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FRED HUTCHINSON CANCER RESEARCH CENTER
WINTER 2016

microbiome

EXPLORING THE WILDERNESS WITHIN

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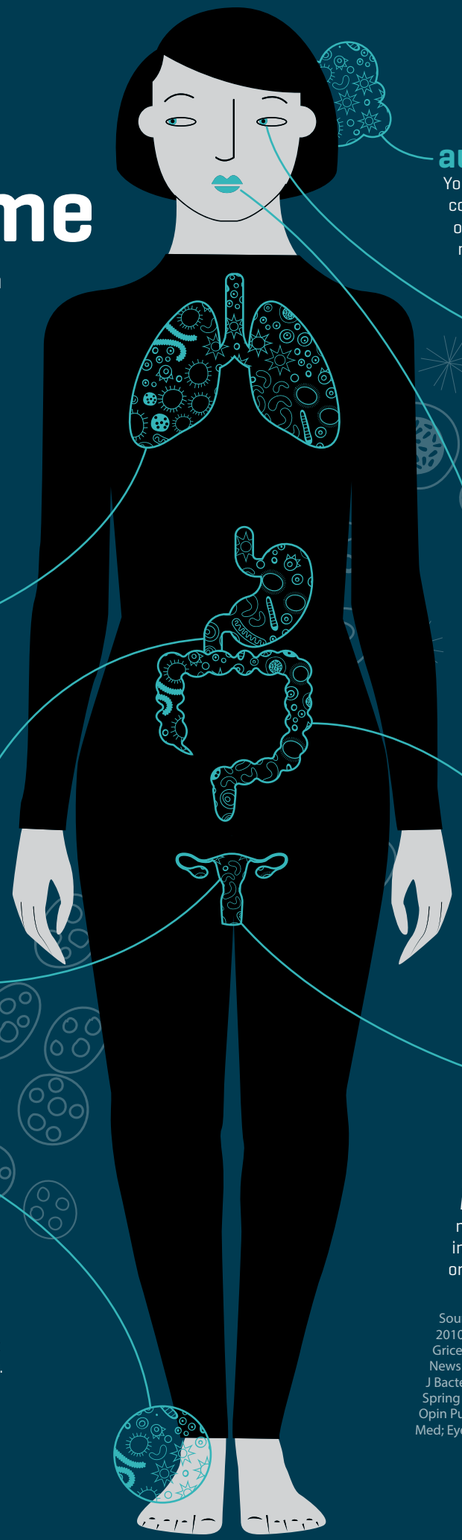
Cover design by Kim Carney

A BODY MAP OF THE HUMAN

microbiome

Each of us contains trillions of inhuman cells — the bacteria, viruses, fungi and other tiny creatures that make up the human microbiome. By the latest estimate, a full half of our cells are not our own. Here is a quick peek at the microbiome zones most closely studied in biomedical research.

REPORTING BY RACHEL TOMPA
DESIGN BY JIM WOOLACE
ILLUSTRATION BY KIM CARNEY



aura

Your microbiome is not technically contained to the edges of your body. Each of us exudes a cloud of microbes that might someday be used in forensics as a sort of bacterial fingerprint.

eye

Researchers are only beginning to scratch the surface of the eye microbiome. What is clear is that the surface of the eye — the cornea — houses different bacteria than the conjunctiva — the inner eyelids. And early research suggests that contact lenses can alter your ocular microbiome.

mouth

Much like the skin, the oral cavity is home to different niches colonized by their own subsets of bacterial species. Oral bacteria have been linked to both oral and dental diseases as well as systemic illnesses such as cardiovascular disease and stroke.

gut

The human intestine is home to a vast diversity of microbes, containing hundreds to more than 1,000 different bacterial species. Alterations in the gut microbiome can affect human health in myriad ways, from how people react to drugs to their susceptibility to infection to immune function — even changing the risk for certain cancers.

vagina

We generally think of diversity as beneficial in the human microbiome world. But the human vagina is an odd exception — a healthy vaginal microbiome is dominated by *Lactobacillus* bacteria, while the microbiome of women with the common infection known as bacterial vaginosis, or BV, is much more diverse.

lung

The sticky surfaces of the lung are host to a variety of lung microbes, harmless or even helpful organisms that live in the very region of the body designed to act as a barrier against harmful respiratory bacteria and viruses. Changes in the lung microbiome have been linked to COPD, asthma and cystic fibrosis.

stomach

The stomach's acidic contents make it a particularly harsh environs for most microbes to set up shop. But one bacterium thrives here: the ulcer- and stomach-cancer-causing *Helicobacter pylori*.

uterus & placenta

Until very recently, the uterus — and, during pregnancy, the placenta — was thought to be a sterile environment. But new studies have shown that both the uterus and placenta harbor their own microbiomes, which are distinct from the vaginal microbiome and which may play a role in supporting healthy pregnancies.

skin

Like a world unto itself, the skin contains different ecosystems that support their own unique microbial communities. You have an armpit microbiome that's different from your knee microbiome that's different from your nose microbiome that's different from — yes — the microbiome of your bellybutton. All told, the skin is as diverse as the gut, with 1,000 different species of microorganisms.

Sources: Sender et al. 2016 PLoS Biol; Gut: Qin et al. 2010 Nature; Aura: Meadow et al. 2015 PeerJ; Skin: Grice et al. 2009 Science; Vagina: Keown, Fred Hutch News Service, April 30, 2015; Mouth: Dewhirst et al. 2010 J Bacteriol; Uterus/placenta: Prince et al. 2015 Cold Spring Harb Perspect Med; Lung: Dy and Sethi 2016 Curr Opin Pulm Med and Dickson et al. 2013 Expert Rev Respir Med; Eye: Shin et al. 2016 mBio

FROM THE DIRECTOR

A new frontier that's changing how we think about our bodies and cancer

ONE OF THE BEST THINGS ABOUT BEING A SCIENTIST is knowing that new frontiers are always waiting to be discovered. And sometimes, explorations into unknown or poorly understood areas of human biology lead us to better treatments and cures for disease.

