BRENDAN: Hi, *ThinkResearch* listeners. This is Brendan Keegan, one of the hosts of the show. The episode you're about to hear was recorded over Zoom, and the audio quality is a little different than what you're used to hearing on *ThinkResearch.*

We've had to adapt to this new way of working, just like you. We're also launching a new series and want to hear from you. Tell us how you've been adapting to working remotely and how your clinical or translational research has changed.

You can either tweet a response @Harvardcatalyst, using the hashtag COVID-19, or using the voice memo app on your phone, record a short clip of yourself. Try to keep it under two minutes, and email it to us at onlineeducation@catalyst.harvard.edu. We might use your clip in an upcoming episode. We look forward to hearing from you and sharing more stories of clinical research.

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OBY: From the campus of Harvard Medical School, this is *ThinkResearch,* a podcast devoted to the stories behind clinical research. I'm Oby.

BRENDAN: And I'm Brendan, and we are your hosts. *ThinkResearch* is brought to you by Harvard Catalyst, Harvard University's Clinical and Translational Science Center.

OBY: And by NCATS, the National Center for Advancing Translational Sciences.

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BRENDAN: Many of us are all too familiar with common types of cancer and their treatments. For decades, cancer tumors have been surgically removed, targeted by chemotherapy, or killed off by radiation therapy. When these treatments aren't enough, researchers and oncologists must take a closer look at the tumor, the patients, the therapies, and more.

At Dana Farber Cancer Institute, Dr. Osama Rahma researches the acute differences not only among patients but among the tumors that may or may not respond to regular course of treatment. In response to this, targeted immunotherapy specifically tailored to a tumor's genomics is necessary in killing cancer. Dr. Rahma is a medical oncologist at Dana Farber Cancer Institute who specializes in GI oncology with a research focus on cancer immunotherapy.

OBY: Hi, Dr. Rahma. Welcome to the show. As a medical oncologist, your work focuses on different types of cancer and their treatments. Can you tell us more about how cancer is treated?

OSAMA RAHMA: Traditionally, cancer had been either treated by surgery, especially when the cancer is localized to one area that you can actually remove it. Radiation therapy is another modality of treatment, and both surgery and radiation therapy are meant to be more of a localized treatment. That means it treats only the cancer in one area where you deliver this modality.

The surgical way of doing this is that you just remove the tumor. However, with the radiation therapy actually trying to kill cancer cells by delivering radiation that can kill the DNA of the cancer cells, and therefore, they cannot survive. They cannot replicate anymore, and there are actually many other mechanisms by which radiation can be helpful to treat cancer, in general.

And then we have what we call the systemic way of treating cancer, and that's using chemotherapy. And chemotherapy has been a modality to treat cancer for many decades now, and the way that chemotherapy works, it has also many different mechanisms of action. And each of those target one part of the cycle by which the cancer cells replicate. Most of them also work by suppressing the DNA of the tumor, and therefore, the tumor cannot form another tumor, meaning a cancer cell cannot form another cancer cell, and they die off.

And then, we have the targeted therapy approach and that had started in the early 2000s, when tumors were noted to not just be a similar entity as of breast cancer or ovarian cancer or labeled as one. Right? It's either ovarian or colorectal cancer, or it's a breast cancer, but rather, it is a more personalized way to go after cancer. So two patients may have the same tumor, but their tumor may look differently, when you start looking at the genomics of the tumor, and what does that mean?

That means that if there is a certain mutation in a certain gene, that can actually drive the cancer. That can make abnormal or not normal proteins, and those proteins can lead to addiction of the cancer cells to grow and make more cancer cells. So that's what's called a personalized medicine or personalized cancer treatment, where we sequence the tumors, and we try to identify what gene could be a good target.

And keep in mind, there are many different genes that we can find that are abnormal or mutated, but there are genes or proteins where we have a targeted treatment for, and there are others that we don't. And where we find that, then the drug of choice could be matched with that mutation or gene mutation or abnormal protein, and that could actually help to suppress the cancer cell. Lastly, which is what's been called the breakthrough of cancer treatment in the past decade, which is the cancer immunotherapy, where we actually try to mobilize, or activate, the immune cells to go after cancer, and we can talk about this more.

