

0:00:00 -> 0:00:13.5 Support for Yale Cancer Answers is provided AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com.

0:00:13.5 -> 0:00:44.2 Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about the role of bacteria in the development of colon cancer with Dr. Seth Herzon. Dr. Herzon is the Milton Harris '29 Ph.D. Professor of Chemistry at Yale University. Dr. Chagpar is a Professor of Surgery at Yale School of Medicine.

0:00:44.2 -> 0:00:49.8 Seth, maybe you could start off by telling us a little bit about yourself and what you do.

0:00:49.8 -> 0:01:11.3 So, I was trained as an organic chemist and my laboratory focuses on making chemicals that are found in nature. These are typically chemicals that are produced by bacteria or plants. We try to recreate them in the laboratory from scratch, so that we can then study their properties.

0:01:11.3 -> 0:01:20.5 Okay. So, you find these chemicals in plants and in nature. What does that have to do with cancer?

0:01:20.5 -> 0:01:58 That is a great question. So, a lot of these chemicals are actually evolved to kill other cells. Bacteria use them to kill other bacteria, and plants and other species will generate very complicated chemicals, almost as a defense mechanism. What we have found historically as humans is that we can re-purpose these chemicals and use them to kill cancer. And so that is one of the directions that my laboratory goes in, ultimately when we make these chemicals, we can then evaluate their cancer-killing properties.

0:01:58 -> 0:02:20.6 But I would think that when a plant makes some chemicals to kill off bacteria that might come and destroy itself, that would be really different than a cancer, how do you figure out which chemicals you can repurpose into cancer-fighting properties and how exactly do you do that?

0:02:20.6 -> 0:03:00.9 That is the entirety of my job. That is a challenging proposition, you are absolutely right, in most cases, the molecules or the chemicals as they come directly from nature are not in fact optimized to kill cancer. We have to make changes to their structures and that is often very difficult. We do not always have a good idea of what types of changes we would like to make, it is almost as if we were told to build an automobile but were not given the specs and we sort of have to guess as what this automobile should ultimately look like and be capable of doing.

0:03:00.9 -> 0:03:45.2 So, how do you do that? Give me an example of how you do that, because I am just thinking you have got a plant in nature, it makes a bunch of chemicals, and these chemicals have various properties to do various things, and you really want to repurpose it into a completely different job, maybe related in terms of fighting off an invader, but an entirely different

job now in humans fighting cancer, and cancer itself is really complicated, I mean not all cancers are the same, how do you go about doing that? Give us a glimpse of how that works in real life. Can you give us an example?

0:03:45.2 -> 0:04:48.1 Yeah sure. It is a very interesting process. Historically, the way this has been done is that you will actually have scientists that will go out into the field, into various places. The lucky ones get to go scuba diving in the Pacific or hiking in some remote island, and they collect samples and they bring those samples back to the lab and essentially what they do is a process called activity-guided fractionation where they basically start to see if these samples can kill cancer. And if they do, they start to invest more time trying to figure out what chemicals are actually in the sample and what their structures are. And so that is how it starts. And at that point, it typically gets handed off to someone like myself. And if we understand to some degree, even to just a small degree, how the compounds are killing cancer cells, that can give us an idea of what types of structural changes we need to make.

0:04:48.1 -> 0:04:53.4 So, give us an example of a project that you are working on in your lab where you have kind of done that.

0:04:53.4 -> 0:05:49.5 One of the molecules that we worked on for a long time in my group is produced by a bacteria that was actually found in a marine sponge in the ocean. And this molecule has a very complicated structure, is a very potent anti-cancer agent. It is one of the most potent anti-cancer compounds ever known. So, at very low concentrations, it will kill cancer cells and one of the things that we spent some time doing is taking this very complex structure and trying to separate off different parts of it to get to something that is simpler that will still kill cancer effectively, and we are able to do that with this molecule and we ultimately had much smaller, we call them derivatives, much smaller simplified structures, they were easy to make and they were quite active against cancer.

0:05:49.5 -> 0:06:18.6 So, why couldn't you just give this marine sponge to animals to eat, and see if the animal could then fight off cancer. Why do you have to go through the whole rigmarole of finding the molecule, creating the derivatives, making the derivatives simple if they occur in nature, why cannot we just consume that molecule as it is?

0:06:18.6 -> 0:07:02 People are trying to do that. You know, there is an area of science looking at using bacteria, we have certainly heard of probiotics, you take probiotics, these are bacteria that can make molecules and do things that are beneficial. People are now starting to look at engineering bacteria to make these types of molecules that can do other things, such as kill cancer. But in this case, it will be very difficult to have just taken those bacteria and feed them to someone, it is difficult to get the bacteria to grow outside of their natural habitat and so that is why we are really sort of stuck with figuring out what they make and then trying to recreate it.

