

GUT BACTERIA

A KEY TO IMPROVING RESPONSE TO CANCER TREATMENT

By Cathy Clark

The word in modern scientific circles is that we are not 100% human. We are only 10% human, and the microbes in our bodies comprising the other 90% hold keys to health.

So claims author and biologist Alanna Collen in her book titled *10% Human*.

The percentages do not pertain to the weight of the cells, but rather correspond to the numbers of microorganisms (including bacteria, fungi and viruses) in and on your body compared to the number of your own various types of cells. Nevertheless, some scientists estimate the average human microbiome weighs in at a hefty two and a half pounds. The density varies throughout the body with most of the microbiome residing within the intestinal tract.

The human microbiome is considered the collection of microbes, which include bacteria, viruses, fungi, that exist in and on our bodies – and also in our environment.

“Everything is littered with microbes – every surface you touch, the air you are breathing – and every part of your body has a different community of bacteria and viruses and fungi,” says Moffitt epidemiologist Christine Pierce, PhD, MPH.

That being the situation, why aren’t we sick more often? Actually, it is the microbes – that is, microbes in balance – that keep things in check, says Dr. Pierce.

She describes the three general types of human-microbe relationships:

COMMENSAL

Commensal means there is usually a benefit to the microbe and a rather neutral experience to the human. We would not benefit from the presence of commensal microbes nor would they harm us, but the microbe benefits.

SYMBIOTIC

Symbiotic means that both the microbe and the human would benefit by the presence of the symbiotic microbe.

PATHOGENIC

Related to the word pathogen, pathogenic microbes are harmful to the human and are often disease causing.

Our bodies are usually pretty good at keeping things in balance, and that balance of microbes helps lead to health. Having ecological balance between the commensal and symbiotic microbes – and preferably very few of the pathogenic microbes – then we usually are healthy and things are in a good, calm state.

But when our bodies’ microbes are out of balance, disease occurs. And that is where the association with cancer comes in.

MICROBES, collectively, include bacteria, viruses, fungi, and parasites. The microbiome is the collection of all microorganisms residing in a given environment, including parts of the human body, such as the digestive system.



“We now are starting to understand how the microbiome can actually impact the development of our immune system and that absolutely ties in with cancer,” says Dr. Pierce. “The scientific community has been investigating the role of infections, particularly viruses and bacteria, in cancer development for a long time. But how these microorganisms contribute to cancer remains understudied.”

Dr. Pierce became interested in understanding how infections can contribute to chronic diseases when she was in graduate school.

We know that certain microorganisms are involved with cancer. For example, *Helicobacter pylori* is known to cause stomach cancer, and infection with some types of human papillomavirus (HPV) can lead to cellular changes that, if untreated, may progress to various types of cancers, notes Dr. Pierce. But the study of a collection of organisms – the microbiome – is emerging, with numerous studies in place and more clinical trials on the horizon.

Christine Pierce, PhD, MPH (LEFT), AND LARY ROBINSON, MD



Photography: Ray Reyes

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EPIDEMIOLOGY AND SURGERY INTERSECT

Dr. Pierce’s research focuses on understanding complex interactions between the human microbiome and the immune system. Her aim? To understand how the microbiome influences the effectiveness of cancer therapies, especially immunotherapy. The studies will improve our understanding of the role of the microbiome in cancer treatment and it might also help in the development of personalized strategies to optimize anticancer therapies through interventions that involve personalized microbiota-based interventions.

This is where her research interests and those of Moffitt thoracic surgeon and senior member Lary Robinson, MD, converge.

An accomplished surgeon, Dr. Robinson says he enjoys helping patients by removing cancers – something he has successfully

been doing for a long time. His extensive career includes having served as a Flight Surgeon at the rank of Major, USAF, and in 1975 was awarded the Air Force Commendation Medal for Meritorious Service in Thailand.

About eight years ago he began reading up on Crohn’s disease because a family member had been diagnosed with the illness. As he read, he became curious about the relationship between the disease and gut bacteria. This led to more reading, and he became increasingly interested in how microorganisms contribute to cancer.

“We now understand that approximately 20 percent of cancers are known to be caused by some type of microorganism,” says Dr. Robinson. HPV causes virtually all cases of cervical cancer, the majority of oropharyngeal cancer, vaginal cancer, penile cancer, anal cancer and a number of other cancers.

Hepatitis B and hepatitis C viruses cause liver cancer. A variety of different viruses, such as Epstein Barr virus, cause some types of lymphoma.

But while many cancers have a strong microbial cause, the mere fact that one is exposed to a pathogen known to cause cancer does not necessarily mean that an exposed person will develop cancer. Other factors, including genetic differences, environmental factors and immune suppression all influence how the body responds to various infections and whether cancer develops.