OBY: What are some important differences that you see among patients and their various cancers?

OSAMA RAHMA: Right. So cancer is just a very big word, and it's a very general word that underneath it you have many different types and subtypes. Right? So you have cancers that actually tend to have a good prognosis, meaning those are cancers that are, in general, detected earlier. And when they're detected earlier, it could be treated more aggressively, and patients can do as well as a patient who doesn't have cancer, if you do the treatment as recommended.

Example of that is breast cancer which is very common, and if you remove the lump of the breast cancer, and you basically administer what's needed afterwards, if needed, such as radiation therapy, chemotherapy, hormone therapy. Most of the patients with very early detected breast cancer, they actually survive it, and they have a normal lifespan. And you think about the same thing in terms of colorectal cancer, for example, if you detect what we call a stage one, so very early colon cancer, and you remove that, the patients tend to do well.

On the other hand, you have cancers that are more aggressive that are hard to detect, and a big example of that, or an important example of that, is pancreatic cancer, a cancer that I specialize in treating. Where most of the patients present where it's too late, and that's not because they didn't pay attention to their symptoms, but rather because there was no symptoms to begin with. Because those type of cancers spread before you even started developing symptoms, and that's one reason what drives the bad prognosis of these cancers, that they are advanced at the time that we discover them.

And also, there are cancers that replicate much faster than other cancers. There are cancers that go to the other organs and develop metastases using either the blood or the lymph nodes, for example, and that's differences in different tumors. So tumors are different by the way they metastasize, by the way they grow, by whether they are found early, and you do have symptoms where they could be removed. Or they actually form and metastasize where you don't have enough time to detect them early, and therefore, that can drive a worse prognosis.

Patients also are different, because it's not just the cancer itself. It's what we call the host as well. The host is the person who, unfortunately, hosts that tumor, and what's the difference between patients is that you actually can see the same tumor in many different patients, and it would function or act differently. We don't understand fully the reason behind that, but there is a lot of research going on to understand this more.

So there are things that come to mind, such as, well, do these patients have different comorbidities? Do they have different types of diseases that they're pretty much not in good shape as other patients maybe? We call that performance status, functional status, and the better the functional status is, the better that patients do and respond to treatment.

Patients may have different immune systems, or they do have different immune systems, and that also can dictate how they do when they get cancer. We do believe that most of us that have developed cancer, those cancer cells happen in all of us, but our body, our immune system, is designed to take care of that and kill those cancer cells. However, it is when the cancer evades the immune system where it starts to actually develop and further and then people would have problems with that.

We also know that there is an environment effect, especially common cancers, like breast cancer and colon cancer, for example. We know that the more active you are, the less likely to get cancer, in general. And you would do better, if you get cancer, and you are in very good shape, you exercise, and you have good nutrition and balanced nutrition.

And lastly, we are also currently trying to understand what we call a microbiome, the bacteria that lives in the gut. And that bacteria also is found to play it all on the immunity. And how is that controlled cancer, or doesn't control cancer depends on what different bugs that we all have and we all carry. It's very hot area of research.

OBY: Can you talk a bit more about your research and how you're studying these differences?

OSAMA RAHMA: Of course. So my role at Dana Farber Cancer Institute, where I work, and Harvard Medical School is to, one, develop novel immunotherapy drugs for cancer, not just one type of cancer. The way we develop these drugs is we have a, say, new target that we are in the process of developing different drugs to go after that. So we try to test the drug in any type of cancer. Sometimes, we have to test it in a specific type of cancer based on what preclinical data we have with animal studies that we have. Researchers have been trying to actually energize the immune system to treat cancer for many, many years.