0:07:02 -> 0:08:26.9 I get the process of, okay some marine biologist goes scuba

diving, finds this marine sponge, brings it back to a lab, and lo and behold finds that there are some properties in what he brought back from the ocean that kills cancer cells potentially in a Petri-dish. And then, from there you kind of figure out what the molecule is. But how do you go about figuring out how you are going to create that in a way that is not only something that you can manufacture, but something that is consumable either edible or through an intravenous route administrable, I do not even know if that is a word, but could be administered to humans and what cancers in particular it is going to fight and then how do you actually get that to the point where it is a real-life medication? I mean because when you start off saying this is the most potent anti-cancer thing on earth, I am sure all of our listeners including me are kind of going well sign me up. I mean, that is the drug we want and yet do all drugs work for all cancers in all people. How do you get from the marine sponge to the clinic making a difference in people?

0:08:26.9 -> 0:09:11.4 It is a great question. That is arguably the harder end of the process. Once we have identified the molecule, we know how it acts, we know how it kills cancer, getting that compound to actually become a drug can be quite challenging. There are a lot of resources here at Yale and at the hospital to actually support those types of research efforts, but to be honest, it is very difficult and it takes a long time. You have to worry about how these things will be administered, how stable are they, what types of cancers you will use them against, we can determine some of that ahead of time, but once you go into people, things tend to get very complicated.

0:09:11.4 -> 0:09:16.7 So, how do you even get to the point where you have got something that could be administered to people?

0:09:16.7 -> 0:09:57 In my lab, we will try to develop what we call synthesis, which is a way to create the compound. We will work out the synthesis such that we can make hundreds of milligrams or gram quantities of the molecule and then we work with people at the medical school to look at the activity of these molecules in different animal models. Obviously, you are not going to go right into a person with a compound that is unproven. And so, you start out with mice and sort of work your way up to more complicated models. Once you get to that point and it seems that it is working and it is not toxic, that is when you start to do clinical trials.

0:09:57 -> 0:10:40 Tell us more about the collaboration that you have with medical schools, because certainly on this show we often have people from the medical school, from the clinical disciplines, all of whom work with patients, it is not often that we get somebody who is a chemist on this show and yet you are having a real impact in terms of cancer management. So, tell us about that collaboration that you have with the medical school, how do you find collaborators, how do you develop those teams where scientists can work with doctors to actually do the work to get drugs to clinical trial?

0:10:40 -> 0:11:32.5 One of the things that is great about Yale is that I found,

so I am in the chemistry department, I am in the faculty of arts and sciences, but one of the things that I found over the last 12 years or so, is that people at the medical school are very open to collaboration. It has been very easy to establish connections here. Sometimes, it is simply just an e-mail. I actually had a collaborator at the med school, we published 2 or 3 papers together before we even met in person. We just sort of did everything remotely, but it worked just fine and they were very nice papers and we really sort of helped each other to advance our research together. So, it has been a very productive environment for my own research.

0:11:32.5 -> 0:12:43.8 And how did you find these researchers in the medical school because it seems to me that you are kind of in the middle right? You are the person, after the marine biologist goes out and finds this sponge in the ocean and says Gee, look what I found, I think it might kill cancer, you are the guy in the middle who says well let me look at that and let me find out what compound it is and let me try and synthesize it and let me try and make it into a derivative such that it is actually usable and then let me connect with somebody in the medical school who can test this in mice and maybe larger animals before it gets to the clinic. So, you are kind in the middle and so, that is really a gray zone for a lot of people. I think a lot of our listeners would have heard about clinical trials and maybe we can talk more about that in a minute. But a lot of people may not know how it is that that middle piece works, it is bit of a black box?

0:12:43.8 -> 0:13:47.3 Yeah. Actually, it is an interesting space to be in. It is one of the reasons I really like chemistry. You know, chemistry truly is the central science. I have taken my research, my research faces more in a biomedical and cancer-focused direction, but there are lots of other directions one can go as a chemist looking at energy and the environment, fuels, things like that, but for me it is really sort of biomedical and really it just comes down to engagement and trying to stay engaged with the people at the medical school, trying to read broadly so that I can understand what they are doing and then not being afraid to basically just reach out for help and see if they are interested in working together. For me, the best sort of mental space to be in as a scientist is when I am being mentally challenged and I am not quite sure what the next best thing to do is, and that is when I feel like I am learning the most.

0:13:47.3 -> 0:14:06 So, it sounds like it is a really interesting place to be, we want to take a short break for a medical minute, but maybe after the break, we will talk more about how these drugs actually get into clinical trials and to the bedside and the impact that your research has had in terms of colon cancer.

0:14:06 -> 0:14:20.4 Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, dedicated to providing innovative treatment options for people living with cancer. Learn more at astrazeneca-us.com.

