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The Gut Microbiome and Checkpoint Blockade Therapy for Melanoma

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Over the last decade, we have seen major advances in melanoma therapy and a decline in melanoma mortality.[1] These advances reflect the achievements of investigators and educators around the world in improving melanoma treatment, early detection and prevention strategies.

One area that holds great promise and warrants close attention in melanoma therapy is the microbiome. Recent evidence indicates that this collection of microbes and their collective genomes that inhabit our bodies — particularly the gut microbiome — may affect host immunity and response to melanoma therapy. This has important implications, as numerous factors impact the gut microbiome, and strategies are being developed to modify it for therapeutic purposes.

The Gut Microbiome and Response to Immunotherapy

Identifying predictors of response and mechanisms of resistance to immune checkpoint blockade (ICB) therapy, as well as targets to enhance response, is an area of active investigation.[2,3] The microbiome has been referred to as the second human genome,[4] and several studies have demonstrated an association between the diversity and composition of the gut microbiome and response to immunotherapy.[5-11]

Two key studies published in 2015 demonstrated differences in response

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From the Editors

Trillions of microorganisms, with a combined weight between two and six pounds, inhabit each human body. They outnumber human cells by a factor of 10. This is the human microbiome.

As early as the fourth century, Chinese medicine appreciated the healing potential of ingesting stool ("yellow soup") as a treatment for diarrhea. However, it would take centuries for Western medicine to identify bacteria and their role in health, and even longer to acknowledge that some bacteria offer distinct benefits.

From the time that Antonie van Leeuwenhoek first identified bacteria in the 1600s, they were conceived of as harmful invaders, and two centuries later, Robert Koch reinforced this idea when he linked microorganisms to human disease. But the concept that some bacteria could be beneficial began emerging in 1958 when Eiseman and

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to anti-CTLA-4 and anti-PD-1 treatments in murine models, depending on the composition of the gut microbiome.[5,6] These studies also showed that changing gut microbiome composition could enhance response to ICB. This work was followed by several studies in human cohorts demonstrating a link between the gut microbiome and responses to ICB.[7-11] This included early work looking at associations between the gut microbiome and response to anti-CTLA-4 treatment, where distinct gut microbiome composition at baseline was associated with both an anticancer response and immune-related colitis in metastatic melanoma patients.[7] Later work focused on microbiome compositional differences between patients responding or not responding to anti-PD-1 treatment with or without anti-CTLA-4 treatment, again finding distinct gut microbiome differences.[8]

Additionally, two studies from preclinical and human cohorts published in 2018 analyzed gut microbiome signatures in responders versus nonresponders to ICB, offering mechanistic insights on the role of the gut microbiome.[9,10] Several "response-associated" taxa were identified in each of these cohorts (including Rumicococcus, Faecalibacteria and Bifidobacteria), though overlap between cohorts was admittedly modest — which may relate to different sequencing approaches used in each of the cohorts, as well as different methods of preprocessing data using different databases. Clearly, other factors could also be at play, such as diet and geographic differences.

Taken together, these studies support the premise of a link between the gut microbiome and immunity as well as the response to melanoma immunotherapy. They furthermore raise important questions. For one, can the gut microbiome be used as a diagnostic and therapeutic target in patients with melanoma and other cancers?

Factors Affecting the Gut Microbiome

Given the potential impact of microbes on response to cancer immunotherapy, we must carefully consider factors that affect the gut microbiome in patients on therapy. Environmental factors show clear predominance over genetic factors as modifiers of the gut microbiome,[12] and current evidence suggests a strong role for environmental and host factors in modifying the composition, diversity and collective metabolic activities of the microbial community.