The story goes back to the early 1900, actually, when Dr. Coley at Memorial Sloan Kettering injected tumors, or injected patients with tumors, with bacteria. Because the thought was that if our immune system can kill bacteria, then if we inject that bacteria in the tumor, then the immune system would come after that and try to kill it and, therefore, kill the cancer. At that time, obviously, those attempts failed, because we didn't have enough understanding of how are immune system functioned and what's the influence of cancer on our immune system. That part was missing.

And then later, after that, we started developing what we call cancer vaccines, and that was pretty much the early '90s, also in early 2000 to 2010. And I was involved in many of these trials, when I was at the National Cancer Institute, at NIH, where we actually developed those cancer vaccines simply by looking at what different proteins, or abnormal or unusual proteins, that cancer cells may carry or have. And what we wanted to do, obviously, is just like flu vaccine. We wanted to trigger the immune system to go after cancer cells.

So what we've seen, we actually have seen that the body does react, and the immune system does react. We have seen, in the blood of those patients, evidence that the immune system recognized this abnormal protein and tried to act against them and tried to kill them. The reason, however, why those cancer vaccines had not seen a light and did not change the way we treat cancer, and they were not efficacious is we didn't know what that reason was for very, very long time. And it wasn't until the discovery of what we call today immune checkpoint and the development of drugs that are called immune checkpoint inhibitors that we started to understand the field.

And then the field started to focus on the different markers, or biomarkers, that are presented on the immune cells and the cancer cells, and those are pretty much labels that are expressed on the surface of these cells. Meaning, they sit on the surface of these cells. And one important or famous biomarker is called the CTLA-4. A CTLA-4 sits on the immune cell.

When the immune cell gets close to the cancer cell, the cancer cell also has its own label that interacts with the CTLA-4 label. Or if you think about it like you are actually using a key to lock a door. Right? And that key fits exactly the lock. Right?

And that's exactly how these markers function. They fit exactly together, and once they see each other, you basically lock that immune cell. So that's the cancer cell locking the immune cells and not allowing the immune cell to function and, therefore, to die, and the cancer-- or therefore, the immune cell would die.

So drugs were developed to actually stop this from happening, and therefore, the immune cell can survive and remain active and can kill the cancer. And along those lines, there was also the discovery of very similar markers on the immune cells and the cancer cells. The discovery is known as the PD1/PDL1 pathway which stands for the Programmed cell Death, and PD-L1 stands for Programmed cell Death Ligand.

And the discovery was that those markers, or labels, that you see on the cancer cell and the immune cells-- so the PD-1 on the immune cell, the PD-L1 on the tumor-- when they get together, the same exact thing happened that we talked about with CTLA-4. They actually communicate, and the cancer cells figure out a way to shut the immune cell down and kill it. And what's very interesting is that physiologically this mechanism of action does exist in our body.

And the reason it does exist, because if we get an infection, our immune system will be very active, and our immune system would try to actually kill that infection. Unless we have a way to put a brake on the immune system, this is going to keep acting, and then we'll develop inflammation, and we'll die. So the normal physiology of our body allows us, or allows our immune system to stop itself from overreact. And what's unfortunate is that the cancer cells hijack this mechanism and actually take advantage of that and use it to stop the immune system, but this time not to kill the infection but rather to kill the cancer.

So those discoveries have truly changed the face of cancer treatment. Since the discovery of those receptors, or biomarkers or markers you want to call them, many drugs have been developed to stop the interaction between these two. And the story goes on and on and on these days, where FDA had approved many of those cancer immunotherapy drugs for many, many indications, and the lists keep getting longer and longer.

However, we still have a long way to go, because not everyone responds. For example, in lung cancer, only 30% of patients respond, and 70% don't. In some cancers, like the cancer that I treat, pancreatic cancer, only 1% of those patients respond, and the rest don't.

So that's basically where the field is heading, and that's what I do for my research is trying to move those cancer immunotherapy to make them work in cancers where they have not traditionally worked, specifically in GI cancers which includes colorectal cancer and pancreatic cancer, liver cancer, and others. We are also trying to build on this discovery by making these therapies work better, because they do stop working after some time.

