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00:00:00.076 --> 00:00:21.769 Announcer Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with the director of the Yale Cancer Center, Doctor Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Doctor Winer.

00:00:21.846 --> 00:01:22.269 Eric Winer Today we're talking about genes and how they influence not just whether an individual might be at risk to develop cancer, but how that cancer might even behave and evolve once it occurs. Our guest tonight is Sarah Aitken who is, in American terms, an MD/PhD. There are different letters when you complete your degrees in the United Kingdom. Sarah joined the faculty about a year and a half ago as an assistant professor in pathology, and is part of the center for Cellular and Molecular Oncology here at the Cancer Center, and is someone who we learned from Cambridge University to come and work with us here at Yale.

00:01:22.346 --> 00:01:34.000 Eric Winer Her own interest as a pathologist is GI pathology and molecular pathology, and we may touch on that as well. Sarah, welcome. Thank you so much for being with us.

00:01:34.038 --> 00:01:35.576 Sarah Aitken Thank you. Eric, thank you for having me.

00:01:35.615 --> 00:01:46.000 Eric Winer Let me just ask you a little bit about you first. So you did go to school in the UK. Did you go to Cambridge?

00:01:46.076 --> 00:02:09.384 Sarah Aitken So first of all, I actually went to Edinburgh University where I studied medicine and did an intercalated degree in experiment with me. And then I started working as a medical doctor in Edinburgh while I was doing my Masters in Translational Medicine. And then after that, I moved to Cambridge to do my residency and pathology, and then did my PhD at the University of Cambridge.

00:02:09.423 --> 00:02:11.576 Eric Winer And where are you from originally?

00:02:11.730 --> 00:02:16.230 Sarah Aitken So I grew up in the very north of England, in a county called Northumberland.

00:02:16.269 --> 00:02:21.192 Eric Winer How many years had you been at Cambridge when we managed to recruit you?

00:02:21.384 --> 00:02:41.269 Sarah Aitken So I had been in Cambridge for 12 years, so I did residency there, PhD and then my what was called there, a clinical lecturer job where you were sort of half a resident and half a postdoc at the same time, and then started my lab there about five years ago now before I moved first.

00:02:41.307 --> 00:02:43.807 Eric Winer What made you go into pathology?

00:02:44.076 --> 00:03:09.500 Sarah Aitken So I, during medical school, did an intercalated degree in experimental pathology. And so medical training worked slightly differently in different countries. And so for me, medical school started straight from high school. But you have the opportunity about halfway through medical school, after you've done the more preclinical part of medicine, to do a full time science honors course, essentially.

00:03:09.500 --> 00:03:27.653 Sarah Aitken So you do the last year of what other people will be doing as their undergrad. And I did that in what was called experimental pathology. And that meant that I spent a year in a research lab studying. I was working on looking at cells in a dish, and we treated them with different drugs to see how they behaved.

00:03:27.692 --> 00:03:41.653 Sarah Aitken And a lot of that was looking down the microscope and seeing how cells change in different, in different ways. And I also during that year worked with several academic pathologists and became interested in what they were doing.

00:03:41.730 --> 00:04:13.230 Eric Winer You know, it's a funny thing, when I was in medical school quite a number of years ago, I thought to myself, why would anyone want to be a pathologist? And I just didn't quite get it. And then I became an oncologist and realized how critical pathologists are in so many different ways. And as clinicians taking care of patients, we rely so heavily on our colleagues in pathology.

00:04:13.230 --> 00:04:20.846 Eric Winer And it really is it's a very interesting field. And of course, you get to make diagnoses.

00:04:21.000 --> 00:04:40.884 Sarah Aitken It's I think it's a really interesting job. And through the whole of our training as residents, we we work across all the different disease types. So we don't pick a disease early on. We learn how to diagnose essentially everything. So it's a very, very broad thing. And it's there's lots of problem solving. You have to work things out.