HOW ONE'S BUGS AFFECT THE IMMUNE SYSTEM

Dr. Pierce and Dr. Robinson are conducting studies to better understand how changes in the gut microbiome affect cancer patients who are undergoing immunotherapy. They believe that an understanding of these variations will help to explain associations between a patient's gut microbiome and response to treatment. They hope their findings will shed light on the potential use of microbes as biomarkers of clinical response and allow for potential microbial modification (through diet, prebiotics or probiotics) to improve treatment response.

Dr. Pierce provides the scientific expertise required in these types of studies, and Dr. Robinson provides the clinical perspective, resulting in a successful collaboration.

“Your bugs determine your immune system...how well it works,” says Dr. Robinson. “And the more diversity of bugs in one's colon the better.”

Two different melanoma studies from other centers involving the relationship between immunotherapy outcomes and the microbiome were recently presented at the 2017 American Society of Clinical Oncology meeting. The investigators obtained gut bacteria through fecal samples before the patients underwent immunotherapy for melanoma. In these observational studies, they found that the composition of the gut bacteria made a difference in how well the patients responded to immunotherapy.

Finding a strong correlation between gut bacteria and response to treatment in melanoma by other investigators encouraged Dr. Pierce and Dr. Robinson to conduct a study in patients with lung cancer at Moffitt. Preclinical research shows promise, but no one has done such a study yet in humans with lung cancer.



CENTER FOR INFECTION RESEARCH IN CANCER

Dr. Robinson and Dr. Pierce actively work with other members of Moffitt's Center for Infection Research in Cancer (CIRC). Dr. Robinson is one of the founding members of the center of excellence, led by Moffitt HPV research expert Anna Giuliano, PhD. The CIRC is designed to identify additional cancer-causing agents, learn more about the role of these infectious agents in the origin of cancer and to translate this knowledge into novel and effective strategies for the prevention and treatment of cancer.



Photography: Rachel Lawrence

Research coordinator Maria Gomez works in Dr. Christine Pierce's lab, where stool samples are processed as part of a study involving evaluation of the potential role of microbes in response to cancer immunotherapy.

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Now Drs. Robinson and Pierce are collaborating with other physician-scientists to find, prospectively, whether the gut microbiome makes a difference in treatment response in humans with lung cancer. This endeavor has far-reaching potential because lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide. The primary purpose of the study is to understand how the gut microbiome of individual patients with advanced lung cancer affects their response to immunotherapy. Ultimately, the changes in the gut microbiome will help explain the associations between the gut microbiome and treatment response and shed some light on the potential use of microbes not only as biomarkers of clinical response, but also offer the prospect of potential microbial modification (through diet, prebiotics or probiotics) to improve treatment response.

So far, no patients are deliberately being treated with anything different that might affect the microbiome since this is an observational study only.

Antibiotics are lifesavers, yet they also are known to temporarily distort the healthy diversity of gut bacteria. Dr. Robinson cites a retrospective study by another group (not yet published) comparing renal cell cancer patients who received antibiotics within two months of starting immunotherapy with patients who did not receive antibiotics. The patients who received antibiotics had a significantly decreased response to immunotherapy. They are now retrospectively looking at Moffitt patients to see if the same negative effect is seen in lung



Photography: Rachel Lawrence

WHAT ARE PROBIOTICS AND PREBIOTICS?

Probiotics are live microorganisms that are intended to have health benefits. Products sold as probiotics include foods (such as yogurt) and certain dietary supplements.

Prebiotics are types of sugars in some foods and supplements that humans can't digest but they nourish or stimulate the growth and activity of certain beneficial bacteria / probiotics.

cancer patients receiving antibiotics before immunotherapy.

“What we really want to do is manipulate the gut bacteria in a way that benefits treatment, but we won't do this until initial studies show that it makes a difference,” says Dr. Robinson. He adds that the gut bacteria can easily be changed within two to three weeks through diet, probiotics and prebiotics.