0:14:20.4 -> 0:15:12.2 This is a medical minute about breast cancer. The most common cancer in women. In Connecticut alone, approximately 3000 women

will be diagnosed with breast cancer this year, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

0:15:12.2 -> 0:15:44.7 Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Seth Herzon. We are talking about research and the role of bacteria in colon cancer, and right before the break, he was telling us about how in the chemistry department, he really is playing a role in terms of finding compounds that occur in nature that might actually have an impact in terms of cancer. Seth, tell us more about your recent work and the impact that that is having particularly in colon cancer.

0:15:44.7 -> 0:16:43.6 Sure. So, one of the projects really that has been arguably one of the most exciting projects in the last couple of years for us has been trying to understand if and how certain bacteria may cause colon cancer. So, back in 2006, other researchers had discovered that people with colorectal cancer seem to have a particular type of bacteria in their colon, and it was thought at that time that the bacteria made a specific chemical that was actually causing their cancer. And so that was over a decade ago now and since then, people have been trying to figure out what this chemical is. And as I told you, in the first half of the show that is something that is frequently done, but in this case it was very difficult to figure out what this chemical was and how it might be causing cancer.

0:16:43.6 -> 0:16:47.6 So, how did you go about doing that then?

0:16:47.6 -> 0:19:27.2 It was a highly interdisciplinary and collaborative project. My colleague, Jason Crawford had been working very hard to try and figure out how the bacteria actually make the molecule. Through those studies, he was able to deduce about half of the structure of the molecule. And so, as a chemist, I said okay we can try and make that and we will try and study it in the laboratory. And so, we set out to create the chemical in the laboratory. We had it in hand and we indeed were able to show that this molecule is quite toxic and it damages DNA. DNA damage is one of the ways that people can get cancer. So, its behavior was consistent with this observation that had been made many years ago. But that was actually the easy part. So, we had about half of the chemical and then we sort of got stuck. We knew there was another half, but we were not able to figure out exactly what it was. And we got stuck for about 2 years and this time last year, we were really not sure what to do next. And one day, one of my students who was working on the project came into my lab with some new data and we sat down with the data and we had a lot of other knowledge from Jason's work and the work of others, and we worked through

the data and with Jason's help, we were able to propose the structure of this chemical, and it was a very exciting moment for me and for the students I think. You know, there are a few times in science where you really feel as excited I think as I did on that day. It was sort of like we are putting together the puzzle and we had the last couple pieces and then you sort of rush to the end once you know where everything has to go and we are putting those last pieces in and then we could see the entire picture. And once we had an idea then of what the chemical was, we literally spent about a month trying to talk ourselves out of it, trying to find data that was inconsistent with the structure of that chemical and we could not, and so we were very excited about that and that led us to then recreate the molecule in the laboratory and show that it had the same effect as the bacteria on human cells.

0:19:27.2 -> 0:19:39.3 Okay, so wait a minute. You made half the molecule and then you get stuck for 2 years and then a student comes in with new data. What new data?

0:19:39.3 -> 0:20:32.4 So, it is a good question. She was working very hard to try and indirectly get at the rest of the structure, and what she had done, we knew that these molecules do what we call an alkylation on DNA, which is where the molecule actually becomes bonded, stuck to the DNA. And so, we used that DNA essentially as a fish hook to catch the molecule and she had samples of DNA with the molecule in it and was using a large number of very sophisticated what we call mass spectrometry experiments to try and figure out the structure, and ultimately that day she came in my office, she had enough data that we could sit down and start to piece it together.

0:20:32.4 -> 0:20:53.2 Okay. So, you figure out the molecular structure and you have your eureka moment and you all are very excited and happy that you figured out how to create this molecule and you find in your experiments that it actually does cause cancer, and then what?

0:20:53.2 -> 0:21:53 So, for us, that was really our goal all along - as a chemist, was to figure out the molecule, but in terms of cancer therapy, it opens up a lot of doors because now that we know how the molecule behaves, we can think about ways to stop it from causing cancer. We also now have a good understanding of how the molecule is made by the bacteria and so we can think about ways to stop the bacteria from making it. But perhaps probably the most practical and sort of useful kind of therapeutic opportunity coming from all of this work will be in early detection. I think it will be very easy for doctors to bring patients into the office and determine whether or not they have these bacteria in their colon, and if so, they can be monitored closely for any sort of cancer.

0:21:53 -> 0:22:00.8 Okay, but why cannot they just take an antibiotic, which kills off bacteria to kill that bacteria?

0:22:00.8 -> 0:22:20.7 You absolutely could, but one needs to be very careful with antibiotics, you have lots of healthy bacteria, beneficial bacteria in your gut, and you do not want to be wiping them out and certainly if you do not

have these bacteria, you do not want to take antibiotics unless you absolutely need to.