00:04:40.884 --> 00:05:03.653 Sarah Aitken Sometimes the physicians or the surgeons have already probably worked out what's going on and we just confirm it, but other times we find something completely unexpected. And then we have to do the problem solving to work out what's going on. And in turn, what we find is what helps to decide how patients get treated. And as part of the multidisciplinary team meeting or here, you call them Cima boards.

00:05:03.769 --> 00:05:15.769 Sarah Aitken We sit and work through what we found, whether that makes sense with what you've seen in clinic, whether that fits with the radiology scans, and then piece together what the best thing is for the patient.

00:05:16.038 --> 00:05:54.846 Eric Winer So years ago, the pathologist only had his or her eyes to use when it came to making a diagnosis. And my guess is at some point, not that much. After those early days, there started to be certain ways of using different kinds of stains to identify abnormalities. So, for example,

when we test for her to in breast cancer, we do it initially with what's called an immuno stain.

00:05:55.000 --> 00:06:14.423 Eric Winer But we're now much more sophisticated than that. And you talk about GI pathology and molecular pathology. Tell us a little bit about what you mean by molecular pathology, and how that has led to really a revolution in diagnosis.

00:06:14.500 --> 00:06:31.692 Sarah Aitken Sure. So pathologists are medical doctors and we diagnose diseases by looking at, as you say, looking at little pieces of tissue down a microscope, or if you have an endoscopy or a biopsy, or if you have an operation and take out a much bigger piece of tissue. We look at that down the microscope and we still do that.

00:06:31.692 --> 00:07:08.500 Sarah Aitken We still always look at what it looks like with our eyes first. Then, as you say, we can do extra stains or special stains in your history chemistry. But then we can also use. I suppose I like to think of it as a molecular microscope or a sequencer to extract different molecules from the tissue so we can extract RNA, or we can extract DNA, and then we can sequence those things to see whether we can look in much closer detail at the specific genes, or look at the the DNA itself, and see if we can find alterations in the DNA that we call mutations that sometimes are what's driving a particular cancer to develop.

00:07:08.500 --> 00:07:19.115 Sarah Aitken And by identifying some of those really specific mutations that can help to identify drugs that can be used to make treatment of cancer more, more personalized and more precise.

00:07:19.115 --> 00:07:50.038 Eric Winer So I'm going to take you a little bit outside of your GI field, and I'm going to talk for a minute about leukemia. So when I was in training in medical oncology training, there were essentially seven types of leukemia. And that was basically coming from the pathologists eyes, because these seven types all looked a little different from one another.

00:07:50.038 --> 00:08:05.769 Eric Winer And now my sense and you know, more about this than I do as a pathologist, is that our ability to characterize leukemias based on molecular fingerprinting is really incredible.

00:08:05.807 --> 00:08:30.230 Sarah Aitken Yeah. So the hematological diseases is probably one of the things that made my exams the hardest thing, because there's so many different types that you have to learn. And we as you say, we look just down the microscope to see what the cells themselves look like. But then we can we can use fluorescent probes that we can use to bind onto the DNA and see sometimes the DNA swaps around between different places in the DNA.

00:08:30.230 --> 00:08:55.230 Sarah Aitken And we can see that using it's called fish, but it makes a fluorescent dye. Or we can sort the cells according to what proteins they have on the outside. And then we can also sequence them. So there's all sorts of different ways. And it means that by being able to be more

precise in in diagnosing than it allows the hematologists in turn to be more precise in their treatments of the patients.

00:08:55.269 --> 00:09:25.153 Eric Winer And so what was seven diseases is now dozens and dozens and dozens of diseases. And what was at one time essentially the same treatment for everyone. I mean, everyone received induction chemotherapy with the same regimen, and now it's ever so much more personalized. How has that played out in your own field of of GI oncology?

00:09:25.230 --> 00:09:48.692 Sarah Aitken So in in each field of pathology we can there's sort of different things that have changed. And one of the things that we can look at is whether some of the so after we've looked at the tissue under the microscope, we can do these different immuno stains to look for different things. And we can find proteins that are meant to be there to repair DNA, to stop accounts of developing.