Table 1: Clinical trials of gut microbiome modulation in melanoma

Trial number	Patient population	Intervention	Key Efficacy Endpoints	n
NCT03341143	metastatic melanoma patients resistant to ICB	FMT from anti-PD-1 responders via colonoscopy + anti-PD-1	ORR; immune profile change	20
NCT03353402	metastatic melanoma patients (cohort 1, anti-PD-1-naïve; cohort 2, anti-PD-1-refractory)	FMT from ICB responders via colonoscopy followed by stool capsules + anti-PD-1	engraftment and safety; immune profile change	40
NCT03595683	metastatic melanoma patients (Cohort 1: anti-PD-1-naïve; Cohort 2: anti-PD1-refractory)	EDP1503 monoclonal microbial + pembrolizumab	ORR; safety	70
NCT03772899	metastatic melanoma	FMT from healthy donor via stool capsules + anti-PD-1	safety, ORR, engraftment, immune profile	20
NCT03817125	treatment-naïve metastatic melanoma	SER-401 oral bacterial consortia + nivolumab vs. placebo + nivolumab	safety, engraftment, ORR, immune profile	30
NCT03819296	melanoma or genitourinary patients with refractory ICB-related colitis	FMT from healthy donor via colonoscopy	safety	100
NCT03934827	solid tumors presurgical resection	MRx0518 (enterococcus) oral vs. placebo 2 to 4 weeks prior to surgery	safety, survival	120
NCT03950635	melanoma survivors	controlled feeding study of high-fiber diet or ketogenic diet	feasibility, microbiome modulation, systemic metabolism	20

ICB = immune checkpoint blockade. FMT = fecal microbiota transplant. ORR = overall response rate.

Diet and other lifestyle factors strongly affect gut microbiome composition. The impact of diet has been extensively studied in the context of gut microbiome composition, and dietary intervention is a potential therapeutic strategy to modify that composition.[13] At least one dietary intervention trial is underway in melanoma patients (**Table 1**). It has been shown that diets high in plant-based fibers (fruits, vegetables and whole grains) and low in processed foods and added sugars, with protein sources from fish and legumes, are associated with lower cancer risk and more "favorable" microbiome and metabolic profiles.[14,15] This has relevance to melanoma patients, as preliminary data presented at the 2019 annual meeting of the American Association of Cancer Research (AACR) demonstrated that melanoma patients who reported eating a high-fiber diet were more likely to respond to ICB.[16]

Other lifestyle factors that have been shown to impact the gut microbiota in other populations include exercise, sleep patterns and stress.[13] Host factors such as age, sex and body mass index also modify gut microbiome composition.[17,18] The causal relationships linking these factors with the gut microbiome are still unclear in the context of cancer, and understanding underlying mechanisms may allow better modification of the gut microbiome.

"Can the gut microbiome be used as a diagnostic and therapeutic target in patients with melanoma and other cancers?"

Medications may also impact the gut microbiome. This includes antibiotics, with studies demonstrating impaired responses to ICB in patients with non-small cell lung cancer who received antibiotics prior to initiation of ICB.[11] Similar findings have been demonstrated in cohorts of melanoma patients.[19]

Numerous medications beyond antibiotics have also been shown to impact gut microbes.[20] Over-the-counter supplements and probiotics may also impact the gut microbiome, with early evidence showing that patients who take over-the-counter probiotics have reduced microbiome diversity;[16] thus, patient use of these compounds should be discussed and carefully considered, perhaps even discouraged outside the context of a clinical trial.

Strategies to Modulate the Gut Microbiome

Given these findings, there is a strong interest in modulating the gut microbiome to improve therapeutic responses, and clinical trials incorporating these strategies are currently underway (**Table 1**). The gut microbiota can be modulated via several different approaches — including fecal microbiota transplant, administration of single bacterial strains or microbial consortia (two or more microbial groups living symbiotically), prebiotics or probiotics, targeted antibiotic approaches and other novel strategies, as well as by diet.

Fecal microbiota transplant (FMT) has perhaps generated the most provocative data thus far in microbiome modulation of patients with metastatic melanoma. FMT has been extensively studied in gastrointestinal diseases such as inflammatory bowel disease (IBD) and Clostridium difficile infection (CDI),[21] and it is now being investigated in the context of cancer.[22] FMT involves the transfer of fecal material from a single or multiple donors to the gastrointestinal tract of a diseased individual and has proven efficacy in certain disease settings. (For example, in refractory CDI, 80 to 90 percent of patients benefit from FMT.[23])