One of these exciting new frontiers is the human microbiome — the many different bacteria, fungi, viruses and more that inhabit our gut, skin, mouths, noses, lungs, and every other nook and cranny of our bodies. Latest estimates show that bacteria alone may make up a full half of our body's cells. In a very short span, a rapid rate of discovery has catapulted us from only a vague understanding of these microscopic ecosystems to detailed genetic catalogs of our microbial passengers — along with tantalizing hints about how our microbiomes affect our everyday health.

As you'll read in this issue of Hutch Magazine, there has been a recent surge in information from our researchers and their colleagues around the globe about how the human microbiome may influence cancer patients' response to antibiotics, chemotherapy and emerging immunotherapies; alter the efficacy of HIV vaccines; play a role in the potentially deadly graft-vs.-host disease in bone marrow transplant patients; and even change a person's risk of developing cancer.

All of these discoveries have implications for the treatments, preventions and cures being developed in our labs and clinics — and, of course, for patients.

Microbiome research is a cutting-edge, early-days field with as yet many more questions than answers. Luckily, this is exactly where Hutch researchers shine — thinking creatively about thorny problems, pulling together hints from all different directions to craft new solutions, deftly sifting through large and complex data sets, and collaborating across diverse disciplines.

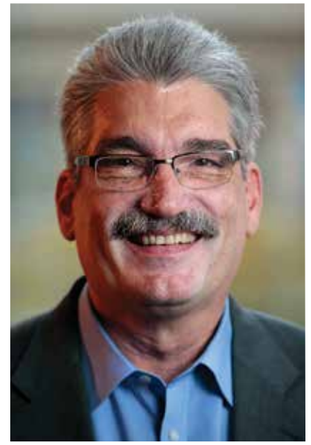
At Fred Hutch, we lead the world in expertise on cancer, infectious diseases and the complex role of the human immune system in disease. Because of our long history in these areas, we're uniquely positioned to better understand the intricate interplay between bacteria, cancer and our immune system to the ultimate benefit of patients with cancer and other diseases.

We have our fingers on the many delicate threads that connect our microbial partners to cancer and infectious disease. We are setting our sharpest minds and latest technologies to trace and understand those connections. I hope you'll be as inspired as I am when you read about the exciting research and discoveries being made about these universes within us.

As always, we are thankful for your continued support in these exciting endeavors.

Cures start here,

Dr. Gary Gilliland
President and Director



Dr. Gary Gilliland
Photo by Robert Hood / Fred Hutch

What science is discovering about the trillions of microscopic organisms that share your body

welcome TO THE MICROBIAL JUNGLE

BY SABIN RUSSELL | PHOTOS BY ROBERT HOOD | ILLUSTRATION BY KIM CARNEY

When Kimberly Loges rode the bus from her home in Seattle's Ballard neighborhood to the Prevention Center at Fred Hutchinson Cancer Research Center, the healthy study volunteer kept a tight grip on the large paper bag she carried. "No, it's not my lunch," she would say when asked.

Indeed. Inside that bag was a newly collected sample of stool, swirling in a liquid preservative. Also in the bag: a white, wide-mouth water bottle, sloshing with every drop of her urine from the past 24 hours. Four times over a half-year stretch she made the trip, delivering her specimens to researchers without incident.

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Write to Sabin Russell at srussell@fredhutch.org

kimberly loges Flax FX study participant Kimberly Loges in her office in Seattle's Ballard neighborhood.

In the name of science, sometimes decorum has to be set aside. And it helps to have a sense of humor. "It was awkward. It's an awkward subject," Loges said. "But the researchers made it easy. The only bizarre thing was delivery by bus." She and nearly 50 other brave souls were enrolled in Flax FX, a Fred Hutch dietary study. They are among the thousands of volunteers who have joined with scientists around the world to explore the usually unseen — and sometimes unmentionable — frontiers of the human microbiome.

The microbiome is the community of bacteria, viruses, fungi and other microorganisms that inhabit our gut, our mouths, our eyes, our sex organs and virtually every square inch of our skin. We each harbor a unique population of about 40 trillion microbes, which mostly set up camp in the first few years of our lives. The human colon alone houses as much as four pounds of gut bugs, a diversified microbial workforce that helps our body break down the food we ingest into fuel sources for colon cells, vitamins and biologically active compounds that may either promote or block cancers. They also appear to provide a chorus of chemical chatter that influences our immune system in ways that can help or harm us.

Researchers are also examining how the mix of microbial communities inside us may be tied to obesity, heart disease, mental health and how we respond to treatments for cancer. Mouse studies suggest that chemotherapy can be less effective against tumors if antibiotic treatments have destroyed or disrupted the balance of gut microbes. And microbial communities help regulate our immune system, which has important implications for new therapies that harness immune defenses to fight cancer. "We know the bacteria in our bodies, which we call the microbiome, actually impacts the way people respond to immunotherapies," said Dr. Phil Greenberg, an immunologist at Fred Hutch, during a recent American Association for Cancer Research conference in New York.

Not long ago, studies of the microbiome were a medical research sideshow, an obscure field that only aroused the curiosity of scientists unfazed by the subject matter. Yet new techniques began revealing the enormous diversity of the human microbiome and its role in health. Then came word of "fecal transplants" — restoring your unhealthy gut microbiome with someone else's — and the topic made headlines. For some patients, these transplants were an effective treatment for a potentially deadly bacterial infection. *Clostridium difficile*, or *C.diff*, strikes patients, often elderly or immunocompromised, who have had their microbiomes radically altered by courses of antibiotics. While a healthy gut microbiome has a broad mix of bacterial species, antibiotics can wipe out healthy bugs — leaving the field wide-open for bad actors. Fecal transplants may restore a more natural balance of bugs that keep *C. diff* under control.

Soon however, fecal transplant "spas" sprang up, making a host of unsupported claims. Now, a major industry has arisen touting products purporting to help consumers improve their own microbiome — drawing the attention of the U.S. Food and Drug Administration. Until more definitive studies emerge on so-called probiotics and microbial transplants, the best advice for consumers is the old watchword, "buyer beware" [See "Separating snake oil from certainty," Page 12].

