Francesca Gazzaniga, PhD

Gazzaniga Laboratory

Francesca S. Gazzaniga, PhD
Katelyn Geisler
Shumeng Hao, PhD
Jack White
Tsering Yanortsang
Sneha Yelemanchili

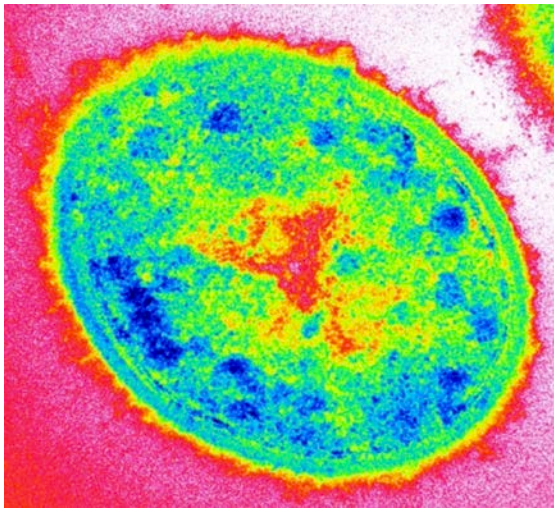
Gut microbiota — the trillions of bacteria, fungi, viruses, and archaea that reside in our gut — contain a dynamic arsenal of products that can protect from or contribute to disease. Diet, medication, exercise and disease impact the composition of the microbiota and influence the products the microbes produce. In turn, specific microbes influence immune cell function in both normal and disease states. **The Gazzaniga laboratory** focuses on unraveling this complex ecosystem that holds huge therapeutic potential, and that reveals the dynamic interplay of environmental factors, microbes, microbial products and immune cells. Specifically, we focus on three main questions: (1) Which bacteria are associated with response in cancer patients? (2) Which gut bacterial produced molecules impact anti-tumor immunity? (3) How do microbe-mediated immune responses impact the anti-tumor response to immunotherapy? Our ultimate goal is to uncover mechanistic information to develop microbe-based therapies that fine-tune the immune system to fight cancer.

The trillions of bacteria that inhabit our intestinal tract as part of our gut microbiota have a dynamic relationship with our immune system. For example, the bacteria in the gut impact the anti-tumor response of immune checkpoint inhibitors on tumors outside of the gut. Treatment with checkpoint inhibitors, such as antibodies targeting programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1), disrupts interactions between PD-1 on T cells and PD-L1 on tumors, reinvigorating T cells to kill cancer cells. Although checkpoint inhibitors are used to treat a wide variety of cancers, the response rates are variable. Understanding what impacts the efficacy of checkpoint inhibitors is critical to increase the number of patients who respond to treatment.

Fecal transplants from melanoma patients who responded to PD-1 blockade can overcome resistance in non-responders. However, the efficacy of the fecal transplants varies with different donors, highlighting the need to understand how bacteria impact anti-tumor immunity. The purpose of the Gazzaniga lab is to translate the notion that the microbiome plays a role in anti-tumor immunity into reliable, microbiome-inspired treatments that increase the number of patients who respond to checkpoint blockade.

Patient stool samples: What is associated with response?

Many studies examining the role of the gut microbiome in response to checkpoint blockade therapy focused on melanoma. However, PD-1 blockade is approved for over 25 different cancers. Depending on the cancer type, PD-1 blockade efficacy ranges from 2%-87%. Therefore, understanding how the microbiome impacts the anti-tumor responses of checkpoint blockade in other cancers is critical to increase the number of patients who respond. We collaborate with clinicians at MGB to analyze stool samples from patients with different cancers at the beginning and end of treatment with checkpoint inhibitors. We investigate which treatments impact the gut microbiome and which bacteria are associated with anti-tumor responses in different cancers.



We isolated Erysipelatoclostridium ramosum from healthy human microbiota and found that it promotes an anti-tumor response to anti-PD-L1 therapy. We are currently isolating the anti-tumor molecule it produces and are investigating the immune pathways it impacts to promote anti-tumor immunity.

Searching for patient-derived therapeutics: What bacterial molecules promote anti-tumor immunity?

Many have sought to identify individual bacteria that could be used as probiotics in the clinic to promote anti-tumor immunity. However, several obstacles make probiotics an unreliable therapy. There are difficulties in delivering live anaerobic bacteria, difficulties in engraftment of probiotics in humans already colonized with bacteria, and differences between lab culture conditions and the human intestine that could contribute to the anti-tumor activity of the bacteria. Bacterial molecules, on the other hand, can be delivered and tested more reproducibly and thus bypass the variability of probiotics and fecal transplants. Using germ-free mice, which lack all microbes, we can investigate how different bacteria impact tumor outcomes. We have isolated two bacterial strains from a healthy human microbiome that promote anti-tumor immunity to PD-1 blockade and are currently identifying the anti-tumor molecules they produce. Next, we will isolate bacterial molecules from patient responder stool to develop reproducibly delivered patient-derived bacterial therapeutics to increase the efficacy of checkpoint inhibitor therapy.

Learning from bacteria: Which microbe-mediated immune mechanisms can we harness to promote anti-tumor immunity?

By comparing mice colonized with healthy human microbiota to mice treated with broad spectrum antibiotics, we have identified several immune pathways in the tumor-draining lymph nodes that are impacted by gut bacteria and associated with anti-tumor immunity. By targeting these immune pathways, we can convert non-responders to responders in multiple tumor models. To make our mouse models more clinically relevant, we compare mice colonized with patient non-responder or responder microbiota to identify immune pathways impacted only by responder microbes. Our overall goal is to learn from bacteria and develop therapeutics that target the immune pathways impacted by responder microbiota to increase the number of patients who respond to treatment.

Selected Publications:

Park JS*, **Gazzaniga FS***, Wu M, Gillis J, Zheng W, LaFleur MW, Johnson SB, Morad G, Park EM, Zhou Y, Watowich SS, Wargo JA, Freeman GJ**, Kasper DL**, Sharpe AH**. Targeting PD-L2–RGMb overcomes microbiome-related immunotherapy resistance. *Nature*. 2023 Jun 28.

Gazzaniga FS, Camacho DM, Wu M, Palazzo M, Dinis A, Grafton FN, Cartwright MJ, Super M, Kasper DL, Ingber DE. Harnessing colon chip technology to identify commensal bacteria that promote host tolerance to infection. *Front Cell Infect Microbiol*. 2021 Mar 12;11:638014

Zheng W, Zhao W, Wu M, Song X, Caro F, Sun X, **Gazzaniga FS**, Stefanetti G, Oh S, Mekalanos JJ, Kasper DL. Microbiota-targeted maternal antibodies protect neonates from enteric infection. *Nature*. 2020 Jan;577(7791): 543-548.

Jalili-Firoozinezhad S†, **Gazzaniga FS†**, Calamari EL†, Camacho DM, Fadel CW, Bein A, Swenor B, Nestor B, Cronce MJ, Tovaglieri A, Levy O, Gregory KE, Breault DT, Cabral JMS, Kasper DL, Novak R, Ingber DE. A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. *Nat Biomed Eng*. 2019 Jul;3(7):520-531

Erturk-Hasdemir D, Oh SF, Okan NA, Stefanetti G, **Gazzaniga FS**, Seeberger PH, Plevy SE, Kasper DL. Symbionts exploit complex signaling to educate the immune system. *Proc Natl Acad Sci U S A. 2019 Dec 26;116(52):26157-26166.*

*Co-first authors
**Co-last authors
†Denotes equal contribution