However, FMT is still an unstandardized treatment with some risks, and therefore interventions using this approach should be performed only in the context of a carefully planned clinical trial. Such studies are currently underway (**Table 1**), and preliminary data from two of these studies were recently reported at the 2019 annual meeting of the AACR. Responses were observed in metastatic melanoma patients who had progressed on anti-PD-1 therapy and were subsequently treated with complete responder donor FMT and reinduction of anti-PD-1 (NCT03817125, NCT03353402). Additional trials are open and accruing patients with metastatic melanoma (**Table 1**). There are also data to suggest that FMT may be successful in treating immunotherapy-associated colitis.[24] Two patients with this condition who were treated with FMT experienced complete resolution of clinical symptoms.[24] Nonetheless, complexities exist with these approaches, and unanswered questions remain regarding optimal donors and consortia, among numerous other factors.[22]

Given the impact of diet on the gut microbiota, there is a strong rationale for dietary intervention trials in melanoma patients going into immunotherapy, and such trials are underway (NCT03950635). This approach holds great promise; however, long-term dietary changes are notoriously difficult to sustain, and it is unclear that such interventions will be effective in patients with widespread metastatic melanoma. Nonetheless, these interventions should be tested and incorporated into other microbiome modulation strategies (for example, with administration of FMT and specific bacterial consortia). Ultimately, they may help inform dietary recommendations to improve immunity and responses, and potentially to abrogate toxicity.

Conclusions and Future Directions

We have made major advances in melanoma therapy; however, tremendous opportunities exist for further improvement. Optimal biomarkers of response to therapy in patients with advanced disease remain elusive, and integrative approaches are needed that incorporate factors both intrinsic and extrinsic to the host.[25] Additionally, we need to embrace novel trial designs (including neoadjuvant trials) and a global team scientific approach (such as that embodied in the International Neoadjuvant Melanoma Consortium). [See **Neoadjuvant Therapy for Melanoma**, page 5.]

Microbiome modulation has shown great potential for increasing the therapeutic efficacy of ICB, but further studies are needed to define optimal strategies in clinical settings. The gut microbiome is strongly influenced by diet and other lifestyle factors; therefore, we need to consider these factors critically when developing individualized treatments. Moreover, the standardization of approaches, extensive data recording from clinical trials and global sharing of data to improve team-based research will be key in developing clinically actionable strategies to further enhance treatment (and ultimately prevention) of melanoma. ■

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Neoadjuvant Therapy for Melanoma

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Neoadjuvant strategies for melanoma have been underway for several years, owing to improved systemic therapy. The use of immune checkpoint blockade (ICB) and targeted therapies in neoadjuvant settings (i.e., prior to surgery) is a promising new treatment strategy for advanced stage melanomas,[1-8] though yet to be approved by the FDA. As reported in Vol. 37, No. 1 of *The Melanoma Letter*,[9] the first issue of 2019, this is an exciting area of investigation, with several studies recently reporting successful outcomes, and many more studies underway (**Table 2, pp. 6–7**). This research is rapidly evolving, with several additional studies published in the months since that issue of the newsletter. These include studies on neoadjuvant targeted therapy[4] as well as a follow-up to the OpACIN-neoadjuvant trial (NCT02977052) exploring optimal dose and scheduling for combination neoadjuvant ICB.[5]

In the OpACIN trial, the investigators identified treatment of metastatic melanoma with two cycles of ipilimumab (1mg/kg) plus nivolumab (3mg/kg) as the best tolerated dosing schedule for neoadjuvant combined ICB.[5] In the NeoCombi neoadjuvant trial (NCT01972347), neoadjuvant targeted therapy with combination dabrafenib-trametinib led to a high rate of complete radiographic and pathological response, and all patients were able to undergo surgery following the neoadjuvant therapy.[4]

At the 2019 American Society of Clinical Oncology (ASCO) annual meeting, a pooled analysis of neoadjuvant targeted therapy and ICB neoadjuvant therapy for patients with clinical stage III melanoma (n=184) was presented.[7] Consistent with previous reports, achievement of pathologic complete response, or pCR (41 percent in the overall cohort, 38 percent with ICB and 47 percent with BRAF-MEK targeted therapy), was associated with better relapse-free survival (RFS) compared with that of patients without a pCR (95 percent vs. 62 percent at 12 months, $p<0.001$).[7] Notably, RFS rates were significantly higher in the neoadjuvant ICB study population compared with neoadjuvant targeted therapy (83 percent vs. 65 percent at 12 months, $p<0.001$), though inherent limitations exist with this retrospective analysis given that in no studies have patients been randomized to one strategy or the other. Data from this pooled analysis and earlier reported trials demonstrate proof of principal for the neoadjuvant approach and provide the foundation for ongoing work.

