Fecal microbiota transplantation as a mean of overcoming immunotherapy-resistant cancers – hype or hope?

Ther Adv Med Oncol
2021, Vol. 13: 1–4
DOI: 10.1177/17588359211045853

Erez N. Baruch, Tanmay Gaglani and Jennifer A. Wargo

Keywords: anti-PD-1, checkpoint inhibitors, fecal microbiota transplantation, immunotherapy, melanoma, microbiome

Received: 21 April 2021; revised manuscript accepted: 25 August 2021.

Correspondence to:
Jennifer A. Wargo
Program for Innovative Microbiome and Translational Research, Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, FCT17.6060, Unit 1484, Houston, TX 77030, USA

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
JWargo@mdanderson.org

Erez N. Baruch
Department of Internal Medicine, The University of Texas Health Science Center, Houston, TX, USA

Program for Innovative Microbiome and Translational Research, Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, FCT17.6060, Unit 1484, Houston, TX 77030, USA
ENBaruch@mdanderson.org

Tanmay Gaglani
Department of Internal Medicine, The University of Texas Health Science Center, Houston, TX, USA.

The gut microbiota has co-evolved with humans for millions of years, creating a complex network of regulations and reciprocal effects.[1,2] However, these networks have been exposed only in the recent decades, thanks to the ability to sequence bacterial genomes and to the technical revolution during the 2000s which turned DNA sequencing into an affordable and feasible lab tool.[1,3,4] Today, the gut microbiota is known to affect not only local inflammatory processes in the gut[5] but also systemic processes such as obesity and diabetes,[6] pregnancy,[7] autism[8] and neuro-degenerative diseases.[9,10] The gut microbiota also affects the immune system. This interaction is so significant that the gut microbiota is essential for the proper development of lymphoid organs and the adaptive immune system.[11] However, the presence of microbes in our gut is not merely an immune "on–off switch", as different microbes can suppress or promote different immune cells, dynamically shaping the overall function of our immune system.[12] Based on these findings, several groups have examined a potential association between the gut microbiota and clinical response to cancer immunotherapy, especially to immune checkpoint inhibitors (ICIs). All groups demonstrated clear microbiota compositional differences between ICI responders and non-responders.[13–17] Since the gut microbiota can dynamically shape our immune system, it is intuitive to assume that replacing a patient's gut microbiota into a more "ICI-favorable" composition will enhance overall ICI effectiveness. Indeed, two clinical trials recently demonstrated that combining fecal microbiota transplantation (FMT) from donors who responded to ICIs into recipient patients with metastatic ICI-resistant melanoma, coupled with ICI re-induction, resulted in objective clinical response rates of ~30%.[18,19] Patients who responded to the combination of FMT and ICI had increased intra-tumoral infiltration of $CD8^+$ T-cells, T-helper type 1 cells and antigen presenting cells while infiltration of myeloid derived suppressor cells decreased.[18,19] These intra-tumoral immune changes are well-established as ICI-favorable features[20,21] and were consistently reported in in pre-clinical models of microbiota modulation.[22] Albeit limited by small sample sizes, the fact that two independent cancer centers in different parts of the world with different patient populations (primary and acquired ICI failures[18,20] *versus* only primary ICI failures[19,20]) using different ICIs (nivolumab[18] *versus* pembrolizumab[19]) reported similar clinical and translational results in accordance with pre-clinical findings is highly supportive of the validity of these preliminary results.

The primary study aim of both FMT–ICI clinical trials was treatment safety. Davar *et al.*,[19] who used a single FMT *via* colonoscopy at the beginning of the treatment protocol, reported good safety results – 72.9% of the immunotherapy-related adverse events (irAEs) were mild (grade 1) and only three patients had severe, grade 3, irAEs (two fatigue, one neuropathy). Baruch *et al.*,[23] who used colonoscopy at the beginning of the treatment protocol followed by repeated FMTs *via* stool capsules every 14 days, reported no grade 2 or above irAEs, even in patients who developed grade 3 irAEs on previous ICI treatment lines.[18] FMT has been reported to ameliorate ICI-related colitis,[23] a use which is currently being assessed in clinical trials (NCT04038619,

NCT03819296). These findings suggest that the combination of FMT and ICI is not only a more effective treatment but may also have a better safety profile. This potential duality of a treatment regimen combining available Food and Drug Administration (FDA)-approved commonly used oncological drugs and a highly available and easily re-produced organic compound (human feces) has sparked great hopes among both clinicians and cancer patients.

