



## **Hope With Answers Podcast**

### **Understanding gut microbiome in lung cancer treatment**

Sarah Beatty:

Okay, Diane, we've got to set the scene for this Hope With Answers: Living With Lung Cancer Podcast. And this one is really fascinating I promise. We just have to get comfortable with one little detail first. Are you ready to hear what we're talking about today?

Diane Mulligan:

Kind of scaring me, Sarah, but okay, I'm ready. Let's hear it!

Daniel Spakowicz:

And, in general, collecting somebody's poop before they start a treatment is not a commonly done practice right now, and it tends to be sort of icky to some people. And that's the essence of what we want to change.

Diane Mulligan:

Well, okay. We're talking about the gut microbiome. We're going to find out how the microbiome may be the next frontier for finding better treatments for lung cancer. And in fact, Lung Cancer Foundation of America has funded not one, not two, but three young investigator grants into the microbiome. So it's really a potentially powerful new area of research.

Sarah Beatty:

And today we're tackling the "ick factor" by talking to LCFA's three young investigators who are going to help us understand what the microbiome is and how it may play a role in lung cancer treatments now and in the future

Diane Mulligan:

Advances in lung cancer treatments over the last few years have made it possible to live with lung cancer for years after diagnosis, but lung cancer research never stops. And in fact, it's critical that research continues to give everyone living with lung cancer the best possible tools for living a longer, healthier life. I'm Diane Mulligan.

Sarah Beatty:

And I'm Sarah Beatty. One of the most interesting new frontiers of lung cancer research is understanding how the microbiome, and the body's own immune system, might work together to help fight lung cancer. Today, we'll hear from the young investigators themselves and find out why they are so excited



about this new area of research. That's today on the Living With Lung Cancer, Hope with Answers Podcast.

Diane Mulligan:

Lung cancer is a tough topic. It's a disease that affects patients, families, friends, coworkers. But first, it's a disease that affects people. The Hope With Answers: Living With Lung Cancer Podcast brings you stories about people living, truly living, with lung cancer. The researchers dedicated to finding you breakthrough treatments and others who are working to bring hope into the lung cancer experience.

Diane Mulligan:

We have a lot to cover in today's podcast, but we're going to start right off the bat by answering a question that we know so many people living with lung cancer want to know; what should I be eating or not eating to best prime my immune system to fight this disease?

Sarah Beatty:

This is such an important question. So many of the patient advocates we work with are deluged with well-meaning advice; eat a plant-based diet, cut out all sugar eat stuff that reduces inflammation. And all of this advice comes from a good place. Trying to help people living with lung cancer, take back control of their lives and beat back the disease.

Diane Mulligan:

So what do we know about the connection between diet and lung cancer?

Sarah Beatty:

That was the question I put to three winners of LCFA's young investigator grants; Doctors Daniel Spakowicz, Jarushka Naidoo, and Zoltan Lohinai. They all three joined me recently to give us some insight into their research on the microbiome.

Daniel Spakowicz:

Well, I don't think there is a really strong evidence right now for each individual to say that this diet will for sure help you. But I think that the types of research that the three of us are describing is how we're going to figure that out. The microbiome is unique to participants, to study participants or to everyone. And that affects how you respond to various nutrients and everything that goes into your diet. So by finally starting to understand what is in each individual's microbiome, I think that's going to be how we make the link from a particular dietary intervention to some phenotype of interest.

Jarushka Naidoo:

Yeah, I couldn't agree more with Dr. Spakowicz. I think this is a really complex area. And I think as people who are in the thick of studying this, we appreciate that there are so many factors that need to be taken into account to truly understand what affects how well patients do with immunotherapy and if they



develop side effects. Diet is one of them, but there are many other factors too, that we need to take into account; age, gender, other medications, geographical location. All of these variables are likely to affect the microbiome and are likely to affect how well we may do with immunotherapy in terms of response or side effects. So I think we have to take it all into account, but as has been mentioned before, I think we are finally starting to scratch the surface. We're finally starting to work towards getting answers for patients and helping them to tailor their approaches. Whereas up till now, I think we knew little about this, so hopefully in the coming years, we will have good data to inform our decisions about diet and how to approach immunotherapy in the future.

Daniel Spakowicz:

Because the microbiome is modifiable, and in theory, once we know what diet a person should be on, that's an aspect of control that we want to give back to patients. So in the context of this extremely disempowering life event, we think this is a way that we can say, here's how you can take an active role in your lung cancer treatment. And we're really excited about that aspect of it.