During the 2019 ASCO Annual Meeting, there was also a meeting of the International Neoadjuvant Melanoma Consortium — a group established to bring key stakeholders together from research institutions around the world, with the goal of harmonizing approaches to neoadjuvant melanoma therapy. The group recently developed guidelines for design and implementation of clinical trials addressing the proposed duration of therapy, response assessment, biospecimen collection and analysis strategies.[8] This group has also provided key resources such as standardized criteria for pathologic assessment after neoadjuvant treatment.[10] Numerous additional neoadjuvant trials are currently ongoing (**Table 2**), and these studies should reveal critical insights on safety, feasibility and response. ■

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Neoadjuvant Therapy for Melanoma

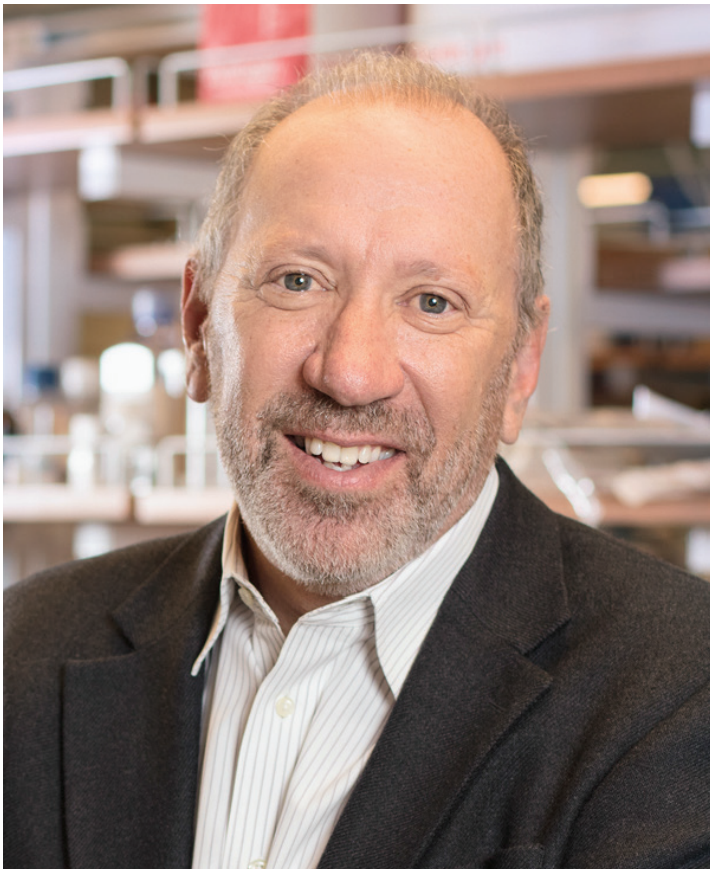
Table 2: Clinical trials assessing systemic and/or intralesional therapies for cutaneous melanoma in the neoadjuvant setting

NCT Number	Patient Population	Intervention	Key Efficacy Endpoints	n
Recruiting				
NCT02036086	BRAFV600-mutated melanoma, palpable lymph node metastases	vemurafenib + cobimetinib	resectability rate	20
NCT02231775	BRAFV600-mutated resectable stage IIIB/IIIC melanoma	dabrafenib + trametinib	RFS, OS and pathological complete response rate	78
NCT02434354	clinical stage III or resectable stage IV melanoma	pembrolizumab	Unspecified	30
NCT02519322	resectable stage IIIB-IV melanoma	A: nivolumab. B: nivolumab + ipilimumab. C: nivolumab + relatlimab	pathological response rate, T cell infiltration, objective response rates, RFS, OS	53
NCT02858921	BRAFV600-mutated resectable stage III melanoma	A: sequential dabrafenib + trametinib, then pembrolizumab. B: concurrent dabrafenib + trametinib + pembrolizumab. C: pembrolizumab only	pathological response rate, objective response rate, RFS, OS	60
NCT02977052	stage III melanoma	three dosing schedules for ipilimumab + nivolumab	objective response rate, pathological response rate, RFS	110
NCT03554083	clinical stage III melanoma	vemurafenib + cobimetinib + atezolizumab	pathological complete response rate, RFS	30
NCT03567889	clinical stage IIIB/IIIC	Daromun (intralesional)	RFS, OS, local recurrence-free survival	248
NCT03618641	resectable nodal stage IIIB-D melanoma	CMP-001 + nivolumab	major pathological response rate, RFS, OS	40
NCT03698019	resectable stage III/IV melanoma	pembrolizumab	EFS, OS, objective response rate, disease control rate	556
NCT03757689	stage IIB/IIC melanoma	pembrolizumab	sentinel lymph node positivity rate	63
NCT03972046	BRAFV600-mutated stage IIIB-IVA melanoma	TVEC (intralesional) + dabrafenib + trametinib	RFS, melanoma-specific survival, DMFS, radiographic response rate, pathological response rate	20