Nevertheless, the microbiome beckons serious researchers, at Fred Hutch and across the country, with the allure of a newly discovered frontier. It is a medical wilderness now being scouted with every tool of modern science, from the humble cotton swab to the supercomputer. Someday, understanding our unique, individual microbiomes could be critical to developing more precise, personalized medicine — and nothing is more personal than your microbiome.

david fredricks
Fred Hutch microbiologist Dr. David Fredricks studies the role of the gut microbiome and the body's natural defense system.

microbiome and cancer treatment

Dr. David Fredricks and his colleagues in the Vaccine and Infectious Disease and Clinical Research divisions at Fred Hutch are exploring the interplay of the gut microbiome and the body's natural defense system, particularly in immunocompromised cancer patients who have received blood stem cell transplants. The immune system is designed to detect and destroy foreign microbes, yet gut microbes have evolved a peaceful coexistence with the immune cells that line the colon. That relationship is challenged in cancer patients.

Graft-vs.-host disease, or GVHD — in which transplanted blood stem cells from the donor attack the patient's healthy tissues — remains a serious and sometimes fatal complication in transplant patients treated for blood cancers. Fredricks and his colleagues are studying how a transplant patient's population of gut bugs, which can be dramatically disrupted by chemotherapy and antibiotics, may play a role in GVHD. The hope is

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that picking apart these interactions will help Fredricks' team "come up with novel ways of treating it through manipulation of the microbiota," he said.

Information about the microbiome may also help doctors manage the risk of infectious diseases in patients after cancer therapy or a transplant. "We might be able to generate, in real time, information that would tell us we are seeing a bloom of a species, such as *C. diff*, and that we should tweak their antibiotics or alter their microbiota to reduce infectious complic ations," Fredricks said.

Fredricks began exploring the microbiome at Stanford in the 1990s and developed genomic tools that have since helped his own microbe-detection research at Fred Hutch, where he has worked since 2001. With grants from the National Institutes of Health and its Human Microbiome Project, he carried out some of the first comprehensive studies of the microbial populations that cause bacterial vaginosis, or BV, which affects nearly one in three women in the United States. Unpleasant and embarrassing, BV is also associated with preterm birth, pelvic inflammatory disease and elevated risk of sexually transmitted infections, including HIV.

Microbiome research has shown that the more diverse a microbial community, the healthier it is for the host. But Fredricks' work has revealed that women with BV have a strikingly different and more complex vaginal microbiome than women without it, and further research may reveal why. That could lead to treatments that tip the balance in favor of healthy bacteria, and relief for millions of women.

liz wagner Seattle digital products manager Liz Wagner voluteered for the Flax FX study in hopes of helping others. As a part of the study, she was assigned to take a daily pill — either flaxseed or placebo — for 60 days

in hopes of helping others

Among the longest-running microbiome research projects at Fred Hutch are dietary studies that take a close look at the chemicals released when different communities of microbes break down foods in the gut. Some of these reactions can turn healthy foods into carcinogens. Others metabolize byproducts thought to have anti-cancer and anti-inflammatory properties.

Dr. Johanna Lampe of Fred Hutch's Public Health Sciences Division has led the ongoing Flax FX study for three years. "A key issue is how critical the microbiome is in developing and maintaining a healthy immune system," she said. As a nutritionist, Lampe has spent her career studying the role of diet in preventing or promoting disease. Her current work on the microbiome is a natural progression from earlier studies that explored the benefits of diets rich in lignans, substances that are abundant in flaxseed. Lignan byproducts may include enterolactone, a compound thought to inhibit development of cancer.

"What we find when we give everybody a dose of the same flaxseed lignan extract is that some people produce tons of enterolactone, and others produce hardly any," Lampe said. There is good reason to think that those differences may have more to do with our microbiomes than our own genes.

The full set of human genes varies from that of chimpanzees by only about 4 percent, but the microbial mix within a human gut microbiome may differ by two-thirds from one person to the next. Those diverse legions of bugs in the colon ferment the fibers and other organic substances that can't be broken down by enzymes in the stomach and small intestine. As such, they are also consumers of the food we digest, and they may have the means to signal what they prefer to eat. "When you eat a meal," said Lampe, "You are not just eating for one."

Liz Wagner, a Seattle digital products manager for a large coffee company, volunteered for the Hutch's Flax FX study in hopes of helping others. Just like Loges, she and other participants were assigned to either a daily flaxseed preparation or an identical-looking sugar pill — a placebo — to be taken for 60 days. She was not told which one she was assigned. Wagner collected and delivered her own urine and stool specimens, and had blood drawn at the lab. After a pause of several months, the 60-day process was repeated. Whether she was assigned flaxseed or placebo in the first round, she received the opposite pill in the second.

At the end of each two-month stint of pill-taking, the volunteers also endured a colorectal biopsy — a few bits of tissue smaller than a rice grain were removed in what might be described as a short version of a colonoscopy. Why go through all that? For Wagner, it's personal. Her mother had colon cancer and died three years ago. "Compared to what my mom went through for 10 years, I can put up with a little discomfort," she said.

Lampe and her Fred Hutch colleagues are just now analyzing the information collected over three years from the flaxseed study. Sophisticated tests of the biopsy samples will show which genes inside each participant's gut tissues are turned on or off when flaxseed is in the dietary mix. Patterns of such gene expression can show whether those cells are behaving in ways that lower colorectal cancer risk. Those genetic results will be matched to the variety of gut bugs in each participant.

Breakthrough technologies such as gene sequencing,

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microbiome factoids

An estimated **800** different bacterial species inhabit the human gut.

Newborns are first exposed to microbial communities on their skin as they pass down the birth canal. It takes about **21 days** for a newborn to begin developing a personalized microbiome; up to **two years** for their own unique microbiome to become established in the gut.

The human genome differs from that of the chimpanzee by only **four percent**. One person's microbiome may differ from another's by about **60 percent.**

Don't fear the beard. The internet is periodically plagued with rumors that facial hair is a nest of nasty germs. Quite to the contrary, a 2014 study of 408 male hospital workers, published in the Journal of Hospital Infection, found bacterial colonization rates were roughly the same among those with beards and the clean-shaven — and bearded men were less likely to be harboring the most dangerous bacteria such as MRSA.