Despite these hopes, FMT use in cancer immunotherapy has several key limitations. The transfer of fecal content from one human to another bears significant infectious risks which may even result in patient deaths.[24] For this reason, FMT is not an FDA-approved treatment, even for recurrent *Clostridioides difficile* colitis – a clinical setting in which FMT has been used for decades with well-established response rates of up to 90%.[25,26] The COVID-19 pandemic has added more safety concerns, as even asymptomatic healthy individuals may carry the SARS-COV-2 virus in their feces and infect recipient patients *via* FMT.[27] To minimize FMT-associated risks, regulatory bodies and professional guidelines recommend rigorous pre-donation safety screening for potential donors.[28,29] Those safety restrictions require a large pre-screening donor pool. It is more feasible to recruit potential donors among the general healthy population than among cancer patients who responded to ICIs – a significantly smaller donor pool. However, in both FMT–ICI clinical trials[18,19] the donors were metastatic melanoma patients who achieved complete or partial responses to ICIs. As different microbiota compositions may have different immune effects, it is unclear whether fecal implants from the general healthy population can induce similar immune and clinical effects to that of "ICI-proven" implants. Assessment of the compatibility of healthy donors is currently in progress (NCT03772899). Another layer of complexity is added by evidence suggesting that there may be an effectiveness variability even among ICI-responding donors. All of the three responders from the Baruch *et al.*[18] cohort received implants from the same donor (Donor #1). In the Davar *et al.*[19] cohort there were overall three responders; two of them received FMT implants for the same donor (PT-18-0014). In both cohorts there were patients who got FMT implants from other donors without any clinical benefit. On the other hand, both cohorts included patients who received FMT implants from Donor #1 and PT-18-0014 but failed to respond. Currently, there is no consensus regarding a "good" or even a "good enough" microbiota composition for donors. Several microbiota markers have been associated with clinical response, such as higher alpha diversity[13,30] (number of different bacteria per microbiota community) and the presence of specific taxa such as Ruminococcaceae[13] and Akkermansia.[15] However, none of these suggested markers has been thoroughly validated and there is still great variability among reports.[31] It is also still unclear why some patients responded to the combination of FMT and ICI while others did not. Lack of response to FMT and ICI may be explained by the presence of additional ICI resistance mechanisms, such as additional immune checkpoints (TIGIT, IDO-1) or lack of proper antigen presentation machinery in tumor cells.[18,20,32] Nevertheless, as both patients with primary ICI and acquired ICI failure responded to the combination of FMT and ICI, and as the pre-treatment intra-tumoral PDL-1 expression did not correlate with response to treatment,[18] there are currently no available screening tools or prognostic factors which may be used to stratify potential recipient patients for the FMT–ICI treatment.

To overcome some of these limitations, new research efforts focus on two disparate goals. The first goal is to enhance donor selection and donor–patient matching processes. Some of the proposed matching criteria are as simple as age,[33] while others may be sequencing-based biomarkers.[34] An efficient selection and matching process will probably require highly specialized groups and might be available only in a selected number of major cancer centers, similar to the current adoptive cell therapy technology. The second goal is to decipher the mechanisms behind the FMT-induced clinical effect. Understanding how microbiota modulation affects anti-cancer immunity may lead to identification of druggable targets and eventually to non-organic therapeutics that will render safety screening and donor–recipient matching phases. However, only the first steps in this direction have been made so far,[22] and such novel therapeutics are unlikely to be available in the near future.

In conclusion, microbiota modulation by FMT in combination with ICI re-induction has a promising therapeutic potential. However, it is not a magic bullet. Due to significant uncertainties regarding characteristics of both donors and recipient patients, we urge against the use of FMT and ICIs outside of clinical trials. With current technology and limitations, it seems that the combination of FMT and ICIs will remain at this point confined to

large academic centers capable of mounting tight collaborations between oncological, gastroenterological and infectious disease groups. That being said, the true strength of the FMT and ICI combination is in its concept – modulation of the gut microbiota can enhance clinical response to ICIs. As research in this field continues to progress, future scientific advances may lead to more efficient and feasible methods for microbiota modulations, or drugs that mimic these modulation effects, turning the microbiota into a powerful weapon in our anti-cancer arsenal.

Acknowledgements

J.A.W. is supported by NIH (1 R01 CA219896-01A1), Melanoma Research Alliance (4022024), American Association for Cancer Research Stand Up To Cancer (SU2C-AACR-IRG-19-17), and MD Anderson Cancer Center's Melanoma Moon Shots Program.

Conflict of interest statement

J.A.W. is an inventor on a US patent application (PCT/US17/53.717) relevant to the current work; reports compensation for speaker's bureau and honoraria from Imedex, Dava Oncology, Omniprex, Illumina, Gilead, PeerView, medimmune, and Bristol-Myers Squibb (BMS); serves as a consultant/advisory board member for Roche/Genentech, Novartis, AstraZeneca, GlaxoSmith Kline (GSK), BMS, Merck, Biothera Pharmaceuticals, and Micronoma.