Not yet recruiting				
NCT03842943	stage III melanoma	TVEC (intralesional) + pembrolizumab	pathological complete response rate	28
Active, not recruiting				
NCT01321437	stage III melanoma	axitinib	overall response rate, PFS	11
NCT01972347	BRAFV600-mutated resectable stage IIIB/IIIC melanoma	dabrafenib + trametinib	pathologic response rate, objective response rate, RFS, OS	35
NCT02211131	resectable stage IIIB/IIIC/IVA melanoma	TVEC (intralesional)	overall response rate	150
NCT02303951	borderline or unresectable limited metastasis stage IIIC/IV melanoma	vemurafenib + cobimetinib + atezolizumab	conversion to resectability, objective response rate, PFS, OS	90
NCT02339324	resectable stage III melanoma	pembrolizumab + high-dose interferon alfa-2b	radiologic response, pathological response rate, PFS, OS	30
NCT02437279	palpable axillary or groin nodal stage IIIB melanoma	A: adjuvant ipilimumab + nivolumab. B: neoadjuvant plus adjuvant ipilimumab + nivolumab	RFS, T cell response assessment	20
NCT03259425	resectable stage IIIB/IIIC/IVA melanoma	nivolumab + HF10	pathological response rate, RFS, OS, completeness of surgical resection	7
Completed				
NCT00525031	resectable stage IIIC/IVA	temozolomide +/- pegylated interferon alfa-2b	clinical response rate (CR + PR + SD)	55
NCT00588341	resectable palpable stage III/IV melanoma	temozolomide	objective response rate (CR or PR)	24
NCT00972933	stage IIIB/IIIC melanoma	ipilimumab	unspecified	59
NCT01341158	stage IIIB/IIIC melanoma	interferon alfa-2b	overall response rate, disease control rate, pathological complete response rate	42
NCT01608594	resectable stage III melanoma	ipilimumab 3mg/kg or 10mg/kg + high-dose interferon alfa-2b	pathological response rate, radiologic preoperative response rate, PFS, OS	30
NCT01781026	untreated BRAFV600-mutated melanoma brain metastases	vemurafenib	radiologic response	2
NCT02306850	potentially resectable (currently unresectable) stage III/IV melanoma	pembrolizumab	resectability rate, response rate	10

RFS = relapse-free survival. PFS = progression-free survival. EFS = event-free survival. OS = overall survival. DMFS = distant metastasis-free survival. PR = partial response. CR = complete response. SD = stable disease. Note: Due to recent adoption of the AJCC eighth edition staging system, the stage classifications listed may refer to the seventh or eighth edition system. See individual trial listings for details.

A Fascinating (and Unexpected) Discovery:
A Potential Cancer Fighter in the Skin Microbiome



Richard Gallo, MD, PhD, is Distinguished Professor and founding chair of the Department of Dermatology at the University of California, San Diego. Dr. Gallo and his team recently discovered that a strain of common bacteria on the skin produces a chemical that can kill melanoma and several other types of cancer cells, while sparing healthy cells.

Mark Teich, editor of The Melanoma Letter *and scientific director of The Skin Cancer Foundation, interviewed Dr. Gallo about his discovery, the possibility of harnessing the chemical to prevent as well as treat melanoma, and the important role the skin microbiome plays in staving off infection and disease.*

Mark Teich: Can you share a bit of your background and tell us how you made your recent discovery as an unexpected offshoot of your usual research?

Richard Gallo, MD, PhD: I'm trained as an immunologist and biochemist, as well as a dermatologist. I mostly focus on the skin, studying the field of innate immunity. More than 20 years ago, we discovered that mammals produce antimicrobial peptides on the skin, key products that kill bacteria.