For years, scientists accepted that the average human adult microbiome harbored **100 trillion cells**, outnumbering human cells by 10:1. But researchers taking a closer look have recently challenged those numbers. New estimates are that number of human cells and microbial cells is roughly the same, about **40 trillion.**

which revealed the vast complexity of microbial life in the human gut, are now helping us understand why healthy foods might work for one person but might not for someone else. As Lampe pointed out, "It's the microbes that are producing the compounds that are beneficial or detrimental."

unlocking clues to stomach cancer

Dr. Nina Salama, a Fred Hutch Human Biology Division researcher and holder of the Dr. Penny E. Petersen Memorial Chair of Lymphoma Research, has been exploring the microbiome for more than 15 years with a singular focus: *Helicobacter pylori*. It is a bug that thrives in the acidic environment of the human stomach and is implicated in stomach cancer, the world's third leading cause of cancer death.

However, with half the world's population infected with *H. pylori*, only a fraction are diagnosed with stomach cancer. Salama and her Hutch colleagues are asking whether the cancer-causing mechanics of this bug are tied up in complex interactions with other microbes and the enzymes and tissues of their human hosts. "We have to be less 'one-bug-centric,'" she said.

Salama attributes the surge in interest in the microbiome to the arrival of new tools that finally made it possible to identify hordes of bacteria by their genetic fingerprints. Scientists learned to zero in on an ancient gene common to almost all bacteria. Embedded within that gene is a strip of DNA that is different for every species and can be read almost like a barcode. What a difference that made: Previously, scientists would not try to catalog a microbiome because it took months to isolate, grow and identify a single species. Now, a gene-sequencing machine could run a barcode census of entire communities of bacteria, spotting every species in a matter of days, with no need to isolate or grow any of them.

Refined during the 1990s at universities such as Stanford, where Salama received her postdoctoral training, this 16S rRNA sequencing — the name refers to that ancient gene — revolutionized the field. Like a microscope that suddenly throws an invisible world of tiny, living creatures into focus, these genomic tools cracked open the microbiome.

Since those early days, the resolution of these genomic microscopes has substantially improved. So-called "next generation" gene sequencers — blindingly fast and highly automated — are bringing greater precision to microbiome analysis. The technology allows researchers to identify not only bacterial species but specific strains. "I work on *H. pylori*, and we know that not all strains are created equal," Salama said.

With this better tool, she is researching *H. pylori* strains that pose an even higher risk of stomach cancer. These strains, which carry a suspect gene, are more prevalent in some East Asian populations that have more gastric cancers than others. "The association is clear, but nobody has come up with a causal mechanism to explain it," said Salama. So, one discovery leads to another puzzle, the process that drives science at the leading edge.

the brain and the microbiome

Dr. Meredith Hullar is a microbial ecologist at Fred Hutch who got her start at Harvard studying the complex metabolism of microorganisms in the sea. She collaborates closely with Lampe on dietary research and the role of microbial metabolism in human health. Hullar is a fan of large studies that bring together huge amounts of disparate data, searching for patterns. One such project she and Lampe are involved in is the Multi-Ethnic Cohort study, which is comparing the microbiome profiles of 6,000 men and women from five different ethnic groups in Hawaii and California. It's a massive undertaking, sequencing microbial genes from 7,200 stool samples and matching data from questionnaires, medical exams and whole-genome screens that can spot gene variants in each participant. The goal is to link the makeup and function of the gut microbiome to risks of obesity and cancer.

But the study is also exploring the connection between gut bugs, the brain and behavior. While signals from the gut to the brain help determine whether a person "feels full" after a meal, certain gut bacteria may alter that communication, influencing behavior linked to weight gain. "Understanding how the gut microbiome influences the brain's regulation of body fat may add to our understanding of how to prevent and control obesity, which is linked to increased risk of certain cancers," said Hullar.

drs. meredith hullar & johanna lampe Hullar and Lampe are working to understand the mechanisms by which components of diet, particularly constituents of plant foods, alter risk factors for cancer.

To probe this gut-brain link, brain-imaging scans, including MRIs, are being offered to 100 women participants in Hawaii, who also fill out standardized behavioral surveys. These scans will add data on brain chemistry and structure to the other health information already gathered. It is a breathtaking illustration of how sophisticated microbiome research has become. A project that began with stool samples now has high-speed computers crunching big data from genomic screens, proton spectrographs and MRI readouts.

new chapter of exploration

When the microbiome is taken into account, it changes how we think of the human body. In the more traditional model, a human being is like a machine with important moving parts: Think heart, lungs, brain, liver, intestines. When trillions of microorganisms are added to the picture, the model morphs into an ecosystem, chock-full of complicated interactions, cycles and interdependent relationships — not just among organs but among different species. It becomes a little harder to determine what actually makes us human: the cells that define our bodies, or the relationships our own cells forge with their surrounding environment. In this ecological model, our health is intertwined with that of the microbial world that surrounds us.

Early interest in the human microbiome, in fact, was driven by research from microbial ecologists who study the community of bugs that inhabit soils, oceans, decaying matter on forest floors, and even extreme environments like volcanic hot springs. It is a field that keeps the big picture in mind.

To date, the exploration of the human microbiome is a story of hints. Finding associations between obesity and the microbiome are not the same as finding cause and effect. The field is still young, and its findings, while often intriguing, will have to stand up to the scrutiny that comes with volumes of studies, large surveys and replication of results. These hints, however, are firing the imagination of researchers who scour for every possible edge against cancer and other deadly diseases. At Fred Hutch, the microbiome has come into focus, and a new chapter of exploration has begun. •

To read more about Fred Hutch's latest research and stories, go to ***fredhutch.org/news.***

Write to Bill Briggs at bbriggs@fredhutch.org

SEPARATING snake oil FROM CERTAINTY

Early understanding of the microbiome provides ripe space for scientists — and marketers

BY BILL BRIGGS | ILLUSTRATION BY BREANNA WELSH

SOME OF THE TINIEST LIFE FORMS are generating some of the biggest hype. Our microbiomes — ecological communities of bacteria and fellow microbes residing within us — are fertile ground for shaky medical claims and shady websites vowing to cure everything from anxiety to autism.

Hucksters hoping to profit from the legitimate excitement springing from this Lilliputian landscape are increasingly drawing criticism from scientists working to crack the microbiome's tantalizing promise. Some researchers use a Twitter hashtag to call out such quackery: #microbiomania.

"The science here has enormous potential and I do not want that potential to be damaged by the BS and the hype," said Dr. Jonathan Eisen, an evolutionary biologist at the University of California, Davis. He uses his science blog, "The Tree of Life," to pick apart what he sees as microbiome lies or misconceptions.

