begin to define criteria and move towards standardization.

There was general consensus from the group that while the field has focused primarily on metagenomic pipelines and compositional data, FMTs would benefit a multi-omic analytical approach with a combination of platforms. Dr. Sergaki cautioned that adding multiple approaches will increase the complexity of data, and that proof of concept studies to demonstrate reproducibility of the methods is crucial for successful implementation. Dr. Sergaki, reiterated that limitations of current technologies, specifically the level of variability associated with microbiome measurements, is a major hurdle in the field. Biases introduced using current technologies are recognized and efforts are underway to better understand and characterize the effect of these influences. Until we can improve the accuracy and confidence in the compositional measurements of complex donor material, it will be difficult to move

forward to the more challenging questions of efficacy that have been raised during this webinar.

7. Conclusion

FMT has been used with remarkable success in the treatment of rCDI. Beyond rCDI, there are 134 active clinical trials using FMT (46 Phase II, 18 in Phase III) for numerous diseases ranging from: cirrhosis to ankylosing spondylitis or anorexia nervosis [19]. In addition to FMT, the development of live biotherapeutics (LBPs) using specific components of the microbiome are also ongoing. While the first LBP has cleared phase 3 clinical trials, the development in this field is slow, with many formulations displaying reduced efficacy compared to FMT [20]. This webinar identified several key gaps and challenges for FMT to overcome; from donor selection and screening, to measuring therapeutic efficacy. The webinar also provided a starting point to define the current state of FMT research and identify how standards may be introduced to facilitate the advancement of this therapy. The goal in the development and use of standards in FMT is to support innovation. Standards are critical to improve measurement pipelines and build confidence in them. Once we have confidence in what is in the FMT and what is in the recipient, then we can get closer to regulating this process. Finally, future engagement within the FMT community through webinars and face-to-face workshops will be critical to overcome the challenges highlighted in the Evolution of FMT – From Early Clinical to Standardized Treatments webinar.

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