E.N.B and T.G. have no conflict of interest and nothing to disclose

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Erez N. Baruch https://orcid.org/0000-0001-6001-6598

References

1. Ursell LK, Metcalf JL, Parfrey LW, *et al.* Defining the human microbiome. *Nutr Rev* 2012; 70(Suppl. 1): S38–S44.
2. Wang B, Yao M, Lv L, *et al.* The human microbiota in health and disease. *Engineering* 2017; 3: 71–82.
3. Land M, Hauser L, Jun S-R, *et al.* Insights from 20 years of bacterial genome sequencing. *Funct Integr Genomics* 2015; 15: 141–161.
4. Shendure J and Ji H. Next-generation DNA sequencing. *Nat Biotechnol* 2008; 26: 1135–1145.
5. Ni J, Wu GD, Albenberg L, *et al.* Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol* 2017; 14: 573–584.
6. Fan Y and Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 2021; 19: 55–71.
7. Nyangahu DD and Jaspan HB. Influence of maternal microbiota during pregnancy on infant immunity. *Clin Exp Immunol* 2019; 198: 47–56.
8. Sharon G, Cruz NJ, Kang DW, *et al.* Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell* 2019; 177: 1600–1618.e17.
9. Kowalski K and Mulak A. Brain-gut-microbiota axis in Alzheimer's disease. *J Neurogastroenterol Motil* 2019; 25: 48–60.
10. Sampson TR, Debelius JW, Thron T, *et al.* Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 2016; 167: 1469–1480.e12.
11. Belkaid Y and Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; 157: 121–141.
12. Geva-Zatorsky N, Sefik E, Kua L, *et al.* Mining the human gut microbiota for immunomodulatory organisms. *Cell* 2017; 168: 928–943.e911.
13. Gopalakrishnan V, Spencer CN, Nezi L, *et al.* Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science* 2018; 359: 97–103.
14. Matson V, Fessler J, Bao R, *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018; 359: 104–108.
15. Routy B, Le Chatelier E, Derosa L, *et al.* Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* 2018; 359: 91–97.
16. Sivan A, Corrales L, Hubert N, *et al.* Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015; 350: 1084–1089.
17. Vetizou M, Pitt JM, Daillere R, *et al.* Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015; 350: 1079–1084.

18. Baruch EN, Youngster I, Ben-Betzalel G, *et al*. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 2021; 371: 602–609.

19. Davar D, Dzutsev AK, McCulloch JA, *et al*. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 2021; 371: 595–602.

20. Sharma P, Hu-Lieskovan S, Wargo JA, *et al*. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell* 2017; 168: 707–723.

21. Wei SC, Levine JH, Cogdill AP, *et al*. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell* 2017; 170: 1120–1133.e17.

22. Baruch EN, Wang J and Wargo JA. Gut microbiota and antitumor immunity: potential mechanisms for clinical effect. *Cancer Immunol Res* 2021; 9: 365–370.

23. Wang Y, Wiesnoski DH, Helmink BA, *et al*. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med* 2018; 24: 1804–1808.

24. DeFilipp Z, Bloom PP, Torres Soto M, *et al*. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. *N Engl J Med* 2019; 381: 2043–2050.

25. U.S. Food and Drug Administration. *Fecal microbiota for transplantation: safety alert - risk of serious adverse events likely due to transmission of pathogenic organisms*, https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission (2020, accessed April 17, 2021).

26. Baunwall SMD, Lee MM, Eriksen MK, *et al*. Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: an updated systematic review and meta-analysis. *EClinicalMedicine* 2020; 29–30: 100642.

27. U.S. Food and Drug Administration. Fecal microbiota for transplantation: new safety information - regarding additional protections for screening donors for COVID-19 and exposure to SARS-CoV-2 and testing for SARS-CoV-2, https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening (2020, accessed 24 July 2021).

28. Cammarota G, Ianiro G, Tilg H, *et al*. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 2017; 66: 569–580.

29. Kim KO and Gluck M. Fecal microbiota transplantation: an update on clinical practice. *Clin Endosc* 2019; 52: 137–143.

30. Batten M, Shanahan E, Simpson R, *et al*. Gut microbiota predicts response and toxicity with neoadjuvant immunotherapy. *Cancer Res* 2020; 80: Abstract 5734.

31. Gopalakrishnan V, Helmink BA, Spencer CN, *et al*. The Influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell* 2018; 33: 570–580.

32. Trujillo JA, Sweis RF, Bao R, *et al*. T cell-inflamed versus non-T cell-inflamed tumors: a conceptual framework for cancer immunotherapy drug development and combination therapy selection. *Cancer Immunol Res* 2018; 6: 990–1000.

33. Okahara K, Ishikawa D, Nomura K, *et al*. Matching between donors and ulcerative colitis patients is important for long-term maintenance after fecal microbiota transplantation. *J Clin Med* 2020; 9: 1650.

34. Duvallet C, Zellmer C, Panchal P, *et al*. Framework for rational donor selection in fecal microbiota transplant clinical trials. *PLoS One* 2019; 14: e0222881.