About 10 years ago, we started looking at beneficial products that the microbes of the skin can produce, and we have found many. But the studies were always designed to detect anti-inflammatory molecules or those that could kill bad bacteria. This discovery of an anti-neoplastic agent came out of that research.

We were looking at many different kinds of bacteria from human skin, and we found there was something with unique chemical properties that was produced by one isolate of the bacteria Staphylococcus epidermidis (S. epidermidis). We were not biased toward anticancer actions; we were looking at antibacterial action. But when we discovered what chemical was responsible for the activity of S. epidermidis, the chemical itself dictated that we ask the question, "Could this be an anticancer molecule as well?"

MT: What was the chemical?

RG: This isolate of S. epidermidis can produce a chemical compound called 6-N-hydroxyaminopurine (6-HAP), which appeared to exert a selective ability to inhibit the growth of some cancers. Not all S. epidermidis makes this. It's a very special strain with the genes that allow it to synthesize 6-HAP. Some people have it, but most do not.

When we looked at human skin bacterial genomic data with Julia Oh, our collaborator, we saw that about 20 percent of human patients have this strain of molecule with 6-HAP. This might mean that about one out of five patients could benefit — the lucky ones to be colonized by this particular strain.

MT: How exactly did you pinpoint 6-HAP, and how did you verify that it could work against cancer?

RG: When we first found there was biological activity in S. epidermidis, we collaborated with an excellent chemist, William Fenicle, who ultimately coauthored the paper with us. He helped us solve the structure of the molecule.

Once we solved its structure, we saw it had the potential to inhibit DNA synthesis. Then we tested it in a petri culture dish against both mouse and human cancer cells, and saw that by inhibiting DNA synthesis, it could stop the out-of-control growth of certain cancers.

But the real surprise to us was its selectivity: Lots of things can kill cells in a dish, but 6-HAP seemed to kill a number of tumor cells, without killing nontumor cells. It selectively killed transformed cells, those with a collection of mutations that no longer allow them to control their growth. But when 6-HAP was mixed with normal cells, it didn't kill them.

MT: What accounted for that?

RG: It's complicated. It turns out that the chemical itself could kill all cells, but the normal cells have an enzyme that deactivates it. The transformed cells, at least the ones we saw, lose that enzyme.

MT: It sounds like a normal immune function, where the immune system attacks diseased cells but not healthy cells.

RG: That's what it looks like, like a detoxification.

MT: What was the next step?

RG: We needed to test the chemical's overall toxicity, so we injected it at high concentrations into mice and found it did not affect the health of normal mice. It didn't appear to be toxic. In the next experiment, we injected a mouse melanoma into a mouse and let that grow, then injected it with 6-HAP, and we could show that it would shrink the tumor without making the mouse sick. The tumor didn't have the ability to detoxify the chemical like the normal cells in the rest of the body.

MT: How effective was 6-HAP at killing the melanoma cells?

RG: Well, using the chemical alone the way we did, injecting it alone, the tumor still grew, but I'd say it was something like 50 percent effective. Way up the road, one hopes that combining it with other treatments might greatly enhance those treatments.

But the next question, logically, was whether 6-HAP from bacteria that are simply growing on the skin, as opposed to the chemical being injected, could have an anticancer function. Since we had found it in a bacterium that naturally grows on the skin surface, it was not likely that we were testing its normal biological function by injecting it. We needed a strategy to test what it means if you have a bacterium on your skin that is making 6-HAP.

So, we did a controlled trial. We put the same number of bacteria on different groups of hairless mice, one group with S. epidermidis that could make 6-HAP and one with S. epidermidis that could not. We then exposed those mice to UV light, a carcinogen, for many weeks, causing the mice to make de novo tumors — newly derived skin cancers.

Every once in a while, we reapplied the bacteria to the groups of mice; since these were strains of human S. epidermidis that live on people, not mice, we had to keep repopulating them with the bacteria. At this stage, we were just testing these human strains in the animals. We tried to create a situation where we could accelerate tumor formation in the mice but set it up as if they were actually people with the kind of S. epidermidis that made or didn't make 6-HAP. There proved to be a very big difference in the two groups: Those mice with the right bacteria, which made 6-HAP, grew very few tumors, far fewer than those with the same kind of bacteria that did not make 6-HAP.