Zoltan Lohinai:

In the background we are working on the microbiome interactions with immunotherapy to help increasing outcome. So this project is very inspiring for me and reveals a lot of interesting associations of bacteria, immune system, and immunotherapy. So hopefully we get back to you with new data soon.

Sarah Beatty:

It certainly seems like there's a lot to learn about how the microbiome may play a role in lung cancer treatment. Now, we just heard some medical terms that take a little getting used to like immunotherapy, and we need to find out what the microbiome actually is. And well, that's maybe not the only thing that takes a little getting used to.

Diane Mulligan:

So we all go to the doctor, right? And sometimes we need to have the doctor run some tests or check things that are a little personal or uncomfortable. I would say that for most people, checking your gut microbiome falls in that category. It's a test that requires a stool sample. Here's another way to think about it: what are the simple, painless, non-invasive no needles, no surgery test gave your medical team an incredible amount of data to help steer them toward the best possible treatments specifically for you?

Sarah Beatty:

That's what Dr. Daniel Spakowicz means when he says he wants to change the ick factor around incorporating the gut microbiome into potential new lung cancer treatments. So let's start with the basics. What is the microbiome and why might it be important in the fight against lung cancer?

Daniel Spakowicz:



So the microbiome is the collection of organisms that live on you and in you. So you have about 10 trillion human cells on your body and roughly the same number of microbes, either bacteria, viruses, fungi, and other things. They live all over, but mostly in your gut in terms of concentration. And they've got something like a hundredfold more genes than you do for being able to degrade different carbohydrates, make different molecules. And we're just starting to understand how they affect many different things, including cancer.

Jarushka Naidoo:

And what's really interesting is we understand that some of these microbes may be implicated in the development or growth of cancer, or even how some cancers respond to certain treatments. And that's the basis for a lot of our different studies. And of course, thank you so much to the LCFA for supporting some of this work, which I think will be very enlightening in many different cancers, including lung cancer.

Zoltan Lohinai:

And we can assess also the metabolic activity, like how the bacteria live and how they interact with the food we eat and all the metabolic interactions is the next level of research that we are facing.

Sarah Beatty:

What does the gut have to do, and the microbiome have to do, with lung cancer. I'll start with you, Dr. Spakowicz.

Daniel Spakowicz:

Yeah. I think there's going to be a lot of interesting research that comes out in coming years about the microbiome of the lung and how that has an effect. But what seems to be true so far is that the gut has the tightest interaction with the immune system. And there's good reason to expect that should be the case from some first principles. But that seems to be born out in the data. And that's particularly relevant in the context of some types of cancer treatments that are trying to harness the immune system to fight off the cancer.

Sarah Beatty:

That's fascinating. Dr. Naidoo, you're looking at this too. What are you finding with the combination of the microbiome and lung cancer?

Jarushka Naidoo:

So I think this is obviously a very complex area. And as I was saying before, lots of different organs appear to have different microbes that may have a different impact on why cancer develops and how some treatments work. Specifically with lung cancer, I think a lot of studies have focused on either the microbes in the lungs. So in the fluid around the lung, or maybe even in the cells or around tumors and how they may affect how tumors respond to treatment.



Jarushka Naidoo:

And then as Daniel was explaining, we know that certain cells that line the gut are very important for modifying or changing our immune response. And now that we have new treatments that harness our immune response to fight cancers such as lung cancer treatments called immunotherapy, it becomes very important to understand why some immune responses are the way they are in certain patients. And can we make those immune responses stronger for some patients or change the immune responses so that perhaps patients who develop the side effects of these immune related treatments don't happen as severely or as often. So this is what a lot of my research is focused on. And I think that will be growing interests, not just in the gut microbiome, but the lung microbiome and other effects on the rest of the body.

Sarah Beatty:

That's fascinating Dr. Lohinai, what did you find in your research about the interaction between the microbiome and lung cancer?

Zoltan Lohinai:

So actually we've been focused on weight loss like cachexia and malnutrition and malnutrition can result in delays in treatment or dose reduction, which is usually associated with poor outcomes for patients. So we have been focusing on malnutrition's and malnutrition and the identified bacteria species that are associated with weight loss that can be maybe restored in the future to enhance treatment efficacy in the future.

Sarah Beatty:

The question that I really want to get to is what are you hoping to find, or what are you hoping the outcome of your LCFA grant might be with your research and Dr. Spakowicz, I'll start with you.