"The microbiome is ripe for snake oil because it is so complex and thus easy to lie about and oversell," Eisen said.

Let's put some common microbiome claims under the microscope.

If you consume probiotics like yogurts, which contain billions of friendly bacteria per serving, you will substantially change the microbial community in your colon.

"This is not true," said Fred Hutch's Dr. David Fredricks, who studies patterns of gut bugs in cancer patients who have blood stem cell transplants. "Indeed, the probiotic strains of bacteria tend to be minority species. The normal inhabitants still dominate."

A container of yogurt typically has a few billion helpful bacteria. But a healthy human gut is home to tens of trillions of bacteria and other microbes.

That means yogurt makers cannot legally say eating their products will regulate digestion. In 2010, Dannon ran afoul of the Federal Trade Commission for a series of ads featuring actress Jamie Lee Curtis claiming one daily serving of Activia probiotic yogurt relieves irregularity. In an agreement reached with the FTC, Dannon agreed to pay a $21 million fine and to stop making that assertion.

Changing your microbiome will curb depression, cut anxiety and boost your mood.

The theory is called the "gut-brain connection" — the idea that bacteria in your digestive tract may have some influence on your thoughts and feelings. A 2013 study led by researchers at the California Institute of Technology found that when mice with autism-like symptoms were fed a common bug called *Bacteroides fragilis*, it changed their microbiome and appeared to make them less anxious.

While this and other preclinical studies have provided "very good data" on an apparent microbial link between belly and brain, science still lacks clinical proof tying the microbiome to mental conditions, said Dr. Ted Dinan, a psychiatrist and microbiome researcher in Ireland.

"Many large-scale, spurious claims are [nonetheless] being made" about the health benefits of swapping out your gut bugs, Dinan told the FiveThirtyEight blog. For example, a psychology magazine recently published six steps to balance your intestinal bugs in order to balance your moods. One of their suggested steps: "Eat probiotic foods."

Roll in dirt, eat food dropped on the floor and warmly welcome microbes into your body because they make you healthier.

Welcome to the "hygiene hypothesis," which poses that exposing kids to germs early will prevent asthma later. In 2015, a New York City geneticist told journalists, "I would advise any new parent to roll their child on the floor of the New York subway."

"This is part of microbiomania where people somehow have forgotten about infectious disease and how, not only did it kill billions, it still is one of the biggest killers on the planet," said Eisen.

"No, rolling around in dirt or licking the floor or your toilet is not a good idea," he said. "Yes, increasing microbial exposure on average can be beneficial."

And when it comes to scrubbing away germs, the FDA says there's no evidence that antibacterial soaps stave off illness any better than plain ol' soap and water.

Fecal transplants cure Parkinson's disease, multiple sclerosis and autism.

For some patients whose bodies harbor the potentially lethal bacteria *Clostridium difficile*, transplanting donated poop from a healthy person via colonoscopy may restore the natural balance of bugs that restrain *C. diff*. For now, that's the most definitive statement scientists can make on the procedure.

But a handful of physicians are stretching that truth. At a national medical conference in 2012, a well-known gastroenterologist said "even more exciting is the use of fecal transplantation for a wide range of diseases [including] Parkinson's disease, multiple sclerosis [and] autism."

Citing that same doctor, an alternative-medicine website now proclaims that fecal transplants have "been proven to be a highly effective treatment" for patients with Parkinson's disease, clinical depression, and multiple sclerosis. The website shows readers how to do DIY fecal transplants by liquefying donated feces with a kitchen blender, pulling the poop into a rectal syringe, emptying the syringe into the rectum and advising readers to keep "the liquefied feces inside your colon for at least 2 hours or longer" to be cured.

The website caught Eisen's critical eye. He called it "snake oil" and said such unscientific claims are "dangerous," adding that real risks come from "dishing out false hope."•

Write to Sabin Russell at srussell@fredhutch.org

new things

A SAMPLE OF KEY SCIENTIFIC DISCOVERIES ABOUT THE BUGS INSIDE YOU

BY SABIN RUSSELL

THE HUMAN MICROBIOME had been largely uncharted until the last decade, when high-speed gene sequencing machines cracked it open for study and researchers began pouring into the field. In the past few years alone, the number of studies published in academic journals on microbiome research has soared. To highlight the breadth and excitement of new discoveries about the human microbiome, here is a snapshot of just five recent surprising and important findings that may affect your health.

Gut bugs may affect how vaccines work

When a once-promising HIV vaccine failed completely in a global trial three years ago, scientists wanted to know why. Last year came a revelation: It may have been interference from common bacteria in the human gut. Duke Medicine researchers, with help from Fred Hutch scientists, found the candidate vaccine essentially stirred up the wrong antibodies — showing for the first time that gut bacteria can modify an immune response to a vaccine.

Antibodies are proteins that our immune system generates to target features on the surface of invading microbes. But instead of producing new antibodies against HIV, this experimental vaccine awakened old antibodies formed against gut bacteria acquired during early childhood.

Dr. Jim Kublin of Fred Hutch's Vaccine and Infectious Disease Division helped oversee the HIV vaccine trial, and this fall was awarded a five-year, $4 million grant from the National Institute of Allergy and Infectious Diseases to study exactly how gut microbes can alter immune responses. The study could not only lead to a better HIV vaccine, it could show how the immune response to gut bacteria might be tapped to build more effective vaccines of all kinds.

Gut bacteria could make immunotherapy more effective

A pair of mouse studies, conducted continents apart, has shown that specific kinds of gut bacteria can directly affect the immune system's response against cancer. A University of Chicago study found that mice with the common gut bacterium *Bifidobacterium* had better anti-tumor activity against melanoma than mice without it. Significantly, an immunotherapy drug known as a checkpoint inhibitor — the same treatment credited with saving former President Jimmy Carter's life — worked better in the mice with *Bifidobacterium*. A French study of a different checkpoint inhibitor found that the drug failed against melanoma in "germ free" mice, but the anti-cancer properties of the drug were restored when the mice were fed *Bacteroides fragilis*. Checkpoint inhibitor therapy works for some patients, not for others. Both studies suggest that changes in a patient's microbiome might improve the efficacy of immunotherapy.