That's where we left it and what we reported on — the discovery of the bacterial strain with 6-HAP and its activity both in mouse cells and on human cancers in a lab dish, its innate activity in cells and its ability to be both therapeutic and potentially preventive, in an animal model.

MT: You mentioned that about 20 percent of patients might have this strain. Would there be a way to increase this percentage, somehow giving 6-HAP to more patients?

RG: It would be quite possible to do that. We are now testing a similar strategy, not against cancer but against inflammation and infection. We are putting a live strain of Staphylococcus hominis (S. hominis), with a beneficial gene profile, back on people, showing it can live there and have therapeutic effects.

But human studies of skin cancer patients will be very difficult to do. The first questions would be, if you happen to have the right type of bacteria living on your skin, do you have an advantage over those who don't? Are you more resistant to skin cancer? Is there an existing association in humans between 6-HAP and skin cancer prevention, predicting that it has a protective ability? The mouse model predicts that's the case.

There would be two ways of testing this. Unfortunately, considering the time course of tumors in a human population, doing the study prospectively would take 20 years. It would have to be a very, very long study involving many people. That's tough to do. Another kind of study would be to look backward at people who get a lot of skin cancers versus those who don't, and see if you find these bacteria more commonly in those who don't.

If it proved to be the case that 6-HAP has a protective ability in humans, I could envision one day developing a therapy with it, perhaps using it as a preventive probiotic. First, there

would have to be safety studies. It would be tough to find funding for it, because it would be very large, but we would love to partner with somebody to do it. With the right funding, we could go right to testing in humans today. It would be up to the FDA how to conduct such a study, but the best idea would be a series of increasingly larger studies, at first looking at smaller populations just to be sure it's safe, then, when you've established that it's safe, you would start testing bigger populations over longer periods of time.

MT: What form would the ultimate treatment take?

RG: You'd want a topical cream containing the right bacteria. You'd rub this in so the bacteria could live on the skin. You'd reapply it periodically, but eventually you might not even need reapplication — the preventive and therapeutic bacteria would just be living there.

MT: In other words, this medicine would literally be changing the patient's skin microbiome?

RG: Exactly.

MT: As you know, the other story in this issue of *The Melanoma Letter,* by Jennifer Wargo, MD, and colleagues, focuses on the gut microbiome and what role it might play in patients' response to melanoma therapy, specifically checkpoint blockade immunotherapy. Is there any congruence between the principles, approaches and goals behind gut microbiome research and your skin microbiome research on melanoma? How are they similar or different? Could one complement or interplay with the other?

RG: I certainly think so. The gut microbiome works on different organs and in different ways to help keep us healthy. Since the gut is the site of many ingested contents, including drugs, the idea that a gut microbe might help improve the way an orally administered drug works makes perfect sense.

With the skin, instead of examining feces, you can measure microbes right on the surface. And you can get to it much easier, just by applying a cream. It's much more accessible and tractable for therapy. We have found a large number of bacteria on the skin in addition to 6-HAP that are beneficial, that help us stay healthy in many specific ways. We're in clinical trials now that are showing great promise. We can develop drugs from microbes that live on the skin and deliver them directly through the skin. 6-HAP would be an example of that. Really, it would be just like treating people with microbes that live in the gut in humans, but with different means of drug delivery.

MT: Could the two be used in conjunction as a treatment?

RG: Why not? A multipronged approach would make a lot of sense.

MT: But could certain non-skin treatments reduce the supply of 6-HAP, interfering with the skin microbiome in a way that disrupts overall treatment effectiveness, just as certain treatments might disrupt the gut microbiome?

Are antimicrobial soaps sacrificing the variety of bacteria, losing certain good bacteria? Are we changing the skin microbiome for the worse?

RG: In the skin-care industry, there are ways of treating the skin to maximize good bacteria over bad, just as in the gut. You can potentially have different diets for the gut microbiome, and we know that having a variety of microbes in the gut confers an advantage, as opposed to uniformity of bacteria in the gut, which is a disadvantage.