FIRST, PROVE A CORRELATION

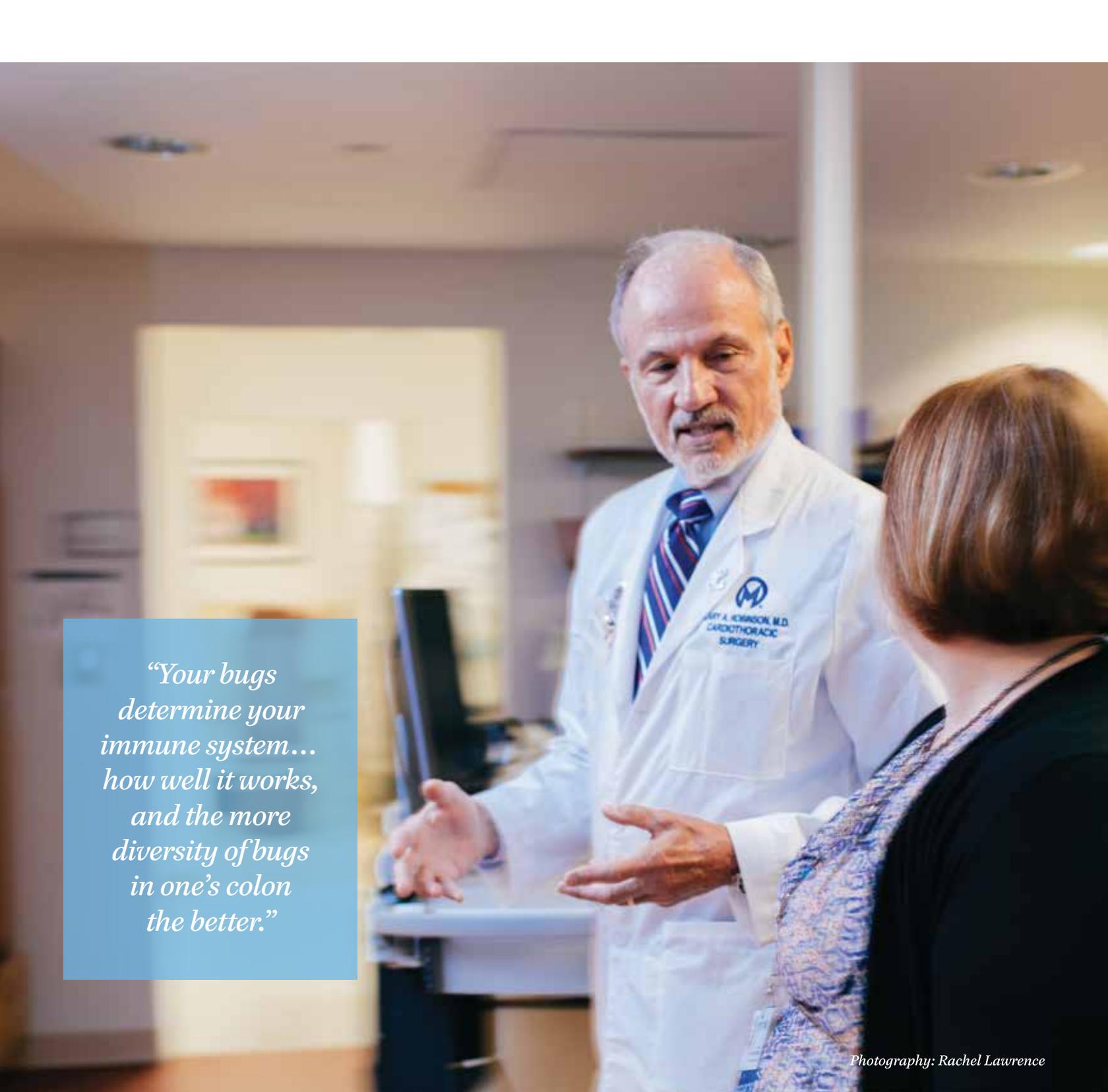
Dr. Pierce and Dr. Robinson eagerly anticipate moving their work beyond retrospective chart reviews and prospective observational collections of fecal samples that they are analyzing for the microbiome.

They want to see patients undergoing immunotherapy first go on probiotics and prebiotics and change their diet so that their gut microbiome is in a healthy state that will enhance the effectiveness of therapy.

And if their studies prove the effectiveness of such an approach – which they believe they will – then they will expand their work further.

“Ideally, we will be able to do some of those interventions, or all of those interventions, prospectively in a trial with patients who are undergoing cancer treatment,” says Dr. Robinson. “But first we must prove a strong correlation.”

This field relating to bacteria keeps expanding. While their studies are centered on the gut microbiome, there are so many different types of microbiome – gut, oral, bronchial, and more. Dr. Pierce is even studying the microbiome within tumors.



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We will be hearing and reading more about the human microbiome in the years ahead. Future anticipated areas of study include:

- Treatment based on the intestinal microbiome
- Manipulation of the intestinal microbiome before treatment
- Study of microbiome in the gut, mouth and other areas of the body
- Study of the microbiome on and within tumors
- Microbiome studies tied to genomics studies

They foresee, within the next five to 10 years, that the microbiome will revolutionize personalized medicine. At that time, they believe, treatment will be based not only on a person’s genetics but also on an individual patient’s microbiome and even on the tumor microbiome.

And in the future, physician-scientists may be doing some adjunctive treatments by way of diet, probiotics, prebiotics or other interventions not yet known to change a person’s microbiome before treatment. 