Sources: Williams et al, Science, July 30, 2015; Science, Verizou et al. and Sivan et al, Nov 27 2015; Nature.com Scientific Reports, June 21, 2016; Clinical and Translational Gastroenterology (2015) Parekh, et al.; Vatanen, Cell, May 5, 2016;

Source for graph: Ann Marie Clark / Fred Hutch research using Web of Science yearly microbiome citations data

Microbes in breast fluid may play a role in breast cancer

A study by the Providence Saint John's Health Center in Santa Monica, California, found that women with a history of breast cancer had a distinctly different community of microbes in their breast ducts compared to healthy controls. Until recently, it was assumed that breast tissue, nipple aspirate fluid and milk were sterile. Studies are underway to find out if the bacteria found in breast fluid could promote or inhibit DNA damage that can turn cells cancerous.

The wrong balance of gut bugs could trigger gut illnesses

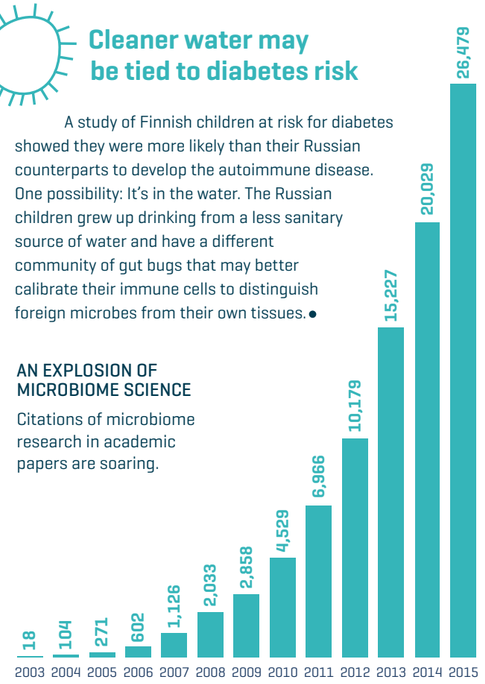
Disruptions to the balance of microbial species in the human gut have been associated with several gastrointestinal diseases, including inflammatory bowel disease, irritable bowel syndrome, nonalcoholic fatty liver disease and bowel cancers.

Cleaner water may be tied to diabetes risk

A study of Finnish children at risk for diabetes showed they were more likely than their Russian counterparts to develop the autoimmune disease. One possibility: It's in the water. The Russian children grew up drinking from a less sanitary source of water and have a different community of gut bugs that may better calibrate their immune cells to distinguish foreign microbes from their own tissues. ●

AN EXPLOSION OF MICROBIOME SCIENCE

Citations of microbiome research in academic papers are soaring.



Write to Diane Mapes at dmapes@fredhutch.org

MAKING A DIFFERENCE

Healing by the numbers

Meet Hutch donor and numbers guy Shubang Gan

BY DIANE MAPES

Shubang Gan at the Fred Hutch Visitor Center. *Photo by Robert Hood / Fred Hutch*

FORTY. That's how old Shubang Gan, a now-retired aerodynamics engineer was when he immigrated to the U.S. from Shanghai to attend Princeton. 2004. That's the year he was diagnosed with a rare cancer known as NK T-cell lymphoma.

Seventeen, he said, is the number of days it took for new bone marrow to start growing after his doctors knocked out his immune system with chemo and radiation therapy, and then performed a blood stem cell transplant to eradicate the cancer.

Two thousand. That's how many calories a day of "really bad" hospital food Gan had to consume before his doctors would let him go home ("The waffle was thick like a brick!" he recalled).

It took one year for Gan to fully recover from his transplant and boldly quit his job in order to pursue a passion project that would provide "something meaningful for the human race." His quest led him to Alaska, the 49th state of the union, which was seeking innovative, sustainable energy solutions.

Three. That's the number of blades on a wind turbine, which Gan knew would be a better energy source for the remote reaches of Alaska than trucked-in diesel fuel, which typically freezes at 10 to 15 degrees Fahrenheit. Alaska's limited roads and rail lines, however, made transporting the huge turbine blades a problem. Tapping his aerodynamics expertise and his manufacturing savvy, Gan designed and shepherded the production and shipment (via container ship across the Pacific, then barge to Alaska) of dozens of 70-foot-long, 600-pound fiberglass blades. Wind turbines now provide electricity in 28 small Alaskan villages 365 days a year.

Four is how many items, including the wind project, Gan has now checked off his post-diagnosis "bucket list." Seeing the 48-mile-long Panama Canal was another; ditto for participating in a Fred Hutch fundraiser. Still active at 69, Gan was one of more than 1,200 supporters who climbed 832 steps to the top of the Space Needle as part of Base 2 Space on Oct. 2. The event raised more than $430,000. It took the Bothell, Washington, resident 14 minutes to make the climb, he said, which he did while wearing a pair of glasses — printed on his 3-D printer — in the shape of the number 5,005. That's how many days he'd been alive since his transplant, he says proudly.

Gan recently commemorated both his survivorship and the "wonderful" team that cared for him during his cancer treatment with a 12-inch by 24-inch slate on Fred Hutch campus engraved with Chinese characters expressing his deep appreciation. "It's a very Chinese tradition to send something to the doctor or physician to show thanks," he said. "Every doctor and every nurse was so kind."

How many people helped him get to this point? Too many to count, he said, with a laugh. •

Solid support: Commemorative bricks and slates

Purchasing an engraved brick or slate is a powerful way to honor a person or occasion that's important to you while supporting Hutch research. Inspired by Shubang Gan's love of numbers, here are eight points of interest about our Brick and Slate Program:

3,138
engraved bricks and slates in Mundie Courtyard on the Hutch campus in Seattle

885
celebrate a cancer-free milestone

201
thank a bone marrow donor

124
thank a doctor or nurse

48
honor BMT pioneer Dr. E. Donnall Thomas

$1,500
helps the Hutch when you buy an engraved half slate with a five-line message

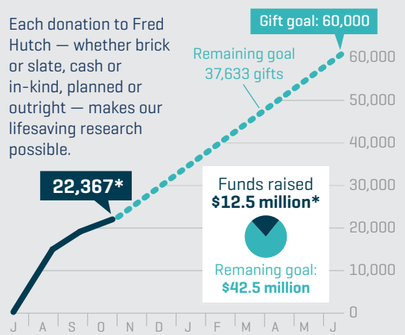
$250
secures your 4-inch by 12-inch brick with one line of engraved text