00:09:48.692 --> 00:10:06.730 Sarah Aitken Sometimes that's not working properly. And so we can see that. And that might make a patient more sensitive to particular types of immunotherapy or other more targeted medicines. So it allows us to to separate patients out into more precise diagnoses.

00:10:06.769 --> 00:10:47.500 Eric Winer And already within the GI system, there are many, many different diseases. There's colon cancer, there's pancreatic cancer, there's biliary that cancer. And with these additional techniques, you can now better understand each of these fairly unique diseases. And of course, thankfully the pharmaceutical industry has been right behind us. And as soon as we identify new abnormalities, it seems there's an interest in trying to make drugs that will have an impact on that specific cancer.

00:10:47.576 --> 00:10:59.692 Eric Winer The result, of course, is that cancer therapy has become extraordinarily expensive, but at the same time, it's become extraordinarily more effective. And it all starts with the pathologist.

00:10:59.769 --> 00:11:19.384 Sarah Aitken It does. We have to get the right diagnosis in the first place. But it's it's a it's a kind of feedback circle. I suppose we have to get the right diagnosis. Then we have to get the right drug. But then we also have to monitor and see whether it is working or not. Because even when we have these really targeted therapies, sometimes for some patients they work really well, but for other patients they don't.

00:11:19.423 --> 00:11:24.884 Sarah Aitken And that's one of the things that we don't understand very well at the moment is to why there's that difference.

00:11:24.884 --> 00:11:55.615 Eric Winer And when they work, sometimes they stop working. So, you know, the minute we develop a new drug, we have to also start asking what what causes the resistance. So I know that in making this move from Cambridge, Cambridge, England, to New Haven, Connecticut, that one of the things that happened is that you suddenly weren't able to practice clinical pathology for some period of time.

00:11:55.846 --> 00:12:16.153 Eric Winer The US requires that you take a number of different tests, and I'm just wondering how much how much you've missed being able to sit behind the microscope and make diagnoses and interact with your clinical colleagues. I realize it's giving you time to get your lab off the ground, but do you miss it?

00:12:16.230 --> 00:12:36.269 Sarah Aitken So it's been it's been good to be able to focus on getting the lab up and running, but it is very strange at only having one job. And although I still look down the microscope at tissue that we have from patients and from our experiments, I still look at those in the research lab, but it's it's different from doing it in clinical practice.

00:12:36.346 --> 00:13:00.000 Eric Winer Yeah. I mean, I guess, you know, one of the things and, you know, as someone who takes care of patients and does research, you know, I find that taking care of patients grounds me and teaches me about what I need to investigate further from a research standpoint. And even though you're not taking care of patients, you're looking at their tissue.

00:13:00.076 --> 00:13:02.500 Eric Winer I'm sure there's the same feeling.

00:13:02.615 --> 00:13:16.576 Sarah Aitken Yes. And as the as the field moves and changes and the discussions in the tumor boards, as new drugs arrive and new diagnostics happen, being involved in those conversations is a really important thing in driving the research as well.

00:13:16.730 --> 00:13:41.692 Eric Winer Well, we're going to need to take just a minute break. I've been speaking with Sarah Aitken a GI and molecular pathologist, who is also very much a basic scientist and involved in cancer research. And when we come back, we're going to talk about some of the research she's been doing that could change the way we think about how cancers behave.

00:13:41.807 --> 00:13:43.423 Eric Winer We'll be right back.

00:13:43.500 --> 00:14:04.307 Announcer Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where experts on the forefront of cancer research and clinical trials, advanced research, prevention and patient care. Smilow's cancer research provides some patients with access to unique cancer clinical trials. SmillowCancerHospital.org.