Daniel Spakowicz:

Well, we have a grand hopes of course, but the narrowest perspective of it is that we want the microbiome to be appreciated in the standard of care for patients with lung cancer. Because we think, first of all, it's a non-invasive biomarker that is able to predict who is going to respond to certain types of treatments. So even though we think of blood is sort of an easy thing to get, I would argue that poop is even easier. But we need everybody to get used to it because we think it's going to be really, really valuable. But more importantly, you can change the microbiome. And so, because it's predictive, but you can change it, makes this immediate therapeutic target to try to modify the microbiome to promote different treatment responses. Or as Dr. Naidoo was saying, differences in the immune related adverse events or other sort of toxicity. So we're really excited about this, this modifiability and really understanding how it affects lung cancer.

Sarah Beatty:



Dr. Naidoo?

Jarushka Naidoo:

Yeah. Just to build on what Dr. Spakowicz said, our project is focused a little bit on how the microbiome might change over time. So far a lot of studies have looked at whether these features of this microbiome in our gut may affect immunotherapy from a particular time point. Usually a time point before a patient starts treatment. How we at Hopkins and with our group hope to move the field forward is to understand how the microbiome changes over time. And if this change over time is something that relates to how well a patient does with immunotherapy, or if they develop the side effects of immunotherapy. And some of that to Dr. Spakowicz we hope that while understanding the change, we may be able to propose an intervention to change the microbiome so that we can harness that change and make a patient either a better responder to immunotherapy, or try to help them with the side effects of immunotherapy through an intervention that uses the microbiome.

Sarah Beatty:

This is really fascinating to get to understand the differences between your research. Dr. Lohinai, can you sort of talk about what you hope comes from your research? I know you've just sort of wrapped it up.

Zoltan Lohinai:

The way I think of microbiome is kind of signatures as it will be integrated I think in the future, as, as a biomarker. Biomarker is a parameter that would tell us the outcome of a treatment that would have microbiome as one part of the puzzle, but to sum up, I think it will be one part of a signature, not an independent biomarker. But that might help us in the future helping diagnosing and helping personalizing the medicine and to translate what is the most important to translate our research into practical applications into the bedside as soon as possible. So I seen there is a great aspect of microbiome research. And even though if we can enhance our research, the three of us, maybe in the future, that would be really a great opportunity.

Sarah Beatty:

I wonder if you can help us understand a little bit about immunotherapy and what the role of immunotherapy in treating lung cancer currently and how that might be impacted by the studies we're talking about here today.

Jarushka Naidoo:

So as, as lung cancer physicians, if you mentioned immunotherapy, you will see smiles on faces because immunotherapy has truly revolutionized the way we treat patients who have lung cancer and notably over the last five to seven years. And there are a number of medicines that are given as infusion treatments that basically reawaken a specific part of a patient's immune system or immune response, and helps our immune system, or helps the patient's immune system, to recognize the cancer and thereby attack the cancer and hopefully help the patient. So that's where we are in terms of how



immunotherapy works. And what we found in the very early studies was that patients who had cancer that had received prior chemotherapy appear to benefit from these medicines. And also the side effects appear to be much less than traditional chemotherapy. So several years ago, giving some of these medicines became a new standard for advanced lung cancer.

Jarushka Naidoo:

In recent years, we also have seen that immunotherapy has now actually replaced chemotherapy for patients who have advanced lung cancer who have a particular marker called a high PD-L1 score. And then very excitingly, we are now seeing that immunotherapy may help patients with earlier stage lung cancer. And there was a pivotal trial in patients with stage three lung cancer, where immunotherapy is given for a year afterwards. And this has nearly doubled the survival of patients with stage three lung cancer. Newer studies are now looking at immunotherapy and even earlier stages of lung cancer, some even before surgery.

Jarushka Naidoo:

So we have really truly seen a revolution in incorporating immunotherapy into our clinical practice. But there's still a long way to go to understand which patients truly benefit the most, to help to refine who should get immunotherapy and who shouldn't. And that's where I think many of our studies will fit in. The second application is how do we make immunotherapy safer? So we know, even though the toxicities happen a lot less, sometimes when they happen, they can be very severe. So hopefully our studies will help to make immunotherapy not only better but safer in lung cancer.