This is the same with the skin. At first glance, you would think that the skin microbiome would be greatly at risk of losing good bacteria because of all the antimicrobial soaps we use. Are these soaps sacrificing the variety of bacteria, losing certain good bacteria? Are we changing the skin microbiome for the worse? However, we're learning that one of the main reasons we have millions of follicles on the skin is to hide all the good microbes. So, those good bacteria are not as exposed or at risk as much as you might think. They're remarkably resistant, but nonetheless, you want to treat them nice. So, many companies are now working on ways of optimizing cleansing, moisturizing and other regimens that will optimize good microbes.

MT: Isn't it often hard to know which bacteria are bad and which are good? How do you pick and choose which bacteria to leave and which to get rid of? And how do you isolate them from one another to deal with them differently?

RG: That's exactly what we're working on. We try to understand what's good and what's not so good. We've come to know a lot about pathogens on the skin, which cause disease, and we surely want to get rid of those. But we know far less about the benefits of other bacteria. We have to keep learning to be more selective in how to get rid of bad germs and pathogens, and to isolate and promote the more beneficial microbes. That's how we found 6-HAP.

MT: How far off do you think we are from being able to put 6-HAP to use?

RG: I think it would be feasible to do next-step experiments in the next few years. I would love to facilitate it, and we might look into it in the future.

But cancer is not my immediate focus. We're already in our third clinical trial testing applications of this same strategy with a different bacterium, but targeting other conditions, not cancer. Right now, my lab is focused on atopic dermatitis. We're having success, and the treatment is showing great promise. All of this is happening today, not tomorrow. ■

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From the Editors

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colleagues showed the benefits of fecal enemas in treating Clostridium difficile infection and pseudomembranous colitis. This marked the introduction of fecal microbiota transplants (FMT) into mainstream medicine.[1] Interest in harnessing the microbiome gathered speed after van Nood et al. published a randomized, controlled trial in *The New England Journal of Medicine* in 2013, confirming Eiseman et al.'s findings.[2] Ever since, appreciation of the entire microbiome's impact on health, disease and therapy has continually grown more intense and sophisticated.

In this issue of *The Melanoma Letter,* we bring you a pair of reports on two different realms of the human microbiome that may have a significant impact on melanoma treatment and prevention — the gut and the skin. Our lead story, by Drs. Thakur, McQuade and Wargo at the University of Texas MD Anderson Cancer Center, explores what we know to date about the gut microbiome's potential benefits in melanoma, especially in enhancing response to checkpoint blockade therapy. The authors touch on what key factors in this microbiome may affect treatment and how to modify those factors to enhance response. While FMT has already proven an effective microbiome modifier for conditions like inflammatory bowel disease, it has also produced very promising early data in melanoma. And now, investigators are also intensively studying how medications, diet and other lifestyle elements can modify the gut microbiome to boost therapy response.

In our companion piece, a Q&A interview with Richard Gallo, MD, PhD, of the University of California, San Diego, Dr. Gallo tells us the fascinating story of how he and his team almost inadvertently discovered that a strain of common bacteria on the skin (Staphylococcus epidermidis) produces a chemical that can kill melanoma and several other types of cancer cells, while sparing healthy cells. It turns out that about one in five humans have this strain on their skin. Dr. Gallo describes what strategies might be employed to harness it as a treatment — and how it might one day be incorporated in a topical *preventive* application that would literally alter patients' skin microbiome, making it more resistant to melanoma.

These stories make it abundantly clear that a long unappreciated symbiotic relationship exists between human health and certain bacteria, and that one day we might well be able to manipulate our microbiome to treat and even prevent melanoma and other diseases. ■

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The Melanoma Letter

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In This Issue...

Jennifer A. Wargo, MD

Our subject is the human microbiome — the microbes and their collective genomes that inhabit our bodies. In our lead story, Jennifer A. Wargo, MD, and colleagues present the latest research on the **gut microbiome**, the role it plays in patients' response to immunotherapy and the investigations underway to modify it as a potential tool for melanoma treatment and prevention.

Richard Gallo, MD, PhD

In a companion Q&A, Richard Gallo, MD, PhD, discusses his lab's exciting early work on the **skin microbiome**. Dr. Gallo tells the story of how his team discovered a novel strain of skin bacteria that appears to selectively kill melanoma and other cancer cells without harming healthy cells. Dr. Gallo envisions the possibility of one day colonizing such bacteria on human skin and thereby modifying the skin microbiome as a melanoma preventive.