100+
bricks and slates installed each year

For more information, please visit ***fredhutch.org/bricks***

The power of every gift

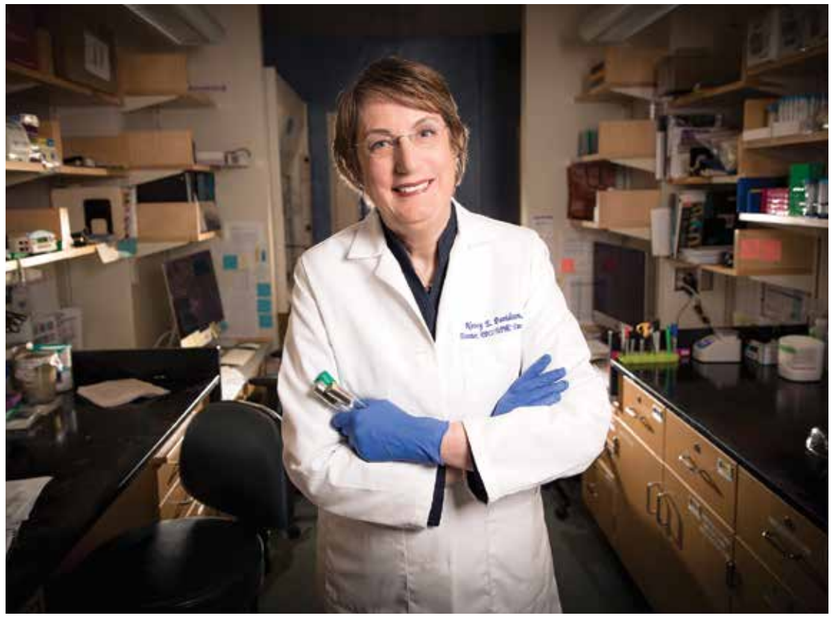
Each donation to Fred Hutch — whether brick or slate, cash or in-kind, planned or outright — makes our lifesaving research possible.



*Individual gifts as of Oct. 31, 2016

LEADERSHIP

Fred Hutch recruits world-renowned oncologist for key leadership role



Dr. Nancy Davidson will begin her role as director of Fred Hutch's Clinical Research Division and president and executive director of Seattle Cancer Care Alliance on Dec. 1. *Photo courtesy of Emily Cousins*

A GIANT IN THE CANCER RESEARCH and treatment world is bringing her talents to Seattle.

Dr. Nancy E. Davidson, director of the University of Pittsburgh Cancer Institute, will become the director of Fred Hutch's Clinical Research Division and the president and executive director of Seattle Cancer Care Alliance (SCCA), Fred Hutch's clinical care partner. Her appointment is effective Dec. 1.

Davidson will serve as a bridge builder across the cancer treatment, clinical, translational, basic sciences and public health research programs of consortium members Fred Hutch, UW School of Medicine, UW School of Public Health, Seattle Children's and SCCA.

Davidson is a world-renowned physician-scientist in cancer biology and treatment, especially in the field of breast cancer. Prior to joining the Pitt faculty, she served as the Breast Cancer Research Professor of Oncology and the founding director of the Breast Cancer Program at Johns Hopkins. She is a member of the scientific advisory boards for many foundations and cancer centers. A member of the National Academy of Medicine, she is a past president of the American Society of Clinical Oncology and current president of the American Association for Cancer Research.

Davidson "is ideally suited to further enrich the already outstanding interactions between the SCCA, UW Medicine and Fred Hutch. I am eagerly looking forward to working with her," said Dr. Gary Gilliland, president and director of Fred Hutch and director of the NCI-designated Fred Hutch/University of Washington Cancer Consortium.

IMMUNOTHERAPY

Remissions after experimental immunotherapy

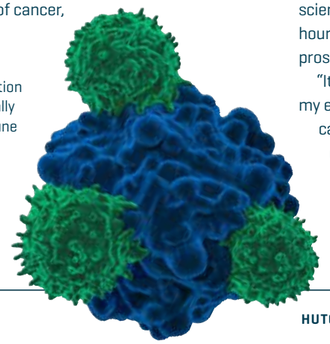
MANY PATIENTS WITH NON-HODGKIN LYMPHOMA participating in an early-phase immunotherapy trial had their advanced tumors disappear completely after their immune cells were genetically engineered into cancer fighters, a new study led by Fred Hutch scientists found.

These short-term results are the latest from this closely watched study of these modified cells, called CAR T cells.

In the trial, 32 participants received an infusion of CAR T cells following chemotherapy, called lymphodepletion, which was given to make space in the body for the infused engineered cells. The team found that the CAR T cells most effectively knocked out the cancer in a group of 11 patients who received a two-drug combination chemo followed by an intermediate dose of the engineered T cells.

Seven of these participants, or 64 percent, went into complete remission — "which is very high" given the advanced stage of these patients' cancers, said Dr. Cameron Turtle, one of the study leaders.

These data demonstrate how dialing in the treatment parameters can make these cells more effective cancer fighters in patients with this particular type of cancer, Turtle said.



Graphical illustration showing genetically engineered immune cells attacking a cancer cell.

CLINICAL TRIALS

'Incredibly ambitious' trial in a deadly cancer

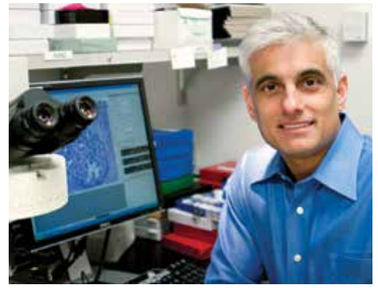
A RADICAL NEW RESEARCH EFFORT was launched this fall for one of the deadliest cancers. Called Precision Promise, the flexible, precision-medicine trial of experimental pancreatic cancer treatments aims to turn the concept of clinical trials on its head.

"This is driven by doing what is best for the individual patient, and that is the most important thing," said Dr. Sunil Hingorani, a Fred Hutch pancreatic cancer expert and principal investigator for one of the effort's initial research sites.