00:14:04.384 --> 00:14:35.807 Announcer There are many obstacles to face when quitting smoking as smoking involves the potent drug nicotine. Quitting smoking is a very important lifestyle change, especially for patients undergoing cancer treatment, as it's been shown to positively impact response to treatments, decrease the likelihood that patients will develop second malignancies and increased rates of survival. Tobacco treatment programs are currently being offered at federally designated comprehensive Cancer center, such as Yale Cancer Center and Smilow Cancer Hospital.

00:14:35.884 --> 00:14:54.807 Announcer All treatment components are evidence based, and patients are treated with FDA approved first line medications, as well

as smoking cessation counseling that stresses appropriate coping skills. More information is available at YaleCancerCenter.org. You're listening to Connecticut Public Radio.

00:14:54.884 --> 00:15:40.461 Eric Winer Welcome back to the second half of Yale Cancer Answers again. I'm Eric Winer, your host, and I'm speaking tonight with Sarah Aitken, who is a cancer researcher and a pathologist. And we're going to now talk about some of the work you've been doing in the laboratory, work that relates to how cancers may behave differently in one person than another, and how our genes, the genes that are in every cell of our body, both affect our predisposition to develop cancer and the way that cancer might behave.

00:15:40.500 --> 00:15:43.884 Eric Winer So educate us a little bit.

00:15:44.038 --> 00:16:04.653 Sarah Aitken Sure. So in my lab we work on molecular and genomic pathology of cancer. And that means that we try to work out what goes on in the DNA to make a normal cell become a cancer cell. And then what makes that cancer cell grow into a tumor? And one of the things that can often initiate cancer is if there's changes in the DNA sequence.

00:16:04.653 --> 00:16:26.538 Sarah Aitken So the DNA is inside, as you said, inside every single cell of our body, a change in the DNA is called a mutation. And one of the biggest challenges in studying and in treating cancer is that every single tumor is unique. And that's partly because every single person is unique, and all of the exposures and risk factors that they have over the course of their lifetime is different.

00:16:26.576 --> 00:16:52.615 Sarah Aitken So each of us has got millions or tens of millions of subtle differences in our DNA that we inherit from our parents. So actually, although we're all very, very similar, we're also quite different. And we also have very different lifestyles. So some people like to sunbathe. Some people smoke and we're exposed to different things in our environment. So things like air pollution can cause changes in the DNA.

00:16:52.653 --> 00:17:09.000 Sarah Aitken And all of these things are going to be different between individual people and between different populations around the world. And so because of those differences in our genes and also in our environments, it alters the risk of acquiring harmful mutations in the DNA that can spark a cancer to develop.

00:17:09.000 --> 00:17:39.500 Eric Winer And of course. And I think that people understand this, but sometimes need to be reminded that all cancers actually develop from what is a cell in our own body. You know, a cell that at one point was presumably not always, but in many people was an entirely normal cell or like all the cells around it. And it changed over time.

00:17:39.538 --> 00:18:04.807 Eric Winer And the reason I said, not always because of course, some people are born with mutations in genes that we know our cancer predisposing. But even there it's oftentimes some other gene perhaps,

or something in the surrounding environment that pushes that cell to actually become a cancer.

00:18:04.846 --> 00:18:32.192 Sarah Aitken Yeah, it's a it's a collection of cells that grow together and become essentially become a lump that have arisen from an essentially normal cell to start with. And lots of the time we think that it's a change in the DNA. That is what initiates that. But it doesn't necessarily make a cancer grow. And actually, we've learned over the last ten years or so that lots of our normal cells have got these changes in them that we used to think was what made a cancer a cancer.

00:18:32.192 --> 00:18:52.115 Sarah Aitken But as you say, sometimes it takes a second mutation to happen. So you could be born with a change in the DNA, but it still needs something else to make the cell go bad, essentially. Or it might be that it starts off as a normal cell, and it takes several different changes in the DNA, and those things interact together.

00:18:52.115 --> 00:18:57.615 Sarah Aitken They changed the way that the cell behaves, and eventually that can become a tumor.