Zoltan Lohinai:

So some medications seem to affect the microbiome like antibiotics or steroids. That's a type of medication that are frequently administered. So before the diagnosis of lung cancer, as a pulmonologist, I can tell that many patients get treated with antibiotics because sometimes it is hard to differentiate between pneumonia. It's looks like a lung cancer or an inflammation in the lung can be misdiagnosed with kind of a sort of lung cancer. So it's frequently treated with antibiotics that might alter the long-term outcomes of immunotherapy. So physicians should think, right, days, or weeks or months ahead of the treatment, even we don't know what treatment the patient will get by immunotherapy, but we have to see what medications we administer months before the treatment. I think it's recommended, there is no evidence, but there is a lot of data that would say that the treatment with antibiotics and steroids should be as the lowest dose. And should be lowered to the minimum to increase the outcomes of some patients because these medications can alter the outcomes of immunotherapy.

Diane Mulligan:

That last point is so critical. We know from working with lots of people, living with lung cancer, that it often takes months or even years, to get the correct diagnosis of lung cancer. And for many people only after antibiotics for various respiratory ailments didn't work. So this research into the microbiome is critically important in many ways.



Sarah Beatty:

That's right. And coming up, you'll hear why one of the LCFA young investigators thinks the microbiome might even lead to the next revolution in lung cancer treatment.

Diane Mulligan:

Are you enjoying the Hope With Answers: Living With Lung Cancer Podcast, consider making a donation to help LCFA produce this resource for patients or anyone seeking answers, hope, and access to updated treatment information, scientific investigation, and clinical trials. Just text "L C F America" to "4 1 4 4 4" to join in this important fight.

Diane Mulligan:

So far in this podcast, we've moved past the ick factor to understand why research into the microbiome might yield incredibly important and useful information for the treatment of lung cancer.

Sarah Beatty:

Now let's find out why one researcher thinks it just might even be bigger than that.

Jarushka Naidoo:

I think so far, two revolutions in lung cancer; the genomic revolution and the immunotherapy revolution. The genomic revolution happened about 10 to 15 years ago with the discovery of several genomic biomarkers that then led to several targeted therapies and understanding that lung cancer is not all created equal. And that some patients may have cancers that do well with special targeted pill therapies that may shrink those cancers. And then from there came the immunotherapy revolution, where we understood that maybe different lung cancers might respond to immunotherapy, which we talked a lot about today that tries to use our body's immune system to fight cancer. I think, and I hope, that our projects are the start of the microbial revolution. That we will understand that our microbiome is somehow intrinsically related to perhaps how lung cancer develops, why lung cancer grows, and how long cancer is treated. And we may be able to understand how to harness that microbial intervention to help patients and pave the way for the future.

Diane Mulligan:

Isn't that exciting to think about research as revolution. The LCFA young investigator grants are designed to help researchers look at lung cancer in new and creative ways, always with an eye toward finding better treatments that help people live longer and healthier lives.

Sarah Beatty:

Dr. David Carbone helps LCFA decide which research to fund and says he looks for a common element in grant applications.





David Carbone:

Well, I think to some extent, we all hope that what we're doing will be the next big breakthrough. I think the most interesting research is the one you feel is going to be the most impactful. And we have a limited time on this earth and what we invest our time in. You know, I would hope that people would think that it would be the most impactful and the microbiome is certainly a very influential factor in those who get cancer, those who respond or don't respond to immunotherapy or chemotherapy. Right now, it's a little phenomenological in a lot of ways. This is associated with that. And we don't really know the mechanism, but we're getting a whole lot better and a whole lot closer to understanding that mechanism. And it really could give us some novel insights, novel therapy targets, novel ways of improving outcomes. And I'm very hopeful that'll be the case. And I think that's reflected in the three grants that have been given for the microbiome research.

Diane Mulligan:

Well, this has been a fascinating podcast into a brand new and very exciting area of lung cancer research. I'm so glad to hear Dr. David Carbone's perspective on why LCFA is investing in three different studies on the microbiome.

Sarah Beatty:

And thank you to doctors Jarushka Naidoo, Daniel Spakowicz, and Zoltan Lohinai, all LCFA Young Investigators on the cutting edge of the newest treatments in lung cancer. Join us again next time on the Hope With Answers: Living With Lung Cancer Podcast.

Diane Mulligan:

Make sure to subscribe to the Hope With Answers: Living With Lung Cancer Podcast. You'll be notified every time a new episode is available. So visit us online@lcfamerica.org, where you can find more information about the latest in lung cancer research, new treatments, and more. You can also join the conversation with LCFA on Facebook, Twitter, and Instagram.