Precision Promise creates a fluid structure through which participants can transition in and out of numerous substudies of various experimental treatment approaches, depending on their cancer's unique and shifting biology. This design prevents patients from having to seek out and enroll in a new trial if one particular option does not seem to be working.

"We believe that you can both learn, in a deep way, about the strategy you're applying and actually maximally benefit that patient at the same time," Hingorani said. This approach is exactly what this deadly malignancy needs, he said.

"On one hand, it's incredibly ambitious," he said, "and on the other hand it's exactly where we need to be to treat this cancer."



Dr. Sunil Hingorani is a pancreatic cancer researcher at Fred Hutch. *Photo by Stefanie Felix*

CAMPUS LIFE

Seattle Mariners GM, broadcaster visit Fred Hutch

BASEBALL BROUGHT THEM TOGETHER. Cancer brought them closer.

Seattle Mariners General Manager Jerry Dipoto and play-by-play broadcaster Dave Sims never knew the similarities linking their stories: two baseball guys with the same team, both knowing the chill of a cancer diagnosis and loss of an organ — and both leaning on the game to survive.

In September, Dipoto, a thyroid cancer survivor, and Sims, a prostate cancer survivor, visited Fred Hutch to learn about the science driving promising cancer therapies..

The men viewed the Cincinnati Reds jersey and baseball mitt once used by Fred Hutchinson himself. They marveled at the wall of baseball cards celebrating past Hutch Award winners. They read personal accounts of people cured by Hutch science at the Visitor Center. And they spent an hour in the lab of Dr. Pete Nelson, a Fred Hutch prostate cancer researcher.

"It has dawned on me that when I share my experiences now with other people [about cancer treatment], maybe it's more about the emotional than the physical," Dipoto said. "Because the physical has changed so much over the years thanks to what people do at places like Fred Hutch."

Mariners General Manager Jerry Dipoto, looking through the microscope, and broadcaster Dave Sims behind him, visit the lab of Fred Hutch's Dr. Pete Nelson, in blue, September 2016. *Photo by Robert Hood / Fred Hutch*

Write to Susan Keown at skeown@fredhutch.org

OFF CAMPUS

Dr. Marie Bleakley

12 questions about life outside the lab for the Fred Hutch pediatric immunotherapy and transplantation researcher

BY SUSAN KEOWN

Dr. Bleakley with her dog, Gypsy. *Photo by Robert Hood / Fred Hutch*

DR. MARIE BLEAKLEY followed her grandfather into medicine. A native Australian, she came to the U.S., and Fred Hutch, in 2002 for a fellowship in pediatric hematology-oncology. Through her research on blood stem cell transplant and targeted immune therapies, Bleakley aims to improve survival and reduce treatment side effects in patients, especially children, who have high-risk leukemia. Recently, she sat down to talk about:

Your grandfather?
He was a family physician in the days where they did everything, including delivering babies. He was very tall and British and quite elegant in his doctoring and family life. He emigrated from the U.K. to Australia. His sideline was that he started the Canberra Food and Wine Club.

I noticed bottles of wine in your office … ?
They're accumulating because I'm too busy to drink them. [They're from] students — I'm not sure if they're gifts or bribes. *[Laughs]*

What do you miss about where you grew up?
Easy contact with family and friends, the climate, bird songs and the smell of eucalyptus.

Did you grow up doing outdoorsy things?
Oh yes. And Seattle in the summer is fantastic for hiking and biking. But then you have these long periods where — well, the skiing is great, but November here is hard before the snow starts, and the days are short.

Did you plan on staying in the U.S.?
[My husband] thought we were coming here for a year, I thought we were coming for three, and here we are 14 years later, with two kids and a dog. He's a very tolerant man.

How did you meet?
At university, through the track club.

Are you still a runner?
We do fun runs quite frequently. We do the Shore Run [a Seattle 5K/10K event] each year to raise money for the Hutch. I do the women's run around Green Lake with my daughter. We do trail running. If I'm pushing in one direction, I don't like to push in another, so the running is more recreational now.

One object you would bring to a desert island, assuming you had food and water?
My Kindle, and an electricity supply.

Do you have a favorite genre?
Biography. I find it relaxing and educational at the same time. Having a broader view of what's happened in the world — it's more enjoyable seeing it through the eyes of an individual.

The most compelling biographies you've read?
Obama's was really inspirational. Also Rosalind Franklin [who helped solve the structure of DNA] — just her determination to follow the science and excel despite the challenges that she had as a woman in science at the time.

If you could be any animal what would you be?
A dog. My border collie, Gypsy, has a good life.

OK, now you're a person again, but you can choose a superpower.
Can I clone myself? An army of clones doing everything I need to do, and a couple that are resting and enjoying life with the family.●

Fred Hutch is a global leader in discovering therapies for kids with cancer. With funds raised at the 2016 Hutch Holiday Gala, we intend to make our biggest investment yet in pediatric cancer research. Learn more at ***fredhutch.org/givenow.***

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Dr. David Maloney named head of new Bezos Family Immunotherapy Clinic

Dr. David Maloney has been appointed the first medical director for cellular immunotherapy at Fred Hutch and the recently opened Bezos Family Immunotherapy Clinic at Seattle Cancer Care Alliance (SCCA).

Maloney is an immunotherapy researcher and blood cancer physician at Fred Hutch, SCCA and the University of Washington, and holds the Leonard and Norma Klorfine Endowed Chair for Clinical Research at Fred Hutch. In his role as medical director for cellular immunotherapy at the Hutch, Maloney has oversight of critical clinical trials infrastructure and provides expertise for effective research operations. As medical director of the new immunotherapy clinic, Maloney leads the clinic's physicians and oversees research and patient care.

He played a key role in the development of the clinic — the only one of its kind in the nation that's designed to meet the needs of patients participating in immunotherapy clinical trials.

The clinic bears the name of the Bezos family, which has provided catalytic philanthropic gifts and galvanized the community to join them in support of our groundbreaking and lifesaving immunotherapy research.

Photo by Robert Hood / Fred Hutch

About Fred Hutch
Fred Hutch is a world-renowned 501(c)(3) nonprofit research organization working to eliminate cancer and related diseases. Located near Seattle's South Lake Union, we are proud to be home to three Nobel laureates.

fredhutch.org

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