So in a year or so, those therapies stop working, and we're starting to understand what we call a resistance mechanism. How does the tumor figure out a way to actually resist the immune cells or the immune system, even if we're able to activate it using what I just described? And we are discovering that, actually, it's not just the CTLA-4 PD1/PDL1 story. There are many, many other what we call inhibitors or suppressors that either the cancer cell has or the other cells around the cancer cells have that actually tried to suppress the immune system and say, hey, stop, and trying to evade that immune activation that we create with those drugs.

OBY: And you just mentioned inhibitors. What are checkpoint inhibitors, and how have they influenced research today?

OSAMA RAHMA: So CTLA-4, PD1/PDL1 which we call immune checkpoints, they're called immune checkpoints, because they actually check on our immune system. They're checkpoints on our immune system. Drugs that inhibit or stop that are called checkpoint inhibitors, because they inhibit the interaction between those checkpoints, therefore, allowing the immune system to bypass that checkpoint and reactivate again. And those are the drugs that I was just mentioning that transform the way we treat cancer.

OBY: Can you describe what the kind of clinical trials you conduct look like? Like what happens in practice, when you're doing your clinical trials.

OSAMA RAHMA: Yes. So we have two types of clinical trials, and we have what we call early drug development clinical trials, or what you call a phase I. And we also have late drug development clinical trials. That's what's called phase II or phase III.

Phase I is when you introduce the drug first to a human being. Right? So a target, say that we were just talking about the immune checkpoints. Right? So say that we discover a drug, an immune checkpoint x, that we believe it's a very good target for us to go after. And we work with our colleagues, the pharmaceutical companies, to actually develop those drugs or manufacturer or make those drugs, and then, we want to try them on patients.

So usually, patients who enroll in phase I trials are patients who have cancer and are treated for their cancer by their oncologist with using the modalities we started this podcast talking about-- chemotherapy, surgery, radiation. But unfortunately, they got to the point where those therapies, or those modalities, are no longer working. So the standard of care, the FDA approved drugs, are no longer working, and they're looking to see what whether an investigational drug can work.

So we get referrals from other physicians within our institution, or actually across the globe, where they come and ask us to see their patients, or they send us their patients, refer their patients. And we sit down with the patients, explain what the target is, how does the drug works. What we've seen in other patients, if we have other patients on the trial, or what we've seen in the lab, and why do we believe this could be a good fit for the patient.

And also, we go over what we call eligibility criteria, so inclusion and exclusion criteria. Does the patient have a certain type of cancer? Does the patient have a certain amount of disease or tumors which we need, for example, to get a biopsy of? Does the patient have a blood level of hemoglobin that's so and so, kidney numbers are so and so? So we go through the list, and then if the patient meets what we call the eligibility criteria, we offer the patient a study and a patient would sign a consent to allow us to administer those drugs with the understanding that this is investigational, meaning we're hoping to benefit, to see a benefit.

But this is a drug that's not used yet in the community, and that's why we're trying to develop this drug. So we don't know yet what exactly the benefit and the risk could be. And then, with the phase I studies, we establish a dose. We establish a safety profile.

And then we move to larger phases, and that would be phase II or phase III studies. So in phase II, we would say, we actually need 20 or 50 patients with pancreatic cancer who had or had not received certain drugs, and now we're looking to actually treat specifically this type of cancer with this specific drug. And the phase II goal, is to actually have a preliminary hint for activity, meaning those are pre-designed. So we say, we want to see out of-- I don't know-- 50 patients that we treat, we want to see five or 10 patients that truly their tumor shrink and respond. And if we see that, then we're going to go to phase III study, and phase III study is what establishes, traditionally, FDA approval.

Phase III studies are studies that are large, and they have what we call a control. So patients are randomized to receive the therapy, investigational therapy, versus what they would have received by their oncologists, so chemotherapy, whatever is the standard of care. And try to establish whether our drugs, or the investigational drugs, are better than the standard, and that gets the drug to approval.

