Dispatches From the Microbial Frontier of Cancer Research

Hutch scientists explore how our immune system can team with our microbiome to fight cancer and other life-threatening diseases.

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As scientists catalog the microbial life living inside our gut, on our skin and in every nook and cranny of our body, disease researchers are hoping to use this collection of creatures — our microbiome — to find better ways to prevent, detect and treat cancer.

We talked with researchers at Seattle's Fred Hutchinson Cancer Center who are combining data science and extraordinary laboratory tools to find surprising connections between cancer, our immune system and the communities of microbes that inhabit us.

The projects below are just a sampling of the ways Fred Hutch scientists are exploring how our immune system can team with our microbiome to fight cancer and other life-threatening diseases.

An Environment That Nurtures Immune Cells

Transplant physician Dr. Kate Markey, a newly appointed assistant professor at Fred Hutch, has been studying how the gut microbiome interacts with the immune system, and in particular how that might affect the outcome of bone marrow and blood stem cell transplantation.

It is well-established that transplant patients who carry a wide variety of bacterial species in their guts tend to do better after transplant than those who harbor a more homogenous microbial environment. Markey is trying to find out why.

These more fortunate patients experience fewer relapses of their blood cancers and have a lower risk of infections and graft-vs.-host disease, or GVHD. The latter is a common complication of bone marrow transplantation where immune cells from a donor may sometimes attack — as foreign — healthy tissues in the cancer patient.

It can be debilitating and, in some instances, life-threatening to transplant recipients.

In her previous position at New York's Memorial Sloan Kettering Cancer Center, Markey and her

team carried out research suggesting the advantage those patients have may lie in a relationship between diverse gut microbes and certain types of circulating immune cells known to congregate in tissues lining the gastrointestinal tract.

Known as “unconventional” T cells, they patrol the mucus-rich territory that marks the boundary between the germy external world and the protected, internal environment of our bloodstream and the organs it serves. The human intestinal tract is ground zero for these interactions, a place where it is essential for our bodies to obtain nutrients from foods while maintaining a mucus barrier to block that teeming microbial life from making a meal out of the rest of us.

In May, Markey and her former colleagues published a paper in Science Translational Medicine that found a correlation between longer survival and fewer side effects in transplant patients and these patients’ ability to generate a healthy population of those unconventional, mucus-loving T cells.

“What we found was rather striking,” Markey said. “These immune cells are protective. We want to see them in our post-transplant patients. They seem to be linked to a good outcome. But when we study their gene expression, they look… super angry,” she said. In more technical terms, the unconventional T cells are highly activated, cranking out chemicals that the immune system uses to kill cells it identifies as threats.

“Are they wiping out cells that have been infected with bacteria? Are they killing cells that are even more highly activated — therefore dialing down an overly aggressive response? They’re among the many questions we’d like to sort out in my new lab here at Fred Hutch,” Markey said.

Significantly, the researchers found that the growth of those protective cells was fostered by the presence of a diverse microbiome, which through their collective metabolism produce just the kinds of nutrients and chemicals those unconventional immune cells need to thrive.

In the long run, Markey said she hopes a greater understanding of the microbiome will help scientists develop more direct ways to harness the immune system to fight cancer and make transplants safer. If the metabolites of gut bugs are the key signals needed to fine-tune our immune response, Markey would be happy to sidestep the bugs and provide the needed metabolites directly to patients.

“You have to have the right bacteria in the gut, and they’ve got to make the right kinds of metabolites. Then those metabolites have to get across the gut, pass through the liver and out in the body. It might be a better strategy to just administer the metabolites directly, and that’s what we’re doing in our mouse studies to try and understand exactly how the metabolites influence the post-transplant immune system,” she said.

Going Beyond Tissue-Typing for Safer Transplants

Dr. Albert Yeh is a Fred Hutch transplant physician-researcher who also would like to reduce the severity of GVHD. He studies what may trigger a transplanted immune system to sometimes

attack the healthy cells of the person it is meant to save.

He is a hematology-oncology fellow in the laboratory of Dr. Geoffrey Hill, who directs the Hematopoietic Stem Cell Transplantation program at Fred Hutch and holds the Jose Carreras/E. Donnell Thomas Endowed Chair for Cancer Research.

Tissue compatibility between donor and patient has been a critical feature of successful transplantation from its earliest days. Gene-based tissue-typing is the well-established way to match donor to recipient. If most or all of six key gene types in donor and recipient match well, the patient is less likely to reject transplanted organs or blood cells, and less likely to experience GVHD. This is why close relatives often make the best match.

At a presentation at the American Society of Hematology in December, Yeh explored the possibility that genetic compatibility alone may not fully explain the immune response leading to GVHD. He described a laboratory experiment that suggests the systemic inflammation of that disease might also be caused by donor immune cells' exposure to the new microbial environment of the recipient.

"Whereas you can control the donor and recipient genetics, it is really hard to control the microbiome," Yeh said. "So, I think one of the questions we have to ask is how different or similar do the microbiota have to be?

In addition to recognizing mismatched tissue types as "foreign" and worthy of attack, donated immune cells may often respond aggressively to other small proteins that are commonly displayed on the surfaces of the recipient's cells. These bits of protein, called minor antigens, are unrelated to the six major genetic compatibilities (or major antigens) required for bone marrow transplants. But they are known to cause GVHD even in patients receiving closely matched tissues.

Yeh's intriguing work is exploring whether bits of proteins from bacteria, viruses and fungi living in the gut of transplant patients may trigger GVHD when new immune cells from a donor respond to those gut microbes, just as if they were minor antigens.