00:18:57.692 --> 00:19:32.384 Eric Winer And, you know, you could imagine someone saying, well, how is it that one cell that has one mutation that, that, that, that cell like acquires this, this second mutation? But what people need to remember is that we have so many cells in every single one of our organs, and they're constantly changing. And by chance alone, these various mutations will develop over time, and our bodies can often handle them.

00:19:32.384 --> 00:19:40.576 Eric Winer And sometimes our bodies just can't quite figure out how to get rid of that, that cell that has become deranged.

00:19:40.615 --> 00:20:02.576 Sarah Aitken That's right. So we have we have trillions of cells and they're dividing all the time. And if you if you add up the length of the DNA that's inside each cell that has to divide, you can calculate that it's about two light years worth of DNA that will replicate over the course of a lifetime. And every single one of those little bases has the potential to change.

00:20:02.615 --> 00:20:15.538 Sarah Aitken And that's going on in every single cell, every time it grows, as as we grow and age, we accumulate all these extra changes. So statistically, actually, I think it's amazing that it doesn't happen more often.

00:20:15.576 --> 00:20:25.384 Eric Winer It still is the case that the majority of people in their lifetime, not by a long shot, but the majority of people don't develop cancer.

00:20:25.615 --> 00:20:48.153 Sarah Aitken That's right. So it's it's still it's very common and it's a very important thing for us to understand. But despite all of these, all of the replication, all of the times that the cells divide, most of

the time, either the cell gets it right or the mechanisms that we have to stop the faulty cells dividing, they kick in and make sure that the cells stay healthy.

00:20:48.230 --> 00:21:23.538 Eric Winer So we appreciate that certain inherited changes in our genes can predispose to the development of cancer. And certain acquired changes can predispose to cancer. But your work has taken this a step further and has suggested that not only do these genetic changes affect the likelihood of developing cancer, but they modify the behavior of the cancer. So tell us a little bit about the experiments that led to that conclusion.

00:21:23.615 --> 00:21:44.846 Sarah Aitken As I said before, in in patients, we all have different genes and we have different exposures that are going on all of the time. So it makes it very difficult to tease apart exactly what sort of cause and effect are in those things. And so what we did in this project was we used experiments that used mice that have natural variation in their genes.

00:21:44.846 --> 00:22:07.653 Sarah Aitken So we didn't engineer anything or modify anything. We used the natural variation that they have, and then used a chemical that we find in the environment all the time. So it's in things like cigarette smoke or in cured meats and watched how the tumors developed. And as you say, there's a different predisposition to get the tumors. But we also found that they have different changes that they acquire.

00:22:07.653 --> 00:22:36.000 Sarah Aitken So depending on what genes they inherited, it alters which gene is the one that then becomes mutated and drives that cancer forwards. And we also found really interesting that the gene that gets mutated, the one that's driving the cancer forward can it's behavior can change other pathways in the cancer. So there's a signaling pathway called p53, which is one of the famous cancer pathways that is really important in driving cancers.

00:22:36.000 --> 00:22:59.884 Sarah Aitken And we found that in some of the situations the inherited genes made a pathway make that p53 go up, whereas in other inherited backgrounds it went down. So even though it had got the same mutation seemingly driving that cancer forward, the inherited genes changed the way they interacted and changed the way that that tumor grew.

00:22:59.884 --> 00:23:48.153 Eric Winer And of course, as a patient, you want your p53 to be driven up because p53 is a tumor suppressor gene and helps damp down a cancer. And of course, loss of p53 is is more of a problem. And so this suggests that two people would have essentially identical cancers. But because one of them has a different genetic makeup for whatever reason, either because of an inherited factor or because of a lifestyle factor that then caused the genetic changes, that person might have a cancer that then grows more rapidly.

00:23:48.230 --> 00:24:13.153 Sarah Aitken Exactly. So it's a really tricky situation because you have what seem to be, you know, down the microscope, they look the same. It might even be that when we look for that targeted thing that

we think is driving the cancer, that might all be the same. But then two different people respond in different ways. And what makes that really challenging is that those two people might have millions of differences in the genes they inherited.