OBY: You talked a little bit earlier on, when you were explaining the different phases and how you move the drug along, about toxicity. So what is immunotoxicity, and how is it related to side effects?

OSAMA RAHMA: Yes. So pretty much everything, unfortunately, comes with a price, and the risk of the traditional therapies are very well known and very well defined. Like chemotherapy, everyone knows chemotherapy causes you to be tired and have nausea and vomiting. We have a very good understanding of that, and we know why. But when we actually start treating patients with immunotherapy, years ago, a new phenomena started to emerge which is the side effect of these drugs, or toxicity, or immunotoxicity.

And to explain this more, most of the patients that receive immunotherapy, they actually do just fine. They don't even develop side effects. What we're doing here, remember, is pretty much activating those immune cells, hoping they can go in and kill the cancer.

But what will happen if the immune cells are mislead, and they actually go in the wrong direction instead of going after the cancer cells? Here, they go after the normal cells. They go after the patient's own body, and that would mimic what you see in autoimmune diseases. That means the immune system attacks the host, attack the patient tissue or organs.

And fortunately, we don't see that happening very often, but when we see it happening, it could affect any organ in the body, starting from the eye, the skin, all the way to the vital organs, including lungs, bowel, liver, kidneys, neurons and brain, and so forth. Most common side effects we see with that is when the drugs affect, the immune cells attack, the skin. You develop itching. You develop rash which is usually manageable.

But my research is very heavily focused also on understanding those toxicities and those side effects. We are trying to understand why some patients have it or develop it and others don't. There are patients who have immunotherapy and have zero side effects, and there are patients who get immunotherapy and get many different immune side effects. So what's different about those patients?

So we study what we call the clinical characteristics of those patients. We study what other drugs they're taking. We study their blood and what markers, what inflammatory markers, they have that may be different than other patients.

So most recently, we had publicly presented data on the role of vitamin D in preventing the development of immune colitis. Where we actually showed that in the group of patients who receive immunotherapy, that the ones that were taking routinely vitamin D as their supplements actually were way less likely to develop immune induced colitis. This is just an example of the program and what we're trying to do.

Because our hope to get to the point where we can prevent those side effects by launching clinical trials to actually decrease the likelihood of having side effects by maybe Vitamin D eventually, maybe other drugs. We have a very active program at the Brigham and Women's Hospital and Dana Farber, where we're trying to mitigate those immunotoxicities. And that's a very heavy area of research for us, and we work in collaboration with nationally and globally as well trying to work with our colleagues who are interested in this more.

OBY: Are there any longer term goals and end goals to find the information your studying now?

OSAMA RAHMA: Yes. So the goals of our team research is, one, to move immunotherapy to cancers where it has not work traditionally. There is a big focus of my group trying to make this work in cancers like pancreatic cancer and colon cancer. We want to move the needle.

We want those immunotherapy drugs to actually benefit more people, not just 30% of lung cancer patients. We really, truly want to understand why not 100% of patients can benefit from that. And then, the way do that it's trying to understand the biology and the immune biology of these tumors and why these drugs work in some cancers and don't work in other cancer.

And then lastly, we want to have a very good safety profile. So we want to prevent these side effects that's happening. So we want to have a balance where we maximize the benefit and minimize the risk when we do these trials. We truly want to change the field and move the field forward in terms of making cancer immunotherapy truly becoming really the front line as we treat any type of cancer.

OBY: Thank you again for joining us, Dr. Rahma. It's been a pleasure to have this conversation with you.

OSAMA RAHMA: Of course. My pleasure. Thank you.

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BRENDAN: Next time on *ThinkResearch.*

ALEX LIN: It's a program that's just fantastic. The aim is to try to give opportunities to those students who normally wouldn't necessarily have these kind of opportunities.

BRENDAN: Dr. Alex Lin returns to talk about the Harvard Catalyst Visiting Research internship program and the importance of mentoring in clinical and translational research.

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