0:22:20.7 -> 0:22:39.8 But if you have a way of telling whether somebody has these particular bacteria, because these bacteria that make this molecule are presumably bad bacteria that you do not want. So, is there a way to tell whether you have these bacteria versus other bacteria?

0:22:39.8 -> 0:23:13.8 Absolutely. Yes. So, you can get fecal samples from patients and then analyze the bacteria in those samples and see if they are present. And one of the other things that we are working on is trying to develop antibacterials that will specifically kill these bacteria, that would really be the magic bullet for us if we could go in there, someone could take a pill and just wipe out these bacteria and leave the healthy ones unscathed.

0:23:13.8 -> 0:23:18.9 And that specific antibacterial does not exist at the moment, is that right?

0:23:18.9 -> 0:23:22.7 It does not, no, but that is something that we are working on.

0:23:22.7 -> 0:23:42.2 And then the other thing is now that you know how these bacteria make this molecule, whether or not you know how to kill off these bacteria if you had a drug that could prevent these bacteria from making this molecule, then that would work too?

0:23:42.2 -> 0:23:48 Yeah, 100%. That would be another therapeutic strategy.

0:23:48 -> 0:24:02.8 You could do these strategies of either killing off this bacteria or killing off the process, whereby the bacteria makes these molecules even in healthy people. So, it is potentially not even therapeutic but really preventative.

0:24:02.8 -> 0:24:13.1 Yeah, prophylactic exactly. That is something that we thought about, in terms of just administering this to people as a way to prevent any sort of cancer formation.

0:24:13.1 -> 0:24:18.6 Did you figure out Seth why this molecule creates cancer?

0:24:18.6 -> 0:24:49 What we have determined is that the molecule damages DNA in the host. So, the bacteria make the molecule and then it sort of swims out and gets taken up in your colon cells and starts to damage the DNA in those cells. And once you get low levels of DNA damage, that is how you can get tumor formation.

0:24:49 -> 0:25:05.7 Well, that's interesting. So, I guess the other strategy is to figure out whether there is some sort of coding or some sort of mechanism that you could get the host cells to have such that it does not take up this molecule and/or that this molecule is not effective?

0:25:05.7 -> 0:25:10.7 Yeah that is right and that would be another strategy that we could try to look at.

0:25:10.7 -> 0:25:56.3 And then, the last point is, it is interesting that these bacteria make this molecule to kind of damage the host, potentially, if the bacteria is in a place where it does not want to be, to kill off the host that it does not like necessarily. You know, DNA damage is one of these things that can cause cancer, but we often have chemotherapeutic agents which also cause DNA damage, it is just that they cause DNA damage in cancer cells. So, is there a way to repurpose this molecule now that you know that this molecule causes DNA damage and reverse engineer it such that you cause DNA damage but in cancer cells.

0:25:56.3 -> 0:26:28.1 Yeah, I think you should come and talk in the lab, you are one step ahead of me. That is also something we are interested in. And so, we are designing ways to essentially cage this molecule in such a way that it will not damage DNA, but then converts into its DNA damaging form once it enters cancer cells, that is precisely what we are trying to do. We are trying to reverse engineer it as you put it, repurpose it as a chemotherapy.

0:26:28.1 -> 0:26:53.2 Because I mean, especially if you could target it into particular cells right? So, you put on some sort of honing agent, like a virus for example or some sort of honing agent that it will go to cancer cells and not normal cells, get into those cells and destroy them. Give cancer to a cancer that is a cool idea.

0:26:53.2 -> 0:27:16.7 That is the idea. Yeah. A lot of people use antibodies to target specific molecules to cancer cells or just to target cancer cells in general, and we have a collaboration with a company in the UK that is interested in attaching this molecule to an antibody so that we can specifically go in and kill cancer.

0:27:16.7 -> 0:27:50.7 Where are you now in terms of thinking about this molecule and all of the things that it can do, I mean is it something that you are still working on in the lab, is this something that is getting into early stage clinical trials, where are we with this and is it only for colon cancer or have you started looking at whether this molecule can play a role either in the etiology and/or the treatment of other cancers?

0:27:50.7 -> 0:28:48.1 Sure. Yes, so we still have a lot of work to do, as a short answer. Now that we know the structure and we have a way to create it, now we can for the first time really study it in detail. And so, in sort of the coming months and years, I expect that we will be looking at trying to understand exactly how it interacts with the host DNA and leads to DNA damage, how those DNA lesions might then be resolved, cells have lots of ways to repair DNA and that is something we want to understand. And then, branching into these more sort of therapeutically oriented directions where we either try to repurpose the molecule as an anti-cancer or try and figure out ways to stop the bacteria.

0:28:48.1 -> 0:29:13.2 Dr. Seth Herzon is the Milton Harris '29 Ph.D. Professor of Chemistry at Yale University. If you have questions, the address is cancer-

answers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.