00:24:13.153 --> 00:24:25.230 Sarah Aitken And so teasing out which ones most important or how how they're interacting together, how that combination of changes influences it is is something that we still need to work out well.

00:24:25.269 --> 00:24:52.076 Eric Winer And it's incredibly complicated. So it's not simply looking at one gene and correlating that with the course of a person's cancer. It's potentially being able to look at many, many different genes and many, many other factors all at the same time, and trying to understand how these complex patterns interact with one another.

00:24:52.076 --> 00:25:10.500 Sarah Aitken It is very complicated and also changing, changing over time because there's new mutations and new changes happening all the time. So there's millions of different things interacting together and using using different machine learning approaches to tackle some aspects of this, maybe a good way to go forward.

00:25:10.576 --> 00:25:33.000 Eric Winer I mean, it does seem like it's a pretty complicated task without some pretty fancy machine learning, AI, computer assisted technology, what have you. Now, all of this work has been done so far in mice. How is that helpful in terms of people?

00:25:33.115 --> 00:25:58.500 Sarah Aitken So the work that we've done so far, as you say, has been in mice. And that's been it's been really important to use that as a model system as part of the basic science approach, to answer some really fundamental questions. And the important part now is to see how that can be applied in a clinical setting. It's more difficult because there's so many more variables in people, but it's something that will be really important to try and work out.

00:25:58.538 --> 00:26:25.692 Sarah Aitken As we've talked about, when you look down the microscope, they might look the same, they might have the same specific change. But what we but what we tend to do at the moment is that when we're diagnosing any disease but a cancer, we look at the we look at the tumor itself, what's going on inside that. But we don't tend to look at any alterations or changes that are going on in the normal tissue or in the rest of that patient, and that's something that's really underexplored at the moment.

00:26:25.769 --> 00:27:04.346 Eric Winer Yeah, it's really it is just incredibly fascinating. And I think, you know, your comment about the work in mice, I think is very important because, you know, in recent weeks, months, what have you, you know, we've heard negative comments about research done in animal models. And while I think we have to think very carefully about what we do in animals versus what can be done in human systems, that there's a real role selectively for work done in animal models.

00:27:04.346 --> 00:27:23.269 Eric Winer And it would be a shame if we weren't able to do that. So I think it's it really is important. Well, we have about a minute left, and I'm going to turn to a favorite subject of yours and mine, which is cycling. And I used to do a lot of cycling a little less now but still do it.

00:27:23.269 --> 00:27:26.423 Eric Winer And I know you are an avid cyclist.

00:27:26.500 --> 00:27:31.846 Sarah Aitken That that is accurate at the moment. Yes. It's been good to explore around here on the bike.

00:27:32.000 --> 00:28:02.192 Eric Winer And that brings us to the fact that we're both riding in Closer to Free, which is the annual ride to support cancer research and cancer care at Yale Cancer Center and Smilow Cancer Hospital. And although we don't like to make too many plugs on this show for any specific entity, I think putting in a good word for a cycling fundraiser is is always worthwhile.

00:28:02.230 --> 00:28:25.730 Eric Winer So I wish you the best in that ride, which is September 19th, and I look forward to seeing you out there. And I just want to say thank you so much for educating us about molecular pathology, about this work you've done, which I think is really is really important and has the ability to help us understand the behavior of cancer so much better.

00:28:25.730 --> 00:28:38.538 Eric Winer I've been speaking tonight with Sarah Aitken in the assistant professor of pathology and a member of the Center of Molecular and Cellular Oncology here at Yale Cancer Center. Sarah, thanks again.

00:28:38.730 --> 00:28:57.692 Announcer If you have questions, the address is CancerAnswers@Yale.edu and past editions of the program are available in audio and written form at YaleCance Center.org. We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.