In short, the search for compatible tissue types alone may not be sufficient to ward off GVHD. If that is the case, Yeh asks, "Are there certain bacteria that are more likely to trigger a minor-antigen-like reaction?"

The answers might be critical to reducing GVHD. Yeh said researchers have known for decades that the microbiome is important in transplant outcomes, and there have been clinical experiments to show that using antibiotics to suppress microbes in the gut can reduce levels of GVHD. However, this bludgeon-like approach comes with risk of side effects and development of antibiotic resistance.

Yeh's work, still very much in the early stages, is to use the modern tools of microbiome research to find out which microbiome-related proteins may be aggravating GVHD in individual patients — and how they are doing so. These tools include fast genomic screens to identify microbiome

components and advanced computational techniques such as machine learning to sort out which proteins of concern might drive an over-active inflammatory response.

He is also exploring whether the donor's microbiome might predispose the donated immune cells to respond aggressively after transplant to the microbial environment of the recipient.

This sort of fine-tuning — tailoring interventions to fit not only the genetics but also the microbial actors within patients and donors — is in keeping with trends seeking better outcomes through more precise, individually focused cancer therapies.

A Better Way to Trap Colorectal Cancer?

Fred Hutch physician-scientist Dr. Neelendu Dey has teamed up with computational biologist Dr. Sam Minot in a new approach using microbiome data to develop a better way to prevent colorectal cancer, the second most common cause of cancer deaths among both men and women in the U.S.

Today's colorectal cancer prevention strategies center around either colonoscopies — a video inspection for abnormal growths called polyps in the large intestine — or at-home stool-collection tests that look for signs of blood or gene markers linked to tumors. The stool screens are far less invasive and much more convenient than colonoscopies, but they miss about a quarter of active cancers and 60% of polyps.

"Those are decent numbers, but if you apply them across the populations, you are going to miss a lot of cancers," Dey said. "So, we want to capture some of those misses by looking at the microbiome for additional factors."

Rather than building a roster of specific gut bugs that are linked to colorectal cancer, the focus of the team's research is to spot common genetic traits that turn up within populations of bugs — regardless of species — found in the microbiomes of patients with colorectal cancer.

"We want to demonstrate the feasibility of looking for these genetic signatures in the microbiome, which may give us some insight into the cancer risk," Dey said.

In an abstract presented at the American Gastroenterological Association's annual conference in May, the Hutch team reported that they had found clusters of such genes in the microbial environments of hundreds of colorectal cancer patients. To generate their findings, the scientists analyzed data pooled from several older studies where all the genes of bugs inhabiting the gut of those patients had been sequenced.

Computational biologist Minot said that focusing on common genetic traits is a more nimble way than identifying species to wrangle important information about the microbiome. By using computers' vast powers to find patterns in data, he has developed techniques that can link diseases to clusters of important microbial genes rather than to specific bugs. He calls these clusters "co-abundant gene groups," or CAGS.

Minot looks for groupings of organisms that that share distinct sets of genes — CAGs with similar stretches of DNA or RNA — rather than for lists of microbes with shared Latin names.

“We can entirely throw out any sort of name or taxonomy,” he said. “It doesn’t matter if we’ve ever cultured this microbe in the lab before. It doesn’t matter if it’s a virus or a bacterium. None of those labels or preconceived notions are included in the analysis. We want to treat any microbes which contain this group of genes as a unit, as a biological entity, because we think those genes provide the biological function.”

The CAG approach is particularly well-suited to exploring whether diseases like colorectal cancer are triggered by groups of organisms, rather than by a single pathogen.

“It may not be that there is any one or a handful of microbes that are the bad actors. It could be that there is a number of different microbes that may increase the risk of cancer to some small degree, and when you combine them together, your risk is increased even further,” Minot said.

Minot’s computational approach is known in the field as an in silico analysis, because it involves only computers and their silicon chips rather than experiments in test tubes (in vitro) or in living creatures (in vivo). He pored over data generated from microbiome specimens received from colorectal cancer patients in prior studies and identified CAGs in numerous organisms, including in bugs thought to be benign or even beneficial.

Dey, Minot and Hutch gastroenterologist Dr. William Grady then tested whether bacteria combinations rich in cancer-linked CAGs could cause colorectal cancer in mice.

Minot reported at the conference that mice fed a diet containing such bacteria had “significantly greater tumor burden” than those given a diet with bugs that lacked cancer-rich CAGs.

“It was in vivo validation of our in silico predictions,” Minot said.

Which brings their work back to the development of diagnostic tests. Instead of searching only for traces of blood in a stool test — which may signal that colon cancer is well underway — his team hopes to design a next-generation test that would spot CAGs that have been linked to the disease. It could identify through microbiome analysis those people who are at higher risk for colorectal cancer, before the disease arises.

To probe for suspect CAGs, the test would likely analyze stool samples using PCR technology. That is the same, highly accurate gene-probing method used in laboratories to confirm COVID-19 infection in nasal swabs collected at drive-in test centers. Those COVID-19 tests work by detecting small, telltale gene sequences of SARS-CoV-2, the virus responsible for the pandemic.

Minot said that as a computational biologist, the work on a potentially more effective screen for colorectal cancer is meaningful. Much of his early work on the microbiome was purely data science, searching for ways to analyze the torrent of information generated by sequencing whole human genomes and identify thousands of microbial species. Now, he is working on ways to

transform that digital knowledge into tests that can help people.

“The next step was going to be translating biological models into the clinic. That’s really the reason I came to Fred Hutch in